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Evidence for assessing drug safety and drug use in older people, volume II

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Published in
Frontiers in Pharmacology

ISSN 1664-8714
ISBN 978-2-8325-3113-6
DOI 10.3389/978-2-8325-3113-6

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Evidence for assessing drug safety and drug use in older people - volume II

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Citation

Elseviers, M. M., Lopes, L. C., Benko, R., Canis, M., Godman, B., Motter, F. R., Oliveira, M. G., eds. (2023). *Evidence for assessing drug safety and drug use in older people - volume II*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-3113-6

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frontiers | Frontiers in Pharmacology

ORIGINAL RESEARCH
published: 18 July 2022
doi: 10.3389/fphar.2022.935764

Increasing Trends of Polypharmacy and Potentially Inappropriate Medication Use in Older Lung Cancer Patients in China: A Repeated Cross-Sectional Study

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Specialty section:
This article was submitted to Drugs Outcomes Research and Policies, a section of the journal Frontiers in Pharmacology

Received: 04 May 2022
Accepted: 21 June 2022
Published: 18 July 2022

Citation:
Tian F, Chen Z, Chen X and Zhao M (2022) Increasing Trends of Polypharmacy and Potentially Inappropriate Medication Use in Older Lung Cancer Patients in China: A Repeated Cross-Sectional Study. Front. Pharmacol. 13:935764. doi: 10.3389/fphar.2022.935764

Objectives: Polypharmacy and potentially inappropriate medication (PIM) use are frequent in older lung cancer patients. This study aimed to examine the trends of polypharmacy and PIM use and explore risk factors for PIM use based on the 2019 Beers criteria in older Chinese lung cancer outpatients with multimorbidity.

Methods: A repeated cross-sectional study was conducted using electronic medical data consisting of the prescriptions of older lung cancer outpatients in China from January 2016 to December 2018. Polypharmacy was defined as the use of five or more medications. The 2019 Beers criteria were used to evaluate the PIM use of older cancer outpatients (age ≥65 years), and multivariate logistic regression was used to identify the risk factors for PIM use.

Results: A total of 3,286 older lung cancer outpatients and their prescriptions were included in the study. The prevalence of polypharmacy was 14.27% in 2016, 16.55% in 2017, and 18.04% in 2018. The prevalence of PIM use, according to the 2019 Beers criteria, was 31.94% in 2016, 35.78% in 2017, and 42.67% in 2018. The two most frequently used PIMs in older lung cancer outpatients were estazolam and tramadol. The logistic regression demonstrated that age 75 to 79, polypharmacy, irrational use of drugs, and lung cancer accompanied by sleep disorders, anxiety or depression, or pain were positively associated with PIM use in older lung cancer outpatients.

Conclusion: The prevalence of polypharmacy and PIM use in older lung cancer outpatients with multimorbidity was high in China, and polypharmacy and PIM use increased over time. Further research on interventions rationing PIM use in the older lung cancer patient population is needed.

Keywords: polypharmacy, potentially inappropriate medication, lung cancer, older, outpatient

INTRODUCTION

Lung cancer is the leading cause of cancer death worldwide, accounting for nearly 1.80 million deaths and causing 18% of total cancer deaths in 2020 (Global Cancer Observatory, 2020; WHO, 2022). Older age is associated with cancer development due to biological factors that include DNA damage over time and shortened telomeres. As the population continues to age, the incidence of lung cancer in older patients is expected to further increase in the coming years (Decoster and Schallier, 2019). Approximately 37% of lung cancer cases occur in individuals over 75 years old. Accordingly, the median age at lung cancer diagnosis is 70 years old for both men and women (Torre et al., 2016). The majority of older lung cancer patients have comorbid chronic diseases and must take multiple medications (Grose et al., 2014; Nilsson et al., 2017; Ding et al., 2020). However, increased number of drug-related problems was associated with age-induced alternations in pharmacokinetics (PK) and pharmacodynamics (PD). Lung cancer also effects pharmacokinetics and pharmacodynamics and occurs more frequently in the elderly. Therefore, lung cancer patients who are elderly are more prone to experience adverse drug events. In addition, previous published studies have confirmed that cancer patients are easily exposed to a higher risk of polypharmacy and inappropriate medication use (Wildiers et al., 2014; Koczwara et al., 2022).

Polypharmacy (defined as the use of more than five medicines) is associated with the prescription of inappropriate medications, and extensive studies have demonstrated the link between polypharmacy and negative outcomes (Maddison et al., 2011; Weng et al., 2013; LeBlanc et al., 2015). Potentially inappropriate medication (PIM) use was firstly proposed in 1991 because PIM use brought a series of drug-related problems, such as adverse drug events, hospitalization, and disability, defined as the use of medications that should be avoided, especially when evidence is insufficient or alternative medicines are available (Hyttinen et al., 2016; Muhlack et al., 2017; Wallace et al., 2017).

Some previous reports have examined the trends of polypharmacy and PIM use in older patients (Davidoff et al., 2015; Moriarty et al., 2015; Muhlack et al., 2018). Approximately half of all cancer care is delivered in an outpatient treatment setting (Maleki et al., 2022). It is necessary to investigate the polypharmacy and PIM use in older lung cancer outpatients. However, no study has specifically reported on the trends of polypharmacy and PIM use in older lung cancer outpatients, and the risk factors for PIM use according to the 2019 Beers criteria in older Chinese lung cancer patients are unclear. Therefore, in this study, we extracted data on the prescriptions of older lung cancer outpatients treated at tertiary hospitals in Chengdu, China over 3 years. The trends of the prevalence of polypharmacy and PIM use were calculated, and PIMs were screened based on the 2019 Beers criteria. The risk factors for PIM use were explored. Ideally, this study will provide useful data for follow-up research.

METHODS

Setting and Sample

A repeated cross-sectional study was performed to examine the trends of polypharmacy and PIM use among older lung cancer (histology: non-small-cell lung cancer, small cell lung cancer, unspecified lung cancer; stage: American Joint Commission on Cancer 8th Edition (AJCC) stage I-III) outpatients with multimorbidity that might receive chemotherapy and chronic disease treatment in tertiary hospitals in Chengdu, a capital city in southwest China. The prescriptions of older (aged ≥65) lung cancer outpatients with multimorbidity (cancer with other diseases) were cluster sampled from a cooperative hospital prescription analysis project led by the Chinese Pharmaceutical Association. In this study, cluster sampling was used to randomly select nine hospitals from all tertiary hospitals in Chengdu between 1 January 2016 and 31 December 2018, and then the older lung cancer outpatient prescriptions were selected from all departments of the selected hospitals as the survey samples. Multimorbidity of patients was determined by the numbers of diagnosis in medical record. All data were retrospectively collected without any possibility of individual identification.

Data Collection

In this repeated cross-sectional study, we included older adults with lung cancer attending outpatient department at tertiary care hospitals in Chengdu from 1 January 2016 to 31 December 2018; thus, the prescriptions of 1,002, 1,009, and 1,275 older lung cancer outpatients were included from 2016, 2017, and 2018, respectively. The data were collected by diagnosis type as follows: 1) basic information (region, prescription code, and department source); 2) patient characteristics (age, sex, and diagnosis); and 3) medication characteristics (generic name, trade name, drug specifications, dosage form, administration route, number of prescriptions, prescription expenditure, and frequency of administration). The criteria in the count of prescribed medications are as follows: 1) duration of prescription (≤1 month); 2) route of administration (oral medications, injection medications, topical medications, inhaler, etc.); 3) medications directly related to treatment for lung cancer were counted as concomitant medications (such as oral tyrosine kinase inhibitor or antiemetic for chemo); 4) Chinese traditional herbal medications were not included.

Evaluation Criteria

The 2019 Beers criteria (By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel, 2019) were used to evaluate PIM use in older lung cancer outpatients who were not receiving palliative care or hospice service. The comments about the rationality of prescription were made according to the Chinese Prescription Administrative Policy. The Chinese Prescription Administrative Policy need pharmacists to evaluate the standardization of prescription and the suitability of clinical use of drugs (medication indications, drug selection, route of administration, usage and dosage, drug interaction, incompatibility, etc.) according to relevant regulations, finding existing or potential problems, formulating and implementing intervention and improvement measures to promote the rational application of clinical drugs. Irrational prescriptions were classified as nonstandard prescriptions, inappropriate prescriptions, and supernormal prescriptions referring to

medication without indications. Any inconsistencies between the two researchers were reviewed by a third professional and then resolved through collective discussion.

Statistical Analysis

Categorical data are presented according to frequency, and the χ^2 test was used to compare categorical variables between groups. Continuous data that were normally distributed are expressed as the mean ± standard deviation (SD), and continuous data that were not normally distributed are expressed as the median (M) and the interquartile range (IQR). Participant sex was categorized as male or female. Age was categorized into four groups: 65–69, 70–74, 75–79, and ≥80 years old, and the number of diseases was divided into three groups: two, three to four, and five or more chronic conditions. For the descriptive analysis, medication use was divided into two strata: the use of one to four medications and the use of five or more medications. Prescriptions were further categorized as rational or irrational. The prescription expenditure was divided into three groups: <500 Chinese yuan, 500–1,000 Chinese yuan, and >1,000 Chinese yuan. Five chronic diseases (sleep disorders, anxiety or depression, pain, pulmonary infection, and chronic obstructive pulmonary disease) were also analyzed. The associations between the risk factors and PIM use (non-PIM use = 0, PIM use = 1) were assessed with a multivariate logistic regression analysis. Statistical analyses were conducted using SPSS version 26.0 (IBM Corp., Armonk, NY). We constructed three models: Model 1 (logistic regression with no adjustment), Model 2 (adjusted for year), and Model 3 (adjusted for year, sex and age). The results are presented as odds ratios (ORs) and 95% confidence intervals (CIs), and $p < 0.05$ was considered to be statistically significant.

Ethics Approval

This study protocol was approved by the Sichuan University West China Hospital Research Ethics Board (2020/651).

RESULTS

Basic Patient Characteristics

A total of 3,286 older lung cancer outpatients were included in this study, 55.90% (n = 1,837) of which were male. The median age was 72 (IQR: 68, 76) years old, and age ranged from 65 to 94 years old; the oldest (≥80 years of age) cancer patients accounted for 11.63% (n = 1,153) of the sample. The median number of medical diagnoses was 3 (IQR: 2, 4). The median number of prescriptions was 2 (IQR: 1, 4), and 16.43% (n = 540) of older lung cancer outpatients had polypharmacy. The prevalence of rational prescriptions was 92.64% (n = 3,044), 7.36% (n = 242) had irrational prescription. The characteristics of 242 participants were 60.74% (n = 147) of which were male, the median age was 72 years older and 42.98% (n = 104) of patients had polypharmacy. The median prescription expenditure was 517.90 (IQR: 189.50, 1309.47) Chinese yuan (CNY). In this study, 19.32% (n = 635) of the lung cancer patients had sleep disorders, 3.13% (n = 103) had anxiety or depression, 24.01% (n = 789) had pain, 11.56% (n = 380) had pulmonary infections, and 5.11% (n = 168) had chronic obstructive pulmonary disease (COPD). The basic patient characteristics are provided in **Table 1**.

Trends in Older Lung Cancer Outpatients With Multimorbidity

There were 1,002, 1,009, and 1,275 older lung cancer outpatients with prescriptions included in 2016, 2017, and 2018, respectively. The prevalence of polypharmacy increased from 14.27% (n = 143) in 2016 to 18.04% (n = 230) in 2018. The prevalence of PIM use increased from 31.94% (n = 320) to 42.67% (n = 544) over the 3 years. The number of medications and diseases showed an increasing trend from 2016 to 2018. The prevalence of rational prescriptions increased from 91.22% (n = 914) in 2016 to 93.65% (n = 1194) in 2018, but the average prescription expenditure showed a decreasing trend from 1,260.77 CNY per prescription in 2016 to 1,170.45 CNY per prescription in 2018 (**Figure 1**).

Prevalence of PIMs and the Most Frequent PIMs Over the Three Years

Among the 1,002 older lung cancer outpatients with prescriptions in 2016, 320 (31.94%) outpatients were identified to have at least one PIM, and a total of 428 PIMs were detected according to the 2019 Beers criteria. Of the patients with PIM prescriptions, 80.00% received one PIM, 15.31% received two PIMs, and 4.69% received at least three PIMs according to the criteria (**Table 2**). Overall, estazolam, tramadol, and megestrol were the most used PIMs according to the 2019 Beers criteria, at 18.60%, 13.44, and 12.92%, respectively (**Table 3**).

Among the 1,009 older lung cancer outpatients with prescriptions in 2017, 361 (35.78%) outpatients were identified to have at least one PIM, and a total of 480 PIMs were detected by the 2019 Beers criteria. Of the patients with PIM prescriptions, 82.27% received one PIM, 11.36% received two PIMs, and 6.37% received at least three PIMs according to the criteria (**Table 2**). Overall, estazolam, tramadol, and megestrol were the most used PIMs according to the 2019 Beers criteria, at 21.25%, 15.70, and 10.62%, respectively (**Table 3**).

Among the 1,275 older lung cancer outpatients with prescriptions in 2018, 544 (42.67%) outpatients were identified to have at least one PIM, and a total of 723 PIMs were detected according to the 2019 Beers criteria. Of the patients with PIM prescriptions, 80.70% received one PIM, 12.13% received two PIMs, and 7.17% received at least three PIMs according to the criteria (**Table 2**). Overall, estazolam, tramadol, and ibuprofen were the most used PIMs according to the 2019 Beers criteria, at 22.44%, 17.47, and 9.34%, respectively (**Table 3**).

Risk Factors for PIM Use

PIM use, based on the 2019 Beers criteria, was the dependent variable in the logistic regression analysis (non-PIM use = 0, PIM use = 1). The logistic regression analysis indicated that age 75–79 (OR: 1.276 in Model 1, OR: 1.273 in Model 2), polypharmacy (OR: 2.587 in Model 1, OR: 2.672 in Model 2, OR: 2.678 in Model 3), and the irrational use of drugs (OR: 2.146 in Model 1, OR: 2.082 in Model 2, OR: 2.078 in Model 3) were positively

TABLE 1 | Basic characteristics of older lung cancer outpatients.

Characteristic	Total	2016 (N = 1,002)			2017 (N = 1,009)			2018 (N = 1,275)		
		PIM Group	Non-PIM Group	*p* Value	PIM Group	Non-PIM Group	*p* Value	PIM Group	Non-PIM Group	*p* Value
N (%)	3,286	320 (31.94)	682 (68.06)		361 (35.78)	648 (64.22)		544 (42.67)	731 (57.33)	
Sex, n (%)				0.434			0.626			0.677
Male	1,837 (55.90)	176 (55.00)	393 (57.62)		206 (57.06)	380 (58.64)		310 (56.99)	408 (55.81)	
Female	1,449 (44.10)	144 (45.00)	289 (42.38)		155 (42.94)	268 (41.36)		234 (43.01)	323 (44.19)	
Age, years (IQR), n (%)	72 (68, 76)	72 (68, 76)		0.561	71 (68, 76)		<0.001	72 (68, 76)		0.199
65–69	1,222 (37.19)	123 (38.44)	251 (36.80)		138 (38.23)	248 (38.27)		183 (33.64)	279 (38.17)	
70–74	959 (29.18)	87 (27.19)	209 (30.65)		86 (23.82)	203 (31.33)		157 (28.86)	217 (29.69)	
75–79	723 (22.00)	71 (22.19)	154 (22.58)		101 (27.98)	125 (19.29)		124 (22.79)	148 (20.25)	
≥80	382 (11.63)	39 (12.19)	68 (9.97)		36 (9.97)	72 (11.11)		80 (14.71)	87 (11.90)	
No. of diseases [IQR]	3 [2, 4]	3 [2, 4]		0.013	3 [2, 4]		0.072	3 [2, 5]		0.275
2	1,061 (32.29)	100 (31.25)	223 (32.70)		128 (35.46)	204 (31.48)		160 (29.41)	246 (33.65)	
3–4	1,492 (45.40)	137 (42.81)	336 (49.27)		153 (42.38)	323 (49.85)		240 (44.12)	303 (41.45)	
≥5	733 (22.31)	83 (25.94)	123 (18.04)		80 (22.16)	121 (18.67)		144 (26.47)	182 (24.90)	
No. of medications [IQR], n (%)	2 [1, 4]	2 [1, 3]		0.001	2 [1, 4]		<0.001	2 [2, 4]		<0.001
1–4	2,746 (83.57)	257 (80.31)	602 (88.27)		279 (77.29)	563 (86.88)		439 (80.70)	606 (82.90)	
≥5	540 (16.43)	63 (19.69)	80 (11.73)		82 (22.71)	85 (13.12)		105 (19.30)	125 (17.10)	
No. of rational prescriptions, n (%)				<0.001			<0.001			0.135
rational prescriptions	3,044 (92.64)	263 (82.19)	651 (95.45)		315 (87.26)	621 (95.83)		503 (92.46)	691 (94.53)	
irrational prescriptions	242 (7.36)	57 (17.81)	31 (4.55)		46 (12.74)	27 (4.17)		41 (7.54)	40 (5.47)	
Prescription expenditure [IQR], n (%)	517.90 (189.50, 1309.47)	597.54 (191.68, 1483.87)		<0.001	521.44 (218.60, 1281.72)		<0.001	487.29 (160.00, 1172.25)		<0.001
<500 CNY	1,597 (48.60)	189 (59.06)	268 (39.30)		220 (60.94)	270 (41.67)		318 (58.46)	332 (45.42)	
500–1,000 CNY	637 (19.39)	43 (13.44)	143 (20.97)		51 (14.13)	147 (22.69)		94 (17.28)	159 (21.75)	
>1,000 CNY	1,052 (32.01)	88 (27.50)	271 (39.74)		90 (24.93)	231 (35.65)		132 (24.26)	240 (32.83)	
Cancer type				0.574			0.007			0.591
Unspecified lung cancer	1,656 (50.40)	149 (46.56)	298 (43.70)		194 (53.74)	304 (46.91)		310 (56.99)	401 (54.86)	
NSCLC	1,503 (45.74)	159 (49.69)	351 (51.47)		161 (44.60)	311 (47.99)		214 (39.34)	307 (42.00)	
SCLC	127 (3.86)	12 (3.75)	33 (4.84)		6 (1.66)	33 (5.09)		20 (3.68)	23 (3.15)	
Type of chronic disease, n (%)										
Sleep disorder	635 (19.32)	101 (31.56)	59 (8.65)	<0.001	147 (40.72)	53 (8.18)	<0.001	229 (42.10)	46 (6.29)	<0.001
Anxiety or depression	103 (3.13)	21 (6.56)	9 (1.32)	<0.001	14 (3.88)	10 (1.54)	0.020	37 (6.80)	12 (1.64)	<0.001
Pain	789 (24.01)	131 (40.94)	103 (15.10)	<0.001	149 (41.27)	90 (13.89)	<0.001	237 (43.56)	88 (12.04)	<0.001
Pulmonary infection	380 (11.56)	48 (15.00)	95 (13.93)	0.652	42 (11.63)	63 (9.72)	0.340	42 (7.72)	90 (12.32)	0.008
COPD	168 (5.11)	10 (3.13)	29 (4.25)	0.390	10 (2.77)	37 (5.71)	0.034	29 (5.33)	53 (7.25)	0.167

PIM, potentially inappropriate medication; IQR, interquartile range; CNY, chinese yuan; NSCLC, non-small-cell lung cancer; SCLC, small cell lung cancer; COPD, chronic obstructive pulmonary disease.

associated with PIM use in older lung cancer outpatients. Older lung cancer patients with sleep disorders (OR: 11.408 in Model 1, OR: 11.433 in Model 2, OR: 11.158 in Model 3), anxiety or depression (OR: 5.079 in Model 1, OR: 5.135 in Model 2, OR: 4.834 in Model 3), and pain (OR: 7.021 in Model 1, OR: 7.047 in Model 2, OR: 6.884 in Model 3) were more likely to have PIM prescriptions (**Table 4**).

DISCUSSION

To the best of our knowledge, this is the first study to assess the trends of polypharmacy and PIM use in older Chinese lung cancer outpatients with multimorbidity. Previous studies based on national representative surveys have shown an alarming increase in the polypharmacy trends in the United States (from 8.2% in

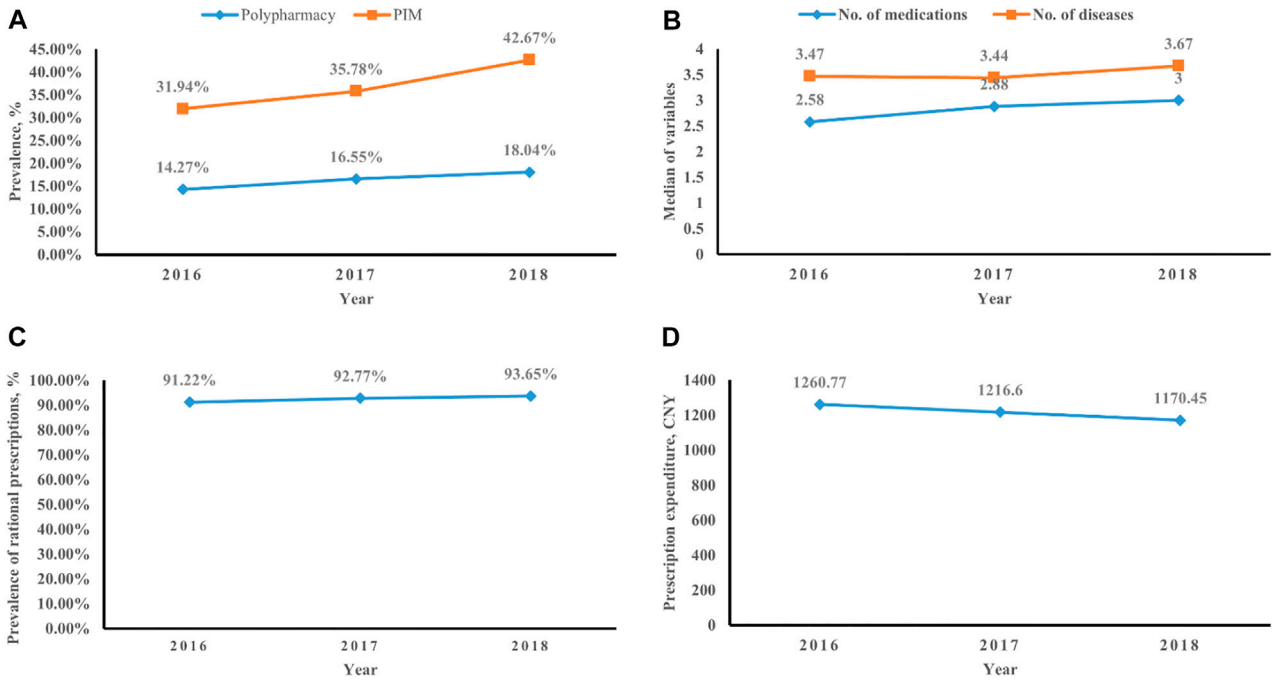

FIGURE 1 | Trends in older lung cancer outpatients with multimorbidity. **(A)** Prevalence of polypharmacy and PIM use. **(B)** Number of medications and diseases. **(C)** Rate of rational prescriptions. **(D)** Prescription expenditure.

TABLE 2 | The number of PIMs used by older lung cancer outpatients.

Characteristic	2016	2017	2018
PIM prescription	320	361	544
PIMs, n (%)	428	480	723
1PIM	256 (80.00)	297 (82.27)	439 (80.70)
2 PIMs	49 (15.31)	41 (11.36)	66 (12.13)
≥3 PIMs	15 (4.69)	23 (6.37)	39 (7.17)

PIM, potentially inappropriate medication.

1999 to 15% in 2012; Kantor et al., 2015), Sweden (from 16.9% in 2006 to 19.0% in 2014; Zhang et al., 2020), and France (from 44.9% in 2011 to 47.8% in 2019; Drusch et al., 2021), which are consistent with regional register-based studies on this period in the United Kingdom (a polypharmacy increase from 11.2% in 1995 to 22.8% in 2010; Guthrie et al., 2015) and those using the University Groningen IADB.nl prescription database in the Netherlands (showing an increase from 56.5% in 2012 to 58.2% in 2016; Oktora et al., 2021). Subjective measures, such as sleep diaries and anxiety and depression screening scales, also assist the diagnosis. As the diagnosis is determined, the use of drugs may be further increased (Hita-Yañez et al., 2013). In our study, the number of medications and diseases showed an increasing trend from 2016 to 2018. Therefore, the prevalence of polypharmacy increased in our study. Some studies in Europe and the United States have reported a decrease in the prevalence of PIMs (Ble et al., 2012; Hovstadius et al., 2014; Davidoff et al., 2015; Muhlack et al., 2018). With the popularization of Beers criteria, clinicians pay more attention to PIMs use in older patients; however, due to the increase of chronic diseases, the number of medications increased. This may be the reason that studies in the US indicate increased polypharmacy yet decrease in prevalence of PIMs use. However, one study in Ireland showed that the prevalence of PIM use rose from 32.6% in 1997 to 37.3% in 2012 (Moriarty et al., 2015). Our previous study showed an increasing trend of PIM use in older inpatients, from 71.17% in 2016 to 73.39% in 2018 (Tian et al., 2021). These results were similar to those of our present study, in which an increased prevalence of PIM use was observed in an older

TABLE 3 | The top five PIMs used by older lung cancer outpatients.

Rank	2016	N = 387 (%)	2017	N = 433 (%)	2018	N = 664 (%)
1	Estazolam	72 (18.60)	Estazolam	92 (21.25)	Estazolam	149 (22.44)
2	Tramadol	52 (13.44)	Tramadol	68 (15.70)	Tramadol	116 (17.47)
3	Megestrol	50 (12.92)	Megestrol	46 (10.62)	Ibuprofen	62 (9.34)
4	Ibuprofen	33 (8.53)	Ibuprofen	36 (8.31)	Alprazolam	51 (7.68)
5	Hydrochlorothiazide	29 (7.49)	Hydrochlorothiazide	34 (7.85)	Hydrochlorothiazide	51 (7.68)

TABLE 4 | Multivariate logistic regression analysis of factors associated with PIM use.

Model 1				Model 2				Model 3			
Characteristic	**OR**	**95% CI**	***p* Value**	**Characteristics**	**OR**	**95% CI**	***p* Value**	**Characteristics**	**OR**	**95% CI**	***p* Value**
Year											
2016	References										
2017	1.069	0.855–1.335	0.559								
2018	1.432	1.161–1.766	0.001								
Sex				Sex							
female	References			female	References						
male	1.176	0.985–1.404	0.074	male	1.172	0.982–1.398	0.079				
Age, y				Age, y							
65–69	References			65–69	References						
70–74	0.793	0.639–0.983	0.034	70–74	0.796	0.642–0.987	0.038				
75–79	1.276	1.016–1.602	0.036	75–79	1.273	1.014–1.597	0.037				
≥80	1.040	1.146–1.525	0.790	≥80	1.056	0.793–1.407	0.707				
No. of diseases				No. of diseases				No. of diseases			
2	References			2	References			2	References		
3–4	0.868	0.710–1.061	0.166	3–4	0.862	0.706–1.053	0.145	3–4	0.859	0.703–1.048	0.135
≥5	0.709	0.545–0.922	0.01	≥5	0.726	0.559–0.943	0.016	≥5	0.749	0.577–0.971	0.029
No. of medications				No. of medications				No. of medications			
1–4	References			1–4	References			1–4	References		
≥5	2.587	1.988–3.367	<0.001	≥5	2.672	2.054–3.475	<0.001	≥5	2.678	2.063–3.478	<0.001
No. of rational prescriptions				No. of rational prescriptions				No. of rational prescriptions			
Rational prescriptions	References			Rational prescriptions	References			Rational prescriptions	References		
Irrational prescriptions	2.146	1.548–2.977	<0.001	Irrational prescriptions	2.082	1.500–2.890	<0.001	Irrational prescriptions	2.078	1.498–2.822	<0.001
Prescription expenditure				Prescription expenditure				Prescription expenditure			
<500 CNY	References			<500 CNY	References			<500 CNY	References		
500–1,000 CNY	0.486	0.383–0.617	<0.001	500–1,000 CNY	0.483	0.380–0.612	<0.001	500–1,000 CNY	0.484	0.382–0.614	<0.001
>1,000 CNY	0.419	0.336–0.521	<0.001	>1,000 CNY	0.404	0.324–0.503	<0.001	>1,000 CNY	0.404	0.325–0.503	<0.001
Type of chronic disease				Type of chronic disease				Type of chronic disease			
Sleep disorder	11.408	9.061–14.362	<0.001	Sleep disorder	11.433	9.091–14.378	<0.001	Sleep disorder	11.158	8.901–13.987	<0.001
Anxiety or depression	5.079	2.987–8.637	<0.001	Anxiety or depression	5.135	3.032–8.695	<0.001	Anxiety or depression	4.834	2.866–8.152	<0.001
Pain	7.021	5.753–8.569	<0.001	Pain	7.047	5.776–8.596	<0.001	Pain	6.884	5.653–8.383	<0.001
Pulmonary infection	0.831	0.629–1.097	0.190	Pulmonary infection	0.811	0.615–1.069	0.137	Pulmonary infection	0.817	0.621–1.076	0.150
COPD	0.772	0.511–1.168	0.221	COPD	0.806	0.534–1.214	0.302	COPD	0.840	0.559–1.261	0.840

PIM, potentially inappropriate medication; IQR, interquartile range; CNY, Chinese yuan; COPD, chronic obstructive pulmonary disease.
Model 1: Multivariate logistic regression analysis of factors associated with PIM use in older lung cancer outpatients.
Model 2: Multivariate logistic regression analysis of factors associated with PIM use in older lung cancer outpatients adjusted by year.
Model 3: Multivariate logistic regression analysis of factors associated with PIM use in older lung cancer outpatients adjusted by year, sex, and age.

lung cancer patient population. Because polypharmacy is associated with an increased risk of inappropriate prescriptions, the prevalence of polypharmacy and PIM use in our studies were related, showing an increasing trend.

Our study was the first repeated cross-sectional study on the prevalence and risk factors for PIM use in older Chinese lung cancer outpatients. A United States study reported that the monthly prevalence of any PIM prior to cancer diagnosis was similar across all three cancer cohorts (breast cancer, colon cancer, and lung cancer), hovering between 37 and 40%, whereas PIM prevalence sharply increased in the first few months following the lung cancer (stage I–II) diagnosis. This may be when the lung cancer is diagnosed, the anti-emetics, antispasmodic drugs, and hydrochlorothiazide were usually used (Lund et al., 2018). The prevalence of PIM use in older lung cancer patients was higher than that in patients with the other two cancers according to the 2012 Beers criteria. The prevalence of PIM use, according to the 2019 Beers criteria, in our study was 37.28% over 3 years, which was higher than that reported in another study on the prevalence of PIM use among older Chinese cancer outpatients which were outside of palliative care and hospice service (32.65%; Tian et al., 2022a). Our previous study found that lung cancer was positively associated with PIM use in older cancer outpatients, which explains the higher prevalence of PIM use in this study. It is of great significance to study

the high-risk population of PIMs use and provide targeted drug intervention for the follow-up. The prevalence of PIM use in our study was slightly higher than that the older advanced NSCLC patients who underwent epidermal growth factor receptor tyrosine kinase inhibitor in Japan, with a prevalence of 31.9% (Hakozaki et al., 2021), and lower than that in older NSCLC and SCLC patients at the end of life in the Netherlands, at 45% (Ham et al., 2021). The high prevalence of PIM use in these end-of-life patients is explained by the fact that these patients are usually in serious condition, both physically and mentally, and are thus highly willing to take more medications. Another potential reason for this difference is that the adverse outcomes in older lung cancer patients at the end of life are highly associated with PIM use; the poor clinical outcome of these patients further aggravates the prevalence of PIM use (Mohamed et al., 2020; Chen et al., 2021).

In our present study, the two most frequent PIMs in older Chinese lung cancer outpatients according to the 2019 Beers criteria were estazolam and tramadol over the 3 years. Sleep disorders can be both complex and common in older age, although reported prevalence varies (Hishikawa et al., 2017; Patel et al., 2018). Although research on the causal effect of sleep disorders on lung cancer incidence is still lacking, many lung cancer patients were also diagnosed with sleep disorders or pain in our study. Use of estazolam, a benzodiazepine, increases the risk of falls in older adults and co-prescribing of opioids exponentiates this risk (Niznik et al., 2022). Meanwhile, long-term use of benzodiazepines will increase the risk of respiratory depression and overdose with administration of benzodiazepine in older patients with sleep disorders. Pain is the most common symptom that occurs in 40% of lung cancer patients (Iwase et al., 2015), which can arise as a result of local effects (i.e., hemorrhaging into the tumor, obstruction/perforation of the lungs) or anti-cancer treatments, such as chemotherapy (Tang et al., 2021). The treatment of cancer pain mostly utilizes the three-step "ladder" treatment principle proposed by the World Health Organization; tramadol is commonly used for mild and moderate pain (Tian et al., 2022b). Although the analgesic effect of tramadol is good, its side effects induce syndrome of inappropriate antidiuretic hormone secretion (SIADH) or hyponatremia, and these risks are higher in older adults, which limits the clinical application of this medication (Li et al., 2021). Older patients with lung cancer need help with sleeping especially if in pain, especially in elderly patients with lower pain threshold levels. Therefore, sedative hypnotic drugs are taken more frequently than elderly patients without lung cancer. In order to ensure the risk-benefit balance of drug use in this population, it is of great significance to develop models that meet the PK/PD characteristics of this population to evaluate the appropriate medication use rather than keeping to a specific number of medicines in this fragile population. According to the logistic regression analysis, risk factors for PIM use were the same among the three models: 75–79 years of age, polypharmacy, irrational use of drugs and lung cancer accompanied by sleep disorders, anxiety or depression, or pain. However, some pulmonary diseases, such as pulmonary infection and COPD, were not risk factors for PIM use. Therefore, we suggest reducing the prescription of unnecessary medications and that doctors or pharmacists carefully perform medication reconciliation for older lung cancer outpatients taking multiple medications.

Several limitations of this study should be noted. First, this study only investigated 3 years of data in China, and more years of data are needed to determine long-term trends of polypharmacy and PIM use in older lung cancer outpatients with multimorbidity. Second, outpatients attending tertiary hospitals were the main focus of the study; thus, lung cancer outpatients who were in nursing homes and communities were not evaluated. In addition, the research aimed at only one area population may have limited popularization.

CONCLUSION

This study investigated the trends of polypharmacy and PIM use in older lung cancer outpatients with multimorbidity in China based on the 2019 Beers criteria. The prevalence of polypharmacy and PIM use showed an increasing trend in older Chinese lung cancer outpatients, and age 75–79, polypharmacy, irrational use of drugs, and lung cancer accompanied by sleep disorders, anxiety or depression, or pain were risk factors for PIM use.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Materials**; further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by this study protocol, which was approved by the Sichuan University West China Hospital Research Ethics Board. Written informed consent from participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

Conception and design: FT. Administrative support: FT. Provision of study materials or patients: FT, MZ. Collection and assembly of data: FT, XC. Data analysis and interpretation: FT and ZC. Manuscript writing: all authors. Final approval of manuscript: all authors.

FUNDING

This work was supported by the Sichuan Science and Technology Program (Project number 2022JDR0326).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.935764/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 24 August 2022
DOI 10.3389/fphar.2022.946415

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Drugs Outcomes Research and Policies, a section of the journal Frontiers in Pharmacology

RECEIVED 17 May 2022
ACCEPTED 22 July 2022
PUBLISHED 24 August 2022

CITATION
Zhao M, Liu C-F, Feng Y-F and Chen H (2022), Potential drug-drug interactions in drug therapy for older adults with chronic coronary syndrome at hospital discharge: A real-world study. *Front. Pharmacol.* 13:946415. doi: 10.3389/fphar.2022.946415

Potential drug-drug interactions in drug therapy for older adults with chronic coronary syndrome at hospital discharge: A real-world study

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Introduction: Polypharmacy are commonly observed among older adults with cardiovascular disease. However, multiple medications lead to increased risk of drug-drug interactions (DDIs). Therefore, identification and prevention actions related to harmful DDIs are expected in older adults. The study aimed to describe the prevalence of potential DDIs (pDDIs) in discharge prescriptions among older adults with chronic coronary syndrome (CCS).

Methods: A single-center cross-sectional study was performed in a tertiary public hospital in Beijing, China. CCS patients aged 65 years and above who were admitted to cardiology wards over a 3-month period and alive at discharge were included. Electronic medical records and discharge prescriptions were reviewed. pDDIs were evaluated through the Lexi-Interact online.

Results: pDDIs were identified in 72.9% of the 402 individuals (n = 293). A total of 864 pDDIs were obtained. 72.1% of patients were found with C DDIs (n = 290) and 20.3% were categorized in D and X DDIs (n = 82). The only X DDI was between cyclosporine and atorvastatin. Under category D, glycemia alterations within antidiabetics and increased chances of bleeding with antithrombotic were the most common. Concomitant use of clopidogrel and calcium channel blockers was a frequent situation within category C, followed by synergic blood pressure lowering agents and increased rosuvastatin concentration induced by clopidogrel.

Conclusion: DDIs exposure was common in older CCS. DDIs screening tools should be introduced to alert potential adverse effects. Prescribers need to rigorously review or modulate therapies to prevent DDI-related adverse outcomes. Clinical pharmacists should be more involved in complex drug regimen management.

KEYWORDS

drug-drug interactions, chronic coronary syndrome, older adults, discharge, drug therapy

Introduction

Drug-drug interactions (DDIs) are defined as alterations in effectiveness or toxicity when drugs are co-administered (Hines and Murphy, 2011). DDIs pose significant challenges in adverse drug events (ADEs), hospital admissions, rehospitalization and emergency visits (Becker et al., 2007; Magro et al., 2012; Gatenby et al., 2020; Limandri, 2020). Concomitantly, this results in increased hospital stays and health care costs (Thomsen et al., 2007; Moura et al., 2009). Therefore, DDIs management is crucial for the improvement of medication safety.

The group with a high risk of DDIs was defined as advanced age, a diagnosed cardiovascular system disorder, complex medication regimen and so on (Yoon et al., 2018; Gallo et al., 2019; Veloso et al., 2019). Given that polypharmacy was commonly observed for the treatment of concurrent chronic conditions, it can be expected that the prevalence of DDIs among older adults will inherently increase (Prince et al., 2015; Yoon et al., 2018; Lea et al., 2019; Ruangritchankul et al., 2020). Notably, older adults were also reported an identifiable a high degree of DDIs in risk rating (e.g., major or severe). For example, 60% older cancer adults in French and 21% of geriatric cases in India were suffering from major DDIs (Nightingale et al., 2018; Shetty et al., 2018). The main reason is that decreased physiological reserves with age results in pharmacokinetic and pharmacodynamic alterations. Conceivably, pervasive use of medications combined with elevated vulnerability to drug effects will exacerbate the likelihood of DDIs exposure (Beinse et al., 2020).

Coronary artery disease (CAD) remains an emerging threat for older people among COVID-19 pandemic (Prince et al., 2015; Zhao et al., 2019; Hessami et al., 2021). Evidence-based medication therapy is emphasized as sacrosanct and lifelong (Bansilal et al., 2015; Knuuti et al., 2020). At the same time, increased medication use has developed a substantial proportion of drug-related problems, including DDIs, ADEs and poor adherence (Gelchu and Abdela, 2019; Plácido et al., 2020; Tsige et al., 2021). A study done in Ethiopia showed that 47.0% of heart failure were exposed to severe DDIs, which were the most common drug therapy problems (Seid et al., 2020). Chronic coronary syndrome (CCS) is a broad group of CAD proposed by the European Society of Cardiology (Knuuti et al., 2020; Ferrari et al., 2021). The presence of CCS nearly doubles the risk of major adverse cardiovascular events (Romero-Farina and Aguadé-Bruix, 2021). All the current literatures advocate the timely medical therapy for CCS patients (Yasuda et al., 2018; Silber, 2019; Zahmatkeshan et al., 2021). Consequently, multiple drug use as well as potential DDIs (pDDIs) are anticipated in older CCS adults. Our previous findings revealed that DDIs accounted for 30% of potentially inappropriate medications in older CCS (Zhao et al., 2021). Unfortunately, fewer studies properly examine pDDIs among older CCS patients in China. As a results, insight into pDDIs is a huge opportunity for clinicians to predict and avoid ADEs and reduce hospital readmission.

In this regard, the aim of the present study was to quantify the prevalence of pDDIs among a group of older patients with CCS from real-world data and to analyze the most common pDDIs in discharge prescriptions.

Materials and methods

Study design and setting

A cross-sectional study was carried out in Peking University People's Hospital, a major public tertiary teaching center in Beijing, China. This study was approved by the Ethics Committee of Peking University People's Hospital and was granted an exemption of informed consent from patients. The information was collected from the electronic medical records anonymously and used for research only.

A sample size of 387 patients was calculated regarding the prevalence of DDIs as 60% (Fettah et al., 2018), with a two-sided 95% confidence interval with a width equal to 0.10.

Participants

Older adults (aged over 65 years) with CCS who were admitted to the cardiology department between October and December 2020 and alive at discharge were included in this study. Only patients with two or more medications at discharge were selected for this investigation.

Data collection and software used for potential drug-drug interactions identification

Demographic and clinical information, including age, sex, diagnosis, the New York Heart Association (NYHA) class and comorbidities was obtained.

Medication regimens often changed during hospitalization. Hospital discharge prescriptions pose patients at new risks of ADEs (Alqenae et al., 2020; Grandchamp et al., 2022). Usually, upon discharge, the attending physician would prescribe a comprehensive discharge prescription based on the patient's diagnosis. Therefore, prescriptions at discharge were collected through the electronic medical records. The Anatomic-Therapeutic-Chemical (ATC) Drug Classification (20th Ed., 2017) formulated by the World Health Organization Collaborating Centre was used for drug classification.

The medication regimens for pDDIs were analyzed using the Lexi-Interact online (Lexi-Comp Inc., Hudson, United States). As a computerized software, easy access to Lexi-Interact is recognized as a

TABLE 1 Definitions of risk, reliability and severity ratings for DDIs by Lexi-Interact software.

Classification	Definition
risk rating	The level of urgency and actions needed to respond to DDIs
A	No known interaction
B	No action needed
C	Monitor therapy
D	Consider therapy modification
X	Avoid combination
reliability rating	The quantity and nature of evidence
excellent	Multiple clinical trials or single clinical trial plus more than two case reports
good	Single randomized clinical trial plus less than two case reports
fair	More than two case reports or less than two case report plus other supporting data; or a theoretical interaction based on known pharmacology
severity rating	Qualify the reported or possible magnitude of DDIs outcomes
major	The effects of DDIs might be life-threatening or cause permanent damage
moderate	Patients with DDIs may require additional care
minor	The effects of DDIs may be tolerable and need no medical interventions

DDIs, drug-drug interactions.

benefit. Lexi-Interact succinctly provides information about the risk, reliability and severity of pDDIs. It also elaborates recommendations on the prevention and management of pDDIs. This database classifies pDDIs into five risk rating according to the degree of clinical significance (category A, B, C, D, and X). In most of studies, C, D and X were considered potential clinically relevant DDIs. Depending on the quality of evidence, reliability is classified as excellent, good and fair-type. Severity indicators include major, moderate and minor. Table 1 lists the definitions of the risk rating, reliability rating and severity rating by the Lexi-Interact database (Moradi et al., 2020). For the purpose of this study, the category C, D and X, reliability rating and severity rating were searched. Clinical consequences and management strategies also conformed to the Lexi-Interact monograph.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp, Armonk, NY, United States). Categorical data are presented as frequencies or percentages, and continuous data are presented as the mean ± SD or median and interquartile range (IQR).

Results

Main characteristics of older chronic coronary syndrome patients

402 eligible older CCS patients who met the inclusion criteria received at least two dispensing at discharge. Overall, females made up 41.8% of the total population. The mean age was 73.8 ± 6.3 years (range 65–90). The NYHA classification of the patients was as follows: 55.7% in NYHA I, 31.1% in NYHA II, and 13.2% in NYHA III and IV. The median number of comorbidities was 5 (range 0–13); hypertension was prominent (77.1%), followed by dyslipidemia (65.7%), peripheral arterial disease (53.5%) and type 2 diabetes mellitus (42.3%). The median length of the hospital stay was 7 days (range 1–33). The general characteristics of the 402 patients are described in Table 2.

Prevalence and characteristics of potential drug-drug interactions in discharge prescriptions

A total of 2,669 medications were prescribed at discharge, with an average of 6.6 ± 2.2 per patient. pDDIs were found in 293 patients (72.9%) with 864 pDDIs in all (Table 3). 202 patients were observed within three pDDIs (50.2%), while six individuals (1.5%) showed more than ten simultaneous pDDIs. The median number of pDDIs was 2 (range 1–17). With regard to the risk category, the vast majority of patients were exposed to class C (n = 290, 72.1%), followed by class D (n = 81, 20.1%) and class X (n = 1, 0.2%). Figure 1 showed the distribution of pDDIs per patient based on risk category. Thirty seven individuals had the most distribution of 5–15 category C pDDIs, and only three patients had 3, 4 category D pDDIs.

Out of 864 drug pairs we considered, 747 fell under category C (86.5%), 116 fell under category D (13.4%) and one fell under category X (0.1%). In terms of reliability, 22 (2.5%) pDDIs were excellent, 246 (28.5%) pDDIs were good, and 596 (69.0%) were fair-type. According

TABLE 2 Characteristics of the study sample (N = 402).

Characteristics	n (%)
Sex	
Male	234 (58.2)
Female	168 (41.8)
Age (years)	
Mean ± SD	73.8 ± 6.3
Length of stay (days)	
Median, IQR	7 (5–9)
NYHA class	
I	224 (55.7)
II	125 (31.1)
III	43 (10.7)
IV	10 (2.5)
Number of comorbidities	
Median, IQR	5 (3–6)
Cardiovascular comorbidities	
Hypertension	310 (77.1)
Dyslipidemia	262 (65.2)
Peripheral arterial disease	215 (53.5)
Type 2 diabetes mellitus	170 (42.3)
Stroke	90 (22.4)
Atrial fibrillation	70 (17.4)
Heart failure	50 (12.4)
Non-cardiovascular comorbidities	
Tumor	55 (13.7)
Chronic kidney disease	54 (13.4)
Psychiatric disorders	38 (9.5)
Benign prostatic hyperplasia	36 (9.0)
Thyroid dysfunction	35 (8.7)
GERD/peptic ulcer	34 (8.5)
COPD/asthma	24 (6.0)
Chronic liver disease	10 (2.5)

COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; IQR, interquartile range; NYHA, New York Heart Association.

TABLE 3 Prevalence of pDDIs among older CCS patients at discharge.

Characteristics	Patient, n (%)
Total number of medications	2,669
Mean prescribed drugs per patients	6.6 ± 2.2
Patients with pDDIs[a]	293 (72.9)
Number of pDDIs per patient[a]	
1	99 (24.6)
2	62 (15.4)
3	41 (10.2)
4	30 (7.5)
5	25 (6.2)
6–9	30 (7.5)
10–17	6 (1.5)
Total number of pDDIs	864
Median (IQR) of pDDIs per patient	2 (1–4)
Patient distribution based on risk category[a]	
C	290 (72.1)
D	81 (20.1)
X	1 (0.2)

[a]Percentage was calculated out of the total number of CCS patients (n = 402).
CCS, chronic coronary syndrome; pDDIs, potential drug-drug interactions; IQR, interquartile range.

to the Lexi-Interact classification, severity was mainly attributed to moderate (760 pDDIs, 87.9%) and major (87 pDDIs, 10.1%) (Table 4).

Drug classes involved in potential drug-drug interactions

In general, nine ATC groups were involved in category C pDDIs (Figure 2). The significantly associated drug class was drugs related to the cardiovascular system (53.9%, 806/1494). Then followed by blood and blood forming organs (22.8%, 340/1494) and the alimentary tract and metabolism (19.4%, 291/1494). Among the seven ATC groups relevant to category D and X, alimentary conditions and metabolism classification increased the exposure to DDIs (60.2%, 141/234) (Figure 2).

Supplementary Table S1 presented the ATC classification of drugs. Regarding category C pDDIs, the highest frequency was found in antiplatelets (331), diabetes drugs (266), calcium channel blockers (CCBs, 179) and diuretics (176). The highest prevalence of interacting drugs within category D and X were attributed to antidiabetics (130), followed by antiplatelets (41) and anticoagulants (26) (Supplementary Table S1).

The most frequently observed drug pairs

Table 5 described the most frequently observed drug pairs and potential adverse effects. The exclusive contraindicated pair was between cyclosporin and atorvastatin. A dominant potential outcome of category D was hypoglycemia related to synergistic hypoglycemic action and the concurrent use of repaglinide with clopidogrel (69, 59.4%). Then it was followed by agents that elevated the risk of bleeding (29, 25.0%).

Exposure to clopidogrel and CCBs (110, 14.7%), as assigned to one main class C interaction, might lead to a reduced antiplatelet response with clopidogrel. Then there were drug interactions that affected blood pressure and lipids (97, 13.0% and 93, 12.4%, respectively). Notably, glycemia fluctuation was more visibly seen in diabetes who used diuretics or β blockers simultaneously (134, 17.9%). Moreover, in the aspirin group, loop diuretics, spironolactone and angiotensin converting

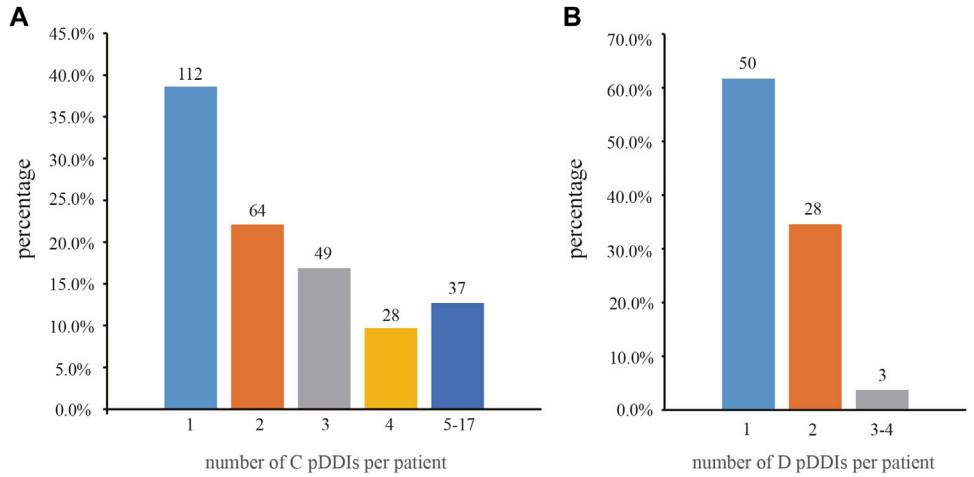

FIGURE 1
Frequency and percentage of pDDIs per patient based on risk category. **(A)** category C (n = 290); and **(B)** category D (n = 81). Percentage was calculated out of number of patients with C or D pDDIs. pDDIs, potential drug-drug interactions.

TABLE 4 Characteristics of drug interactions at discharge.

Characteristics	n (%)[a]
Risk rating	
C	747 (86.5)
D	116 (13.4)
X	1 (0.1)
Reliability rating	
Excellent	22 (2.5)
Good	246 (28.5)
Fair	596 (69.0)
Severity rating	
Major	87 (10.1)
Moderate	760 (87.9)
Minor	17 (2.0)

[a]%: percentage was calculated out of the total number of pDDIs (n = 864).

enzyme inhibitors had an enhanced possibility of renal dysfunction (70, 9.4%).

Management strategies

The Lexi-Interact monograph also provides skilled DDIs management, as shown in Table 5. Adjustment in treatment regimens was required in category X and most category D pDDIs. Adjustments included dosage reduction, e.g. insulin, sulfonylurea and warfarin, titration e.g., repaglinide with a limit of 4 mg daily and simvastatin to 20 mg daily, separate administration time and drug replacement. Vigilant signs/symptoms and lab tests were widely recommended in class C pDDIs, including platelet reactivity index, blood pressure, blood glucose, liver/renal function and any signs or symptoms of myopathy.

Discussion

Polypharmacy is a major concern for older individuals (Soejono and Rizka, 2021). Multiple drugs carries a high risk of DDIs, and their associated adverse events vary from minor toxicity to treatment failure or even death (Malki and Pearson, 2020; Davies and O'Mahony, 2015). Our present study revealed that a high proportion of older CCS patients were exposed to pDDIs; furthermore, one fifth were classified as severe and contradictory pDDIs. pDDIs mostly involved drugs acting on the cardiovascular system, alimentary tract and metabolism, and blood and blood forming organs. It is very crucial for healthcare providers to have this data and help manage drug usage for better scheduling and planning.

Overall, the prevalence of pDDIs in CCS was higher than that in certain other scenarios, such as cancer (18.7%), intensive care unit stays (54%), dementia (43.2%), liver cirrhosis (21.5%) and COVID-19 (38%) (Franz et al., 2012; Uijtendaal et al., 2014; Sönnerstam et al., 2018; Vecchia et al., 2018; Mahboobipour and Baniasadi, 2021). Our findings were comparable with previous studies of DDI prevalence in non-acute cardiac inpatients, such as 100% in Pakistan, 61% in Serbia and 68% in Morocco (Fettah et al., 2018; Kovačević et al., 2020; Akbar et al., 2021). Medication complexity could partly explain the sizable DDIs (Forman et al., 2018). For example, all patients with acute coronary syndrome

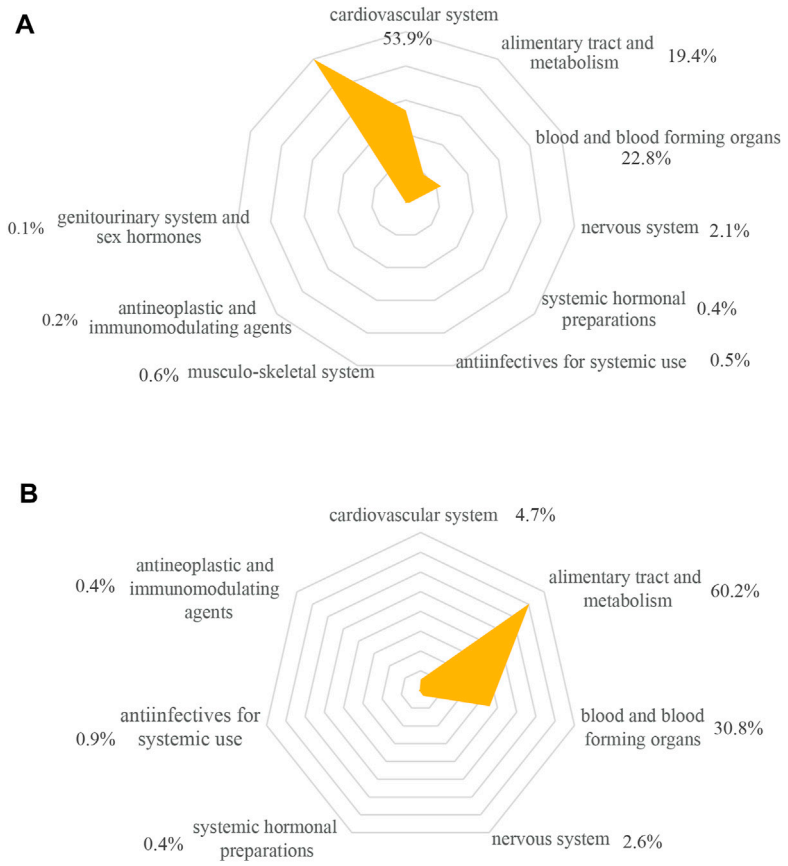

FIGURE 2
ATC classification-wise distribution of pDDIs. **(A)** category C (*n* = 1,494); **(B)** category D and X (*n* = 234). Percentage was calculated out of number of pDDIs in each risk category. pDDIs, potential drug-drug interactions.

were experiencing pDDIs with 9.4 drugs on average, while only 33.4% in hypertension with daily drug use as 4.3 (Pejčić et al., 2019; Ersoy and Ersoy, 2021). Discrepancy in pDDIs could also be due to using different screening tools. In comparison of five DDI programs, including Lexi-Interact, Micromedex, iFacts, Medscape and Epocrates, Lexi-Interact and Micromedex showed the best performance on accuracy and sensitivity (Kheshti et al., 2016). Lexi-Interact was widely used in various diseases and different areas (Ren et al., 2020; Dagdelen et al., 2021; Ramsdale et al., 2022). Meanwhile, Lexi-Interact was available in our health system, as such, pDDIs were reviewed using Lexi-Interact software in this study.

In our study, DDIs of clinical significance were most frequently observed in category C. Pharmacokinetic drug interactions affect at the steps of absorption, distribution, metabolism and elimination. It has been established that the inhibition of CYP3A4 by dihydropyridine CCBs and the inhibition of P-glycoprotein by several CCBs (diltiazem, verapamil and nifedipine) were potentially harmful in clopidogrel biotransformation (Gremmel et al., 2015). However, controversy persisted as to whether CCBs modified the clinical protection of clopidogrel and subsequent changes in major adverse cardiovascular end points (Good et al., 2012; Aggarwal et al., 2016). Until now, it is difficult to determine clopidogrel resistance resulting from the co-administration of CCBs. Monitoring genetic polymorphisms or switching to ticagrelor or prasugrel might be considered for those with low efficacy of clopidogrel (Wang et al., 2015).

Most patients with hypertension required multiple drugs, such as sacubitril/valsartan or rennin-angiotensin system inhibitors with diuretics, β blockers or CCBs (Ersoy and Ersoy, 2021). However, pharmacodynamic DDIs lead to synergic blood pressure lowering, and can reduce cerebral perfusion, presenting as syncope or falls. Older adults who are taking diuretics and polypharmacy is projected a higher incidence of falls (Abu et al., 2021). Physicians and pharmacists may need to conduct a thorough assessment of antihypertensive medications as well as hidden antihypertensive medications, such as tamsulosin and levodopa (Alagiakrishnan,

TABLE 5 Most frequently occurring DDIs and management strategies.

Drug pairs	n (%)a	Potential consequence	Management strategies
Category X	1		
Cyclosporine + atorvastatin	1 (100.0)	Myopathy	Change to pravastatin or fluvastatin or an alternative type of LDL-lowering medication
Category D	116		
Glycemia alterations	69 (59.4)		
Antidiabetic drugs (e.g. insulin/sulfonylurea with acarbose/sitagliptin/SGLT2 inhibitor/thiazolidinedione)	61	Hypoglycemia	Monitor glucose; a decrease in insulin/sulfonylurea dose
Clopidogrel + repaglinide	8	Hypoglycemia	Monitor glucose; titrate repaglinide with a limit of 4 mg daily
Additive bleeding risk	29 (25.0)		
Antiplatelets + oral anticoagulants	27	Bleeding	Monitor signs of bleeding
Warfarin + amiodarone	2	Bleeding	Monitor INR; warfarin dosage reduction
Omeprazole/fluconazole + clopidogrel	6 (5.2)	Decreased antiplatelet effect of clopidogrel	Replacement with rabeprazole or pantoprazole or alternatives of azole
Amlodipine + simvastatin	3 (2.6)	Muscle toxicity	Monitor signs of myopathy; limit simvastatin to 20 mg daily
QT prolongation or serious arrhythmias	3 (2.6)	Serious arrhythmias or death	Monitor ECG
Sodium bicarbonate + polysaccharide-iron complex	2 (1.7)	Reduced effect of iron preparations	Separate oral administration moments
Potassium chloride + spironolactone	2 (1.7)	Hyperkalemia	Monitor potassium concentration
Calcium carbonate + levothyroxine	1 (0.9)	Reduced levothyroxine effect	Separate at least 4 h
Quetiapine + levodopa	1 (0.9)	Diminished levodopa effect	A non-dopamine antagonist alternative
Category C	747		
CCBs + clopidogrel	110 (14.7)	Reduced antiplatelet effect	Monitor platelet reactivity index
Blood pressure lowering drugs (e.g., sacubitril/valsartan, renin-angiotensin system inhibitors, β blocking agents, diuretics and CCBs)	97 (13.0)	Enhanced hypotensive effects	Monitor blood pressure
Clopidogrel + rosuvastatin	93 (12.4)	Myopathy	Monitor the signs of myopathy and liver function test
Diuretics + antidiabetic agents	71 (9.5)	Reduced antidiabetic effect	Monitor blood glucose
β blockers + insulin/sulfonylureas	63 (8.4)	Mask hypoglycemia	Monitor blood glucose
Hypoglycemic agents combination (e.g., metformin, repaglinide, sulfonylureas, insulin)	41 (5.5)	Hypoglycemic effect	Monitor blood glucose
Aspirin + diuretics (e.g., loop diuretics and spironolactone)	38 (5.1)	Nephrotoxicity and diminished diuretics effects	Monitor serum creatinine and diuretic response
Aspirin + ACE inhibitors	32 (4.3)	Nephrotoxicity	Monitor renal function

[a]%: percentage was calculated out of the number of pDDIs in each risk category.
ACE, angiotensin converting enzyme; CCB, calcium channel blocker; CYP, cytochrome; LDL, low density lipoprotein; OATP, organic anion transporting polypeptide; PD, pharmacodynamics; p-gp, p-glycoprotein; PK, pharmacokinetics; SGLT, sodium-glucose cotransporter.

2015). It is critical to emphasize blood pressure monitoring and gradual titration to a tolerance (Oliveros et al., 2020).

Nowadays, combined use of clopidogrel and rosuvastatin is common in practice. However, Pinheiro et al. (2012) reported that clopidogrel introduced impressive growth in the AUC of rosuvastatin. Meanwhile, abnormal liver function could be found in chronic heart failure (Tavazzi et al., 2008). Inhibition of intestinal breast cancer resistance protein (BCRP) transporters by clopidogrel is likely to be a contributor of hepatotoxicity (Ning et al., 2021). Once daily clopidogrel is advised to be taken either in the morning or evening, while rosuvastatin in the evening.

Two-fifths of CCS patients in this study had type 2 diabetes mellitus. Meta analysis showed thiazide diuretics and β blockers increased the risk of developing new-onset diabetes (Nazarzadeh et al., 2021). The diuretic-decreased pharmacologic response was related to a reduction in insulin secretion secondary to potassium loss. The mechanism of β-blocking agents on glycemia-related adverse events is complex, including increased insulin resistance and the inhibition of adrenergic-mediated insulin release (Jain

et al., 2017). Carvedilol seemed superior to metoprolol with a lower impact on glycemic control and more benefits on metabolic syndrome (Bakris et al., 2004). It is necessary to monitor blood glucose and refine the selection of drug choice according to an individual's risk/benefit profile.

Rhabdomyolysis particularly occurs with drugs that potentiate statin concentration. The only interaction of category X was cyclosporine-atorvastatin regimen. Cyclosporine acts as an inhibitor of CYP3A4, p-gp and OATP1B1, resulting in a drastically elevated atorvastatin level (Bellosta and Corsini, 2018). Fluvastatin or pravastatin might be prudent to choose for CCS patients already treated with cyclosporine (Horodinschi et al., 2019).

For decades, emergency department visits for ADEs in older adults were primarily concerned with the augmented proportion of anticoagulants, antiplatelets and antidiabetics (Shehab et al., 2016). In line with this, category D DDIs at large were noted to cause detrimental hypoglycemia and bleeding. To date, add-on therapy was more prevalent than metformin monotherapy in older patients (Kim et al., 2019). Nevertheless, glucose-lowering agents might be associated with serious hypoglycemia when used in conjunction with sulfonylureas or insulin (Gómez-Huelgas et al., 2020). Both SGLT2 inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RA) have been proven to reduce major adverse cardiovascular events with little risk of hypoglycemia (Bertoccini and Baroni, 2021). The utilization of both drugs in the present study was at a low frequency (2.4% for SGLT2 inhibitors and 5.3% for GLP-1 RA). Mitigation of hypoglycemia risk could be achieved by the selection of appropriate antidiabetic drugs, glucose self-monitoring and education on hypoglycemia symptoms.

Another challenge was to maintain balance with regards to ischemic and bleeding risks in CCS with atrial fibrillation. Co-prescription of anticoagulants with antiplatelets, especially in triple therapy, increased the absolute risk of bleeding (Michniewicz et al., 2018). Meta-analysis supported novel oral anticoagulants plus a P2Y12 inhibitor in atrial fibrillation experiencing post-percutaneous coronary interventions (Lopes et al., 2020). Good clinical judgment on drugs with better efficacy, dosage and duration is vital in patients management.

pDDIs is prevalent in older CCS patients, indicating a need to evaluate medication safety and strict monitoring during CCS treatment. DDI screening and alerting systems should be implemented in electronic medical records (Celebi et al., 2019; Horn and Ueng, 2019; Anrys et al., 2021). Pharmacist-driven prescription review system in real time has been allowed to optimize therapy (Lineberry et al., 2021). In certain instances, a multidisciplinary team with a physician, a pharmacist and a nurse was required especially in complex drug regimens (Silva et al., 2015; Aghili and Kasturirangan, 2021). Clinical pharmacists should also make attempts at patient education and counseling to reduce the incidence of serious or fatal DDIs (Riu-Viladoms et al., 2019).

The results of the current real-life setting yields pragmatic information on medications that might pose risk in older CCS patients. Some limitations should be considered. The current design focused on pDDIs and did not identify actual clinical manifestations, such as persistent use and doses of drugs. A follow-up for potential clinical outcomes and relevant interventions is required. Second, a multicenter study might allow data to be more generalizable. Third, although the wide use of Lexi-Interact database, it could not provide information on whether drug combinations were appropriate in certain circumstances. For instance, valsartan and potassium chloride are sometimes concomitantly used in an implantable cardioverter-defibrillator recipient with hypokalemia. Fourth, older adults in China preferred to take herbs as self-medications, and many of them were unwilling to inform doctors or clinical pharmacists. As a result, potential interactions between medicines and herbs tend to be underestimated.

Conclusion

The present study showed a substantial proportion of older CCS patients were exposed to pDDIs at discharge, and one fifth were involved in serious or contraindicated DDIs. Thus, judicious clinicians should be more knowledgeable and cautious in recognizing and minimizing undesirable adverse events. In the multidisciplinary team, well-trained clinical pharmacists are responsible for comprehensive medication reviews. Furthermore, data obtained in this study can be used to design DDIs screening and alert interventions to optimize patient care.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Peking University People's Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

MZ: designing, methodology, data curation, investigation, writing and editing. C-FL: designing, data curation, investigation, supervision, editing and review. Y-FF: methodology, review and

editing. HC: conceptualization, supervision, review and editing. All authors provided final approval of the final version to be submitted.

Funding

This study was supported by the National Natural Science Foundation of China (No. 81970301).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.946415/full#supplementary-material

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frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 29 August 2022
DOI 10.3389/fphar.2022.978871

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Drugs Outcomes Research and Policies, a section of the journal Frontiers in Pharmacology

RECEIVED 26 June 2022
ACCEPTED 27 July 2022
PUBLISHED 29 August 2022

CITATION
Dorj G, Lim R, Ellett LK, Kelly T-L, Andrade A, Widagdo I, Pratt N, Bilton R and Roughead E (2022), Medicine-related problems: A recurrent issue among residents living in nursing homes.
Front. Pharmacol. 13:978871.
doi: 10.3389/fphar.2022.978871

Medicine-related problems: A recurrent issue among residents living in nursing homes

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Aim: To examine the incidence and nature of medicine-related problems over time experienced by nursing home residents.

Method: We analyzed records collected in the Reducing Medicine-Induced Deterioration and Adverse Events (ReMInDAR) trial. The trial pharmacists provided services to reduce medicine-induced deterioration and adverse reactions for residents every 8-weeks over a year. The problems identified by the pharmacists were documented in reports and subsequently classified independently by research pharmacists using the D.O.C.U.M.E.N.T system. The number and type of problems at each service and time to develop a new problem post first session were assessed. All analyses were performed using R software (Version 4.1.1).

Results: The cohort was 115 nursing home residents who received 575 services. In the 12-months, a total of 673 medicine-related problems or symptom reports were identified in 112 residents. Most residents (75%) experienced a new medicine-related problem by the fourth month post the first assessment. After the first session, the proportion of residents with a new medicine-related problem or symptom report declined at each repeated pharmacy session (59% at visit 2 vs. 28% at visit 6, $p < 0.01$).

Conclusion: Residents living in nursing homes frequently experience medicine-related problems. Our results suggest clinical pharmacist services performed every 4-months may have the potential to reduce the medicine-related problems in nursing homes.

KEYWORDS

adverse effects, prescription drug misuse, medication reconciliation, pharmacy services, medication therapy management, inappropriate prescribing, long-term care, medicine-related problems

Introduction

Globally, there were 703 million people aged 65 years and older in 2019 (United Nations, Department of Economic and Social Affairs, Population Division, 2019). By 2050, one in six people will be aged over 65 years (United Nations, Department of Economic and Social Affairs, Population Division, 2019). Australia is no exception, with already 16% of the Australian population aged 65 years or older in 2018; the number is projected to increase to 23% by 2066 (Australian Institute of Health and Welfare, 2020). As of 2019, approximately 7% of Australians aged 65 years and older are living in residential aged care facilities (also known as a nursing home or long-term care facility) (Australian Institute of Health and Welfare, 2020).

People living in nursing homes are generally older, frailer, and have multiple co-morbidities that require the use of multiple medicines on a regular basis (Australian Institute of Health, 2012; Jokanovic et al., 2015). These characteristics combined with aging-related pharmacokinetic and pharmacodynamic changes (Mangoni and Jackson, 2004) result in a population at an elevated risk of medicine-related problems, medicine-induced deterioration, adverse health events, and death (Shah and Hajjar, 2012; Tamura et al., 2012; Onder et al., 2013). Medicine-induced deterioration is a cumulative effect of medicines encompassing symptoms such as cognitive and functional impairment, sedation or falls, loss of appetite, changes in urinary function and bowel function, changes in respiration, and changes in the activity of sleep patterns (Lim et al., 2019). Provision of medicine review by pharmacists is one method to reduce the risk of medicine-related harm and medicine-induced deterioration (Lee et al., 2019).

Pharmacist medicine reviews aim to improve and optimize medicine use, reduce harm, and improve patient outcomes (Australian Commission on Safety and Quality in Health Care, 2021). Pharmacist medicine reviews involve the assessment of medicine history, patient information, and clinical findings. The review considers individualized decisions on whether to continue, cease, or modify medicines and the review considers the interplay of therapeutic efficacy, comorbidities, compliance, medicine interactions, actual or potential adverse effects as well as assessing patients' preferences and understanding of their illness (Zermansky et al., 2002).

In Australia, pharmacists are remunerated to formally perform collaborative medicine reviews in eligible older people living in nursing home, known as Residential Medication Management Review (RMMR) (Australian Commission on Safety and Quality in Health Care, 2021). Older people in nursing home can receive an RMMR if they meet any of the eligibility criteria, including newly admitted residents or existing residents who are currently experiencing medicine harm, or the referring medical practitioner confirms that there is a clinical need for an RMMR service (Australian Government-Department for Health, 2021). The funding rules allow a one-off medicine review visit once every 2 years or earlier if required, with a 2020 funding rule change allowing up to two follow-up visits within 9 months of the first visit (Pharmacy Programs Administrator, 2020).

Australian studies assessing the number of medicine-related problems identified at the time of medicine review in nursing home residents have found on average that there were three medicine-related problems per person (Pharmaceutical Society of Australia, 2019). Studies assessing the frequency of medicine-related problems in nursing home residents are often based on results from RMMRs and therefore represent prevalence estimates based on a single service conducted at a single point in time (Stafford et al., 2009; Nishtala et al., 2011; Kaur et al., 2012; Milos et al., 2013; Gheewala et al., 2014). Studies of pharmacist medicine reviews with follow-up or ongoing clinical medicine reviews are scarce; we located only four studies that had included multiple services or follow-up. None of these studies provided the frequency of medicine-related problems that occurred at each visit (Furniss et al., 2000; Patterson et al., 2010; Lapane et al., 2011; Frankenthal et al., 2014). As such, the ideal interval between pharmacist medicine reviews for older adults is unknown. We identified no studies that investigated how medicine-related problems emerge over time in nursing home residents.

To address this gap, this study aimed to assess the incidence and recurrence of medicine-related problems over time using data collected from participants who were enrolled in the Reducing Medicine-Induced Deterioration and Adverse Reactions (ReMInDAR) trial (Roughead et al., 2022).

Materials and methods

The ReMInDAR trial was a randomized-controlled trial to reduce medicine-induced deterioration and adverse reactions in older adults living in nursing homes of Australia. Requirements to be enrolled in the study at baseline were if older adults were (United Nations, Department of Economic and Social Affairs, Population Division, 2019) aged 65 years and older (Australian Institute of Health and Welfare, 2020) using four or more medicines at the time of recruitment or taking more than one medicine with anticholinergic or sedative properties, and 3) had a frailty score ≤0.4 and were not-cognitively impaired (Roughead et al., 2022). Evidence suggests that frail older adults are at a higher risk of having adverse health outcomes (Shamliyan et al., 2013) when compared to non-frail individuals. To calculate frailty score, we used the frailty index, which is a validated instrument with 39-items encompassing multi-dimensional measures, allowing the assessment of physical, medical, psychological, and social contributors in older adults (Mitnitski et al., 2001; Mitnitski et al., 2005). The frailty score is a continuous score ranging from 0 to 1; a greater score indicates

increased frailty. Furthermore, a frailty index score of 0.4 or greater is predictive of significant frailty, whereas a score of <0.25 is classified as non-frail (Rockwood et al., 2007; Theou et al., 2012; Widagdo et al., 2015).

Participants were randomly assigned to intervention and control groups. The intervention group received sessional pharmacist services for every 8 weeks over the 12-months intervention period. The intervention was focused on the early identification of potential harms from medicines and pharmacists used to validate tools to measure grip strength and cognition, as well as resident interview, patient history, and clinical care record review to identify potential harms from medicines (Roughead et al., 2022). More information regarding the ReMInDAR trial can be found elsewhere (Roughead et al., 2022). In this study, we analyzed data from participants who were enrolled in the intervention group.

Collection of data

Pharmacist assessments, notes, actions, and recommendations were recorded by pharmacists at each session visit. In these visits, the trial pharmacist reviewed the same patient every 8 weeks, assessed their physical and cognitive performances, recorded new symptoms as identified by the resident or as documented in their care record, assessed changes to the medicine regimen, and identified actual or potential adverse medicine events (Roughead et al., 2022). The adverse events were assessed with a modified Naranjo method by a clinical panel. More information were published previously (Roughead et al., 2022).

The global pandemic restrictions due to Sars-Cov-2 have affected the final months (April–June 2020) of ReMInDAR trial, where some pharmacists' sessions in some nursing homes had to be modified or stopped. The modifications allowed remote data review and interview by telehealth where possible. As a result, pharmacists were able to review medication charts and a summary of progress notes and adverse events remotely (Roughead et al., 2022).

Assessment of medicine-related problems

Data classification

Medicine-related problems and symptoms that may be indicative of clinical deterioration or adverse effects were identified by the trial pharmacists and documented in the service report. The identified problems and symptoms were independently classified by research pharmacists using the categories proposed by the D.O.C.U.M.E.N.T classification (Williams et al., 2012). The D.O.C.U.M.E.N.T classification is a system to categorize medicine-related problems and clinical interventions performed in community pharmacy. As opposed to other methods available to assess medicine-related problems, the D.O.C.U.M.E.N.T classification has several advantages, including coding for activities intended to resolve medicine-related problems, assessing the impact of intervention and clinical significance, and it as reported to be well-suited to use in the Australian community pharmacy environment (Williams et al., 2012).

Categories of the D.O.C.U.M.E.N.T classification include inappropriate medicine selection, over-dose or under-dose prescribed, compliance, undertreated, need for monitoring, need for education or information, toxicity, or adverse reaction (Williams et al., 2012). Clinical problems that do not fit under any other category are coded as not classifiable (Williams et al., 2012).

Because of the nature of our study, which focused on identifying signs and symptoms of adverse effects, we created an additional category: symptom reports. Symptoms classified in this category frequently included pain, cognitive decline, sedation, and weight gain. Pharmacists indicated when they observed these problems and whether they thought causality to a medicine was possible. To indicate the causality, pharmacists reported that additional information was required and further assess residents. Symptoms were extracted as verbatim text by one research pharmacist (GD) and visualized using the R package "wordcloud" (Oesper et al., 2011).

One research pharmacist (GD) classified all records documented by the ReMInDAR pharmacists. Validation of the classification was performed by a second independent research pharmacist (RL) on a randomly selected sample of 108 (19%) pharmacist services ($n = 575$). Cohen's kappa to quantify the level of agreement between identification and classifications was used (Cohen, 1960). The computation of kappa values was performed using the vcd package for open-source R Studio Version 1.2.1335 (R Development Core team, 2009) (Friendly and Meyer, 2015). The level of agreement was high with kappa = 0.85 (95% CI, 0.76–0.95, $p < 0.0001$) (Cohen, 1960).

We estimated the proportion of participants who had a problem at each session (Eq. 1)

$$\begin{aligned} &proportion\,of\ people\,with\,medicine-related\,problem \\ &\quad = Number\,of\ people\,with\,medicine-related\,problem \\ &\qquad /Total\,number\,of\ peopel\,enrolled\,and \\ &\qquad visited\,by\,a\,pharmacist \end{aligned} \tag{1}$$

Identification of new medicine-related problems

Because pharmacists were visiting residents every 8 weeks, we were able to investigate when residents developed new medicine-related problems subsequent to the first session. In the analysis of new medicine-related problems, we investigated the proportion of people identified with new problems at each session. A new medicine-related problem was defined as any medicine-related problem that was not identified at the first visit;

TABLE 1 Baseline characteristics of participants enrolled in the intervention group.

Characteristics	Measurement (n, SD)
Age, years	85 (7.4)
Gender: Female	76 (66.1%)
Mean number of unique medicines	15.1 (5.7)
Mean number of anticholinergic or sedative medicines	2 (1.5)

TABLE 2 Number of residents identified with medicine-related problems, by session and by problem type.

Problem Type	Session 1	Session 2	Session 3	Session 4	Session 5	Session 6
	n = 115	*n* = 109	*n* = 106	*n* = 9	*n* = 91	*n* = 57
	n, %	*n*, %	*n*, %	*n*, %	*n*, %	*n*, %
Toxicity or adverse reaction	25, 22%	18, 17%	19, 18%	11, 11%	9, 10%	6, 11%
Education or information	22, 19%	18, 17%	17, 16%	22, 23%	12, 13%	8, 15%
Over- or underdose	15, 13%	10, 9%	17, 16%	17, 18%	13, 14%	5, 9%
Drug selection	14, 12%	9, 8%	9, 8%	5, 5%	2, 2%	2, 4%
Compliance	8, 7%	5, 5%	1, 1%	5, 5%	2, 2%	3, 5%
Monitoring	6, 5%	6, 6%	11, 10%	8, 8%	6, 7%	3, 5%
Symptom report	40, 35%	43, 39%	31, 29%	33, 34%	21, 34%	17, 30%
No problems	24, 21%	25, 23%	27, 25%	27, 28%	32, 35%	22, 39%

the first pharmacist visit was the reference point. Problems identified in the subsequent sessions were analyzed if they were not documented in the previous session.

For example, a patient has received a clinical pharmacist service six times throughout the trial. No problems were identified at the first session. However, between the second session and third session, the patient had a stroke and was no longer able to swallow their medicines. This was assessed as a "new medicine-related problem" that was recorded at the third session.

The proportion of people identified with new medicine-related problems was based on the following equation:

$$proportion\,of\ people\,with\,new\,medicine-related\,problem = Number\,of\ people\,with\,new\,medicine-related\,problem/ Total\,number\,of\ peopel\,enrolled\,and\,visited\,by\,a\,pharmacist \quad (2)$$

Analysis of time to new medicine-related problem

To estimate the time to the first new medicine-related problem after the first session, we included timelines for individual sessions by pharmacists.

Statistical analysis

Continuous variables, including the proportion of patients identified with problems at each session, were compared using the t-test. To estimate the probability to experience a new medicine-related problem, a time-to -event analysis using the Kaplan–Meier method was undertaken (Kaplan and Meier, 1958), censoring for death and end of study.

Descriptive results are provided as median and standard deviation (SD), unless otherwise stated. A p value less than 0.05 was considered statistically significant. All estimates were computed using the R software (Version 4.1.1) and the R packages "survminer," "stats," and "wordcloud" were used (Kaplan and Meier, 1958; Oesper et al., 2011; Team, 2013; Kassambara et al., 2017).

Results

Baseline characteristics of participants

The cohort for this study was 115 participants who received 575 pharmacist services delivered by 29 pharmacists. At baseline, the mean age of participants was 85 years (SD = 7.4) and most were women (n = 76, 66.1%).

FIGURE 1
Nature of symptom related reports documented by the pharmacists..

The mean number of unique medicines per participant at baseline was 15.1, and the participants used, on average, two medicines with anticholinergic or sedative properties (Table 1).

The incidence and nature of medicine-related problems

Over 12 months, residents had on average six medicine-related problems or symptom reports identified by pharmacists. At each session, over 30% of residents had a symptom report identified and 40% of residents had a medicine-related problem other than a symptom report (Table 2). Excluding symptom reports, a total of 277 medicine-related problems were recorded, with a median of three per person (SD = 1.3). In the 12-months trial, three people had no problems. When looking at the distribution of problems by different sessions, the proportion of residents experiencing no medicine-related problems increased over time (21% had no problems at session 1 rising to almost 40% with no problems at session 6). Consistent with the service design, the decline in participants with toxicity or adverse events was the highest, from 22% at session 1 and dropping down to 11% at session 6 (Table 2).

Nature of symptom reports

There were 396 symptom-related reports among 103 participants (90%) Most reports were pain (n = 79), followed by sleeping issues (n = 39), sedation (n = 29), and constipation (n = 25) (Figure 1).

New and ongoing medicine-related problems or symptom reports

In the trial, 71% of residents had a new medicine-related problem identified within the period after the first pharmacist session (~10 months). The median number of new medicine-related problems over the 10 months was two (SD = 1.4). There was a trend towards less new medicine- related problems or symptoms over time (p < 0.01). Pharmacists documented ongoing symptoms or problems in up to 40% (Figure 2).

Review of the pharmacist notes demonstrated that it may take several visits to resolve a medicine-related problem in residents. In the example below, we provide a case where the ReMInDAR pharmacist required four sessions to identify and resolve a medicine-related problem.

At the first visit, the ReMInDAR pharmacist noted that the resident had bright red blood in their stool. The pharmacist notified the nurse and doctor and a review of apixaban (5 mg twice daily). During subsequent visits (Australian Institute of Health, 2012; Australian Institute of Health and Welfare, 2020), the resident was still experiencing blood in their stool. The pharmacist continued monitoring the resident and considering the resident's age (>80 years old), weight (<60 kg), laboratory results (CrCl = 0.66 mg/dl), contacted the doctor again recommending to reduce the dose of apixaban. By session 4, the doctor finally accepted to trial reducing apixaban from 5 mg twice daily to 2.5 mg twice daily. The resident informed the pharmacist at session 5; the blood in the stool had stopped.

Probability to experience a new medicine-related problem or new symptom, post first session

We analyzed the cumulative probability to experience a new medicine-related problem or symptom after session 1 and found that 59% of participants had a new medicine-related problem or a new symptom report by the next session (8 weeks) and 75% had a new problem by the subsequent session (~16 weeks), and 90% by the third session (~24 weeks) (Figure 3).

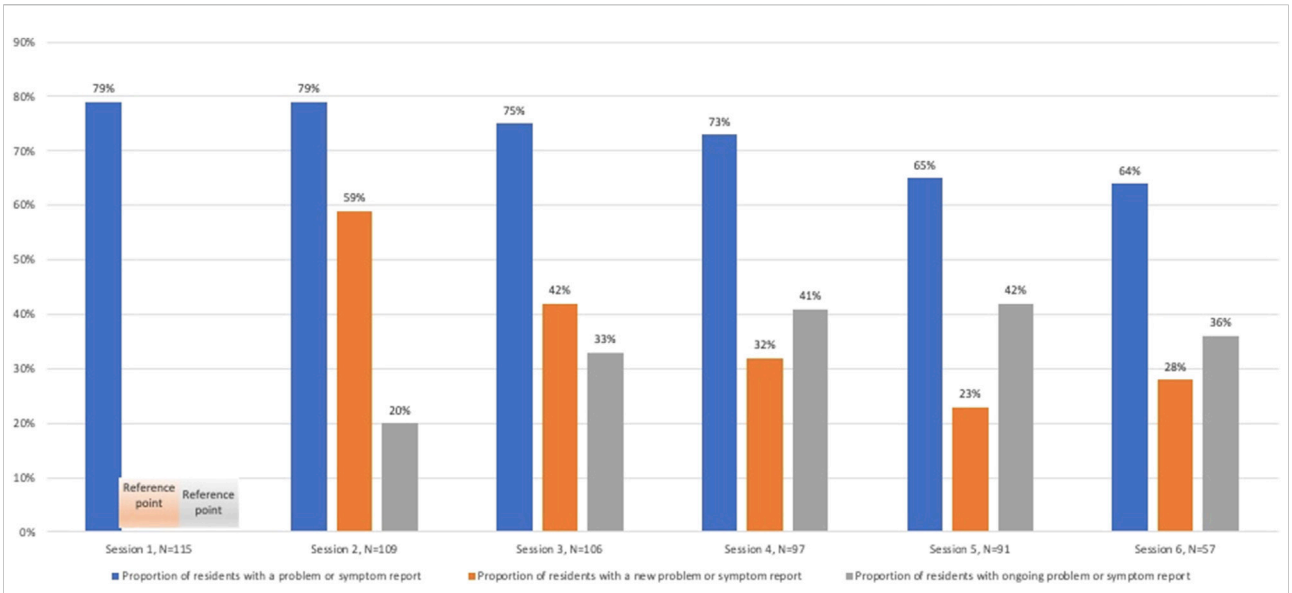

FIGURE 2
Proportion of residents with new and ongoing medicine-related problems or symptoms at each session.

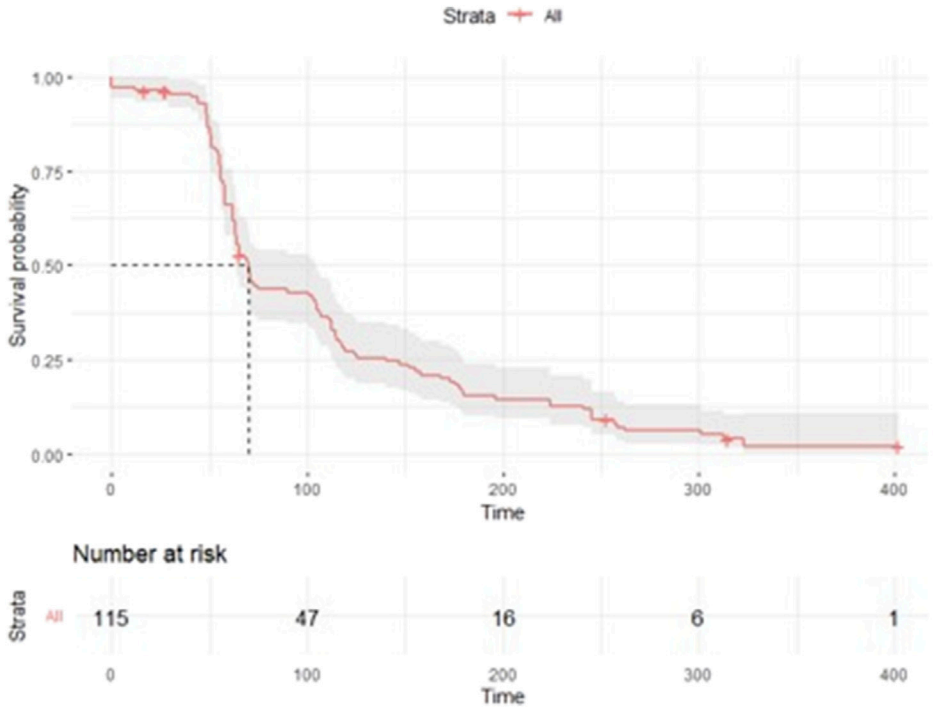

FIGURE 3
Time to experience a new medicine-related problem or symptom.

Discussion

Medicine-related problems

We investigated the frequency and nature of the medicine-related problems in nursing home residents over a 12-month period. In our study, most residents had at least one medicine-related problem, the number of medicine-related problems, or symptom reports was six per person; when limited to medicine-related problems only, it was three per person. This study is the first study to look at the development of new medicine-related problems over time, finding that new problems emerge within 8–16 weeks for the majority of the studied population. The proportion of residents with new medicine-related problem declined over the trial period (39% vs. 25%, $p = 0.05$). The reduction in medicine-related problems over time is likely due to the repeated pharmacist visits in the ReMInDAR intervention, where pharmacists consistently monitored residents for adverse effects of medicines and intervened to resolve them. Previous Australian studies in nursing homes have looked at medication-related problems from a single medication review (Pharmaceutical Society of Australia, 2019), where reviews are usually at least 12-months apart, reporting the average number of medicine-related problems being three per person (Pharmaceutical Society of Australia, 2019).

Symptom reports

Symptom reports were recorded in over 30% of residents at each session, with common symptoms reported as pain, cognitive decline, sedation, and weight gain. Our intervention focused on reducing medicine harms with pharmacists encouraged to assess patients for adverse effects with the help of validated tools including grip strength and Montreal Cognitive Assessment (Roughead et al., 2022). This intervention may have supported the high number of symptom reports documented by the pharmacists. Identification of symptoms, such as drowsiness or change in cognition, is important for enabling the prevention of the consequential, more serious medicine-induced harms of falls and delirium (Inouye et al., 2007). Our review did not locate any repeated pharmacist service trials that reported how pharmacists documented and assessed symptom reports in nursing home residents. Further studies could investigate the utilization of clinical notes, including the symptom reports in nursing home residents to better identify people experiencing medication-related deterioration or harms.

Frequency of medicine reviews

Only four prior studies tested clinical medicine reviews involving multiple services in nursing home residents, but none reported how problems emerge over time (Furniss et al., 2000; Patterson et al., 2010; Lapane et al., 2011; Frankenthal et al., 2014). A previous study in the United kingdom provided a single medicine review by a pharmacist with one follow-up visit but problems by visit were not reported (Furniss et al., 2000). Frankenthal et al. provided a pharmacist service for nursing home residents with two visits over a 6-month period (Frankenthal et al., 2014). While the number of medicines was reduced at the end of the study ($p < 0.001$), how problems emerged at each visit was not reported (Frankenthal et al., 2014). A randomized clinical trial in 2010 assessed the effectiveness of a monthly pharmacist service delivered for nursing home residents (Patterson et al., 2010). In the trial, pharmacists focused on psychoactive medicines and provided reviews based on a previously published algorithm. After 1 year, the proportion of residents taking inappropriate psychoactive medications in the intervention group (25/128, 19.5%) was much lower than in the control group (62/124, 50.0%) (OR = 0.26, 95% CI 0.14–0.49); however, the need for the frequency of the service was not assessed. Finally, a US-based study trialed a pharmacist intervention using an algorithm generated from clinical care records of nursing home residents (Geriatric Risk Assessment MedGuide) (Lapane et al., 2011). Pharmacists visited nursing home every month, and medicine reviews were mandated 1–3 times a year. The residents in control group received a similar number of interventions as the intervention group. Therefore, the study assessed the additional benefits of the algorithm and not really the pharmacist service (Lapane et al., 2011). None of these studies reported the change in medicine-related problems that occurred at each visits.

Medicine reviews are recognized as a key intervention to reduce the risk of medicine-related problems in nursing home residents. Currently, an Australian resident entering a nursing home is allowed to receive a formal RMMR service only once every 2 years, with up to two follow-ups within 9 months of the first service (Pharmacy Programs Administrator, 2020). Our findings suggest that more regular pharmacist-led services, performed at least every 4 months, have the potential to reduce the number of medicine-related problems in nursing home residents over time (Thiruchelvam et al., 2017).

Limitation

The ReMInDAR trial was affected by COVID-19. Pharmacists were scheduled to visit their participants every 8 weeks over a 12-month period. However, due to restrictions during COVID-19 and unavailability of participants, some pharmacist visits had to be undertaken remotely or were delayed ($n = 53$, 9%), while some were unable to be performed ($n = 35$, 6%). Hence, some symptoms and medication-related problems might have been under-reported at visit 6. However, the frequency of problems and symptoms was similar between visit 5 (where COVID-19 had little impact) and visit

6. In addition, the majority of pharmacists' visits (85%) were performed as planned; thus, our findings may represent the current extent of the problem among older people living in nursing homes.

A relatively large number of pharmacists ($n = 29$) engaged in the ReMInDAR trial who assessed residents may have created some bias regarding their judgment. However, the ReMInDAR trial pharmacists reviewed the same patient at every visit consulting and reporting any progress with treating doctor and nursing home staff.

The results were reliant on the completeness of documentation during the pharmacist service. While we cannot ascertain completeness, we were trialing a new intervention, and ongoing pharmacist support and training, including on-site peer visiting, was provided throughout the trial to assist pharmacists with documentation.

Finally, the incidence and frequency of medicine-related problems were identified based on the population aged 65 years old and older living in nursing homes of Australia. However, our findings may be applicable to other countries as there is evidence that medicine-related problems are prevalent in this population living in similar settings.

Conclusion

In summary, we described the nature and frequency of medicine-related problems that occurred over time in nursing home residents. We found that medicine-related problems arose throughout the year as residents' health and medicines changed. Our results suggest that pharmacist review every 4 months may be warranted to ensure the quality use of medicines in nursing homes.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics approvals obtained from the Human Research Ethics Committee of University of South Australia (ID:0000036440) and the University of Tasmania (ID:H0017022). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

ER, as principal investigator, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: ER, GD, RL, NP, and T-LK. Acquisition, analysis, or interpretation of data: all authors. Drafting of the article: GD and ER. Critical revision of the article for important intellectual content: All authors. Statistical analysis: GD, ER, T-LK, IW, and AA. Obtained funding: ER, LE, NP, and RL. Administrative, technical, or material support: GD, ER, RL, NP, T-LK, AA, and RB. Supervision: ER.

Funding

This work was supported by the Australian Government Department of Health Pharmacy Trial Program. The Australian Government Department of Health reviewed the article before submission but played no role in the study design, data collection, management, writing of article, or decision to submit the article for publication.

Acknowledgments

The authors would like to acknowledge all participating nursing homes and residents.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 17 November 2022
DOI 10.3389/fphar.2022.1042418

OPEN ACCESS

EDITED BY
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SPECIALTY SECTION
This article was submitted to Drugs Outcomes Research and Policies, a section of the journal Frontiers in Pharmacology

RECEIVED 12 September 2022
ACCEPTED 27 October 2022
PUBLISHED 17 November 2022

CITATION
Kusuma IY, Matuz M, Bordás R, Juhasz Haverinen M, Bahar MA, Hajdu E, Visnyovszki Á, Ruzsa R, Doró P, Engi Z, Csupor D and Benko R (2022), Antibiotic use in elderly patients in ambulatory care: A comparison between Hungary and Sweden.
Front. Pharmacol. 13:1042418.
doi: 10.3389/fphar.2022.1042418

Antibiotic use in elderly patients in ambulatory care: A comparison between Hungary and Sweden

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Background: The elderly use antibiotics frequently due to their increasing infection susceptibility. Given the high and increasing proportion of elderly in the population, their antibiotic use is substantial. *Objective:* This study aimed to compare antibiotic use in the elderly in the ambulatory care sector between Hungary and Sweden.

Methods: This retrospective, descriptive, cross-national, comparative study included antibacterial use data from the Hungarian National Health Insurance Fund and the Swedish eHealth Agency. Antibiotic use (anatomical therapeutical chemical: J01) was expressed as the number of prescriptions/1000 inhabitants/year or month and was further stratified by age and sex.

Results: Antibiotic exposure was higher in the Hungarian elderly population (649.8 prescriptions/1000 inhabitants/year) compared to its Swedish counterparts (545.0 prescriptions/1000 inhabitants/year). Hungary had a similar scale of antibacterial exposure across all elderly age subgroups, with different trends in males and females, while Sweden had a stepwise increase in antibiotic exposure by age in both sexes. The seasonal fluctuation was high in Hungary and reached a peak of 80.7 prescriptions/1000 inhabitants/month in January 2017, while even antibiotic use was detected throughout the year in Sweden. The pattern of antibiotic use in the elderly considerably differed between the two countries. Penicillin and beta-lactamase combinations, such as co-amoxiclav, were more frequently used in Hungary than in Sweden (19.08% vs 1.83% of corresponding total ambulatory antibiotic use). Likewise, quinolones were more commonly used in Hungary than in Sweden (34.53% vs. 9.98). The elderly in Sweden were mostly prescribed narrow spectra penicillins (26.71% vs. 0.29% in Hungary).

Conclusion: This cross-national comparison revealed important differences in all aspects of antibiotic use in the elderly between the two countries. The identical scale and pattern of antibiotic use cannot be anticipated due to the poorer health status of the Hungarian elderly population. However, the substantial differences indicate some room for improvement in the antibiotic prescription for the Hungarian elderly.

KEYWORDS

drug utilization study, ambulatory care, antibacterials, elderly, cross national comparison, prescrptions/1000 inhabitants/year, public health, antibiotic stewardship

Introduction

Antimicrobial resistance (AMR) implies a threat to global human health. Contributing factors of AMR include antibiotic overuse and misuse in hospital and ambulatory care settings (Ventola, 2015). Current demographic projections show an increasing elderly population in Europe. In 2019, proportion of the elderly population (≥65 years) proportion in Europe, Hungary, and Sweden was 31.4%, 29.3%, and 31.9%, respectively, of the total adult active (15–64 years) population, which is projected as 39.1%, 33.7%, and 34.4% by 2030, respectively (Eurostat, 2019).

The elderly population is at increased risk of many infectious diseases due to progressive functional decline of the immune system, commonly referred to as immunosenescence (Feehan et al., 2021). Age-related immune system changes affect innate and adaptive immune responses (Feehan et al., 2021). Research data on outpatient antibiotic use in the elderly remained scarce despite the growing population size of the elderly in Europe, and most studies focus on long-term care facilities (Raban et al., 2021). Comprehensive country-wide data on antibiotic use in the elderly in ambulatory care have only been published for a limited number of countries, including Denmark (Jensen et al., 2021), Norway (Blix et al., 2007), and the United States (Kabbani et al., 2018). Moreover, no cross-national comparison research has compared antibiotic use for the elderly in ambulatory care between European countries. Therefore, this study aimed to compare antibiotic use in the elderly in the ambulatory care sector in Hungary and Sweden.

Methodology

Study design and setting

This retrospective and descriptive cross-national comparative study collected data on antibacterial prescriptions dispensed at community pharmacies in Hungary and Sweden in 2017. Antibacterials were classified according to the anatomical therapeutical chemical (ATC) classification system defined by the World Health Organization (WHO), version 2022 (WHO, 2020). The use of systemic antibacterials (ATC: J01) was measured as prescriptions/1000 inhabitants/year or month. The elderly population (aged >65 years) of Hungary and Sweden in 2017 served as study populations for this study, including 1,828,226 elderly in Hungary and 1,976,857 elderly in Sweden (data derived from Eurostat). The two populations were further stratified into subgroups according to age (65–69 years, 70–74 years, 75–79 years, 80–85 years, and >85 years) and sex. Seasonal variation of antibiotic consumption was also assessed.

Description of databases

Data on antibacterial use was obtained from the Hungarian National Health Insurance Fund and the Swedish eHealth Agency. Both the Hungarian and the Swedish national health insurance systems cover almost 100% of the population of each country. The database in Hungary contains records of all dispensed and reimbursed ambulatory care prescriptions issued by general practitioners (GPs), specialists, and dentists to ambulatory care patients, nursing home residents, and patients visiting private practices (e.g., gynecologists, dentists). The drug coverage is approximately 95% because non-reimbursed antibiotics are not included in the database.

The Swedish database contains data on all dispensed antibiotic prescriptions providing 100% drug coverage. All medications prescribed to outpatients (irrespective of reimbursement status) that are issued by GPs, specialists, dentists, patients visiting private practices, or nursing homes are included in this database.

Statistics

Excel was used for the statistical analyses, and visualization was done by the R package (version 4.1.2).

Ethical considerations

Ethical approval was not needed because aggregated data were collected for both countries.

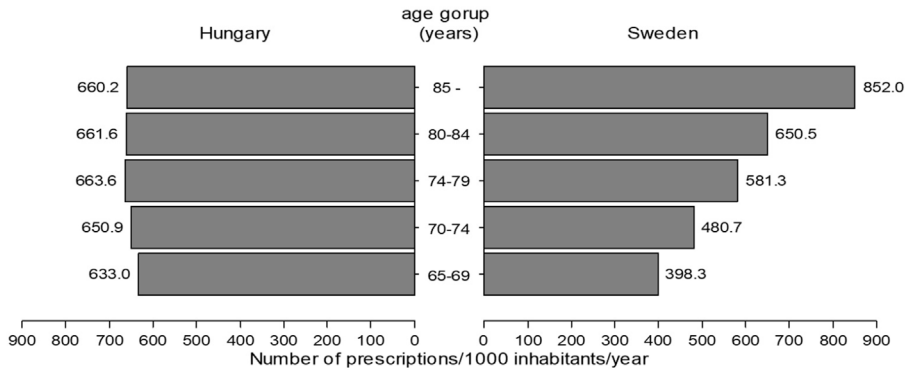

FIGURE 1
Antibacterial use in different elderly age subgroups in Hungary and Sweden (2017).

Results

The scale of antibiotic use

The entire Hungarian population (approximately 9.8 million people) was dispensed 6,792,714 prescriptions of antibiotics in 2017, 17.5% of which were dispensed to the elderly. Concurrently, the entire Swedish population (approximately 10 million people) was dispensed 3,204,838 prescriptions of antibiotics, 33.6% of which were dispensed to the elderly. The antibiotic exposure was 649.8 prescriptions/1000 inhabitants/year in Hungarian and 545.0 prescriptions/1000 inhabitants/year in the Swedish elderly population.

Figure 1 presents the level of antibiotic exposure across the elderly age subgroups. The antibacterial exposure of the Hungarian elderly population was similar across all age subgroups, while a stepwise increase was observed in antibacterial exposure by age subgroups (an increase from 398 [65–69 years old] to 852 (>85 years old) prescriptions/1000 inhabitants/year) in the Swedish elderly population.

The pattern of antibiotic use

Table 1 shows the absolute and relative use of different antibacterial subgroups. Concerning the beta-lactam antibacterials, the penicillin group in Hungary was responsible for one-fifth of total ambulatory care antibiotic use in the elderly, and cephalosporins also had considerable use and share. In contrast, the penicillin group in Sweden was responsible for almost half of antibiotic use in the elderly, and marginal cephalosporin use was observed. The absolute and relative use of macrolides and fluoroquinolones were considerably higher in the Hungarian elderly population than in the Swedish counterparts, with an opposite pattern for tetracyclines and other antibacterials because their use was higher in the Swedish elderly (Table 1).

Table 2 shows the top ten list of antibacterials. Amoxicillin and clavulanic acid (co-amoxiclav) and two fluoroquinolones (levofloxacin and ciprofloxacin) covered almost half (46.6%) of the antibiotic use of the Hungarian elderly population in ambulatory care (Table 2), whereas 40% of all antibiotics used by the elderly population in ambulatory care constituted of the narrow-spectrum penicillin V, flucloxacillin, or pivmecillinam in Sweden. Nitrofurantoin use was almost absent in Hungary but constituted approximately 10.5% of the elderly antibiotic use in Sweden.

Sex-specific antibiotic use

Overall, elderly females used more antibiotics than elderly males in Hungary and Sweden. Elderly females have been exposed to antibiotics at 668 prescriptions/1000 elderly females/year in Hungary, while elderly males at 620 prescriptions/1000 elderly males/year. Swedish elderly females were exposed to antibiotics at 618 prescriptions/1000 females/year, while elderly males at 460 prescriptions/1000 males/year in ambulatory care.

However, the antibiotic exposure of the two sexes of the elderly population showed opposite trends in the age subgroup analysis in Hungary (Figure 2). Antibiotic use decreased from 685 prescriptions/1000 females/year (60–65 years old) to 631 prescriptions/1000 females/year (>85 years old) in Hungary. Conversely, the scale of antibiotic use in the Hungarian elderly male increased by age [from 563 prescriptions/1000 males/year (65–69 years old) to 739 prescriptions/1000 males/year (>85 years old)]. Both elderly females and males in Sweden were exposed to increasing amounts of antibiotics by increasing age (Figures 1, 2) and in all elderly subgroups Swedish females were exposed to more antibiotics than Swedish males).

Seasonal variation

Figure 3 shows the seasonal variation in antibiotic use in the elderly in Hungary and Sweden. The seasonal fluctuation was high in Hungary, reaching a peak of 80.7 prescriptions/1000 inhabitants/

TABLE 1 Absolute and relative use of different antibiotic subgroups in the elderly population in Hungary and Sweden.

	Hungary	Sweden
J01A Tetracyclines	15.46 (2.38%)	52.84 (9.7%)
J01C Beta-lactam antibacterials, penicillins	141 (21.7%)	260.53 (47.81%)
J01CA Penicillins with extended spectrum	15.12 (2.33%)	105.03 (19.27%)
J01CE-CF Narrow-spectrum penicillins	1.90 (0.29%)	145.55 (26.71%)
J01CR Penicillin combinations, including beta-lactamase inhibitors	123.99 (19.08%)	9.96 (1.83%)
J01D Other beta-lactam antibacterials	75.45 (11.61%)	9.14 (1.68%)
J01DB First-generation cephalosporins	0.60 (0.09%)	8.79 (1.61%)
J01DC Second-generation cephalosporins	58.36 (8.98%)	0.01 (>0.01%)
J01DD Third-generation cephalosporins	16.49 (2.54%)	0.26 (0.05%)
J01E Sulfonamides and trimethoprim	36.18 (5.57%)	28.56 (5.24%)
J01EA Trimethoprim and derivatives	-	13.93 (2.56%)
J01EE Combinations of sulfonamides and trimethoprim, incl. derivatives	36.18 (5.57%)	14.63 (2.68%)
J01F Macrolides, lincosamides, and streptogramins	120.06 (18.48%)	32.41 (5.95%)
J01FA Macrolides	82.86 (12.75%)	8.41 (1.54%)
J01FF Lincosamides	37.20 (5.72%)	24.00 (4.4%)
J01M Quinolones	224.38 (34.53%)	54.41 (9.98%)
J01X Other antibacterials	36.17 (5.57%)	106.96 (19.63%)
J01XE Nitrofuran derivatives	0.02 (>0.01%)	57.17 (10.49%)
J01XX Other antibacterials (e.g., fosfomycin, methenamine)	36.12 (5.56%)	49.09 (9.01%)
Other	1.11 (0.17%)	0.11 (0.02%)
Total (J01)	649.81 (100%)	544.96 (100%)

Unit = Prescriptions/1000 inhabitants/year.

month in January. The lowest value in Hungary was 39.2 prescriptions/1000 inhabitants/month in July. Antibacterial use in the elderly population in Sweden was more equally distributed over the entire year, with a peak consumption of 49 prescriptions/1000 inhabitants/month in March and a nadir of 42 prescriptions/1000 inhabitants/month in April.

Discussion

To the best of our knowledge, this is the first study to report on Hungarian data on antibiotic use in the elderly and the first age-specific comparison of antibiotic use between two countries. Our results showed that antibiotic exposure was higher in the Hungarian elderly population than in their Swedish counterparts. Several factors might explain the higher antibiotic exposure in the Hungarian elderly than in Sweden.

Scale of use

Life expectancy is one of the most commonly used measures of the overall health of a population. The average life expectancy in 2017 for those aged 65 years was higher in Sweden than in Hungary (20.40 years vs 16.70 years), meaning that the Hungarian elderly has poorer health status (Eurostat, 2022).

Data on acute infection incidences are unavailable in the national statistics, but data on chronic disease prevalence, which can increase infection risk compared to the healthy population, is retrievable and can partly explain the observed differences between Hungary and Sweden. Two-thirds of Hungarians and nearly half of Swedish elderly (aged ≥65) reported at least one chronic disease (OECD, 2020). An epidemiological research revealed that patients with diabetes suffer infections more frequently than those without diabetes with consequent higher antibiotic use (Alves et al., 2012). The prevalence of diabetes in the elderly was higher in 2014 in Hungary than in Sweden (18.6% vs 12.6%) (Eurostat, 2014c). Obesity has also been an independent risk factor for infections in retrospective and prospective studies (Harpsøe et al., 2016). It increases the risk of pneumococcal respiratory tract infections (RTI), skin, gastrointestinal tract, and urinary tract infections (UTI) in elderly individuals (Frasca and McElhaney, 2019; Ghilotti et al., 2019). The prevalence of obesity in the elderly was much higher in 2014 in Hungary than in Sweden (26.5% vs 14.5%) (Eurostat, 2014a).

Smoking is one of the main risk factors for RTI, and the rate of daily smokers among the elderly was higher in Hungary (10.8%) than in Sweden (7.2 %), however this difference is much higher in the overall population (28 % vs. 7%, in 2020).

TABLE 2 The top ten list of antibacterials used in the elderly population in Hungary and Sweden (2017).

Hungary	Prescriptions/ 1000 inhabitants/year	Percentage	Sweden	Prescriptions/ 1000 inhabitants/year	Percentage
co-amoxiclav	123	18.95	phenoxymethylpenicillin	81.5	14.95
levofloxacin	95.8	14.75	pivmecillinam	72.3	13.27
ciprofloxacin	83.9	12.92	flucloxacillin	64.0	11.75
azitromycin	57.1	8.78	nitrofurantoin	57.2	10.49
cefuroxim	48.2	7.42	ciprofloxacin	52.8	9.68
clindamycin	37.2	5.72	methenamine	48.5	8.90
sulfamethoxazole/ trimethoprim	36.2	5.57	doxycycline	47.9	8.80
fosfomycin	36.1	5.56	amoxicillin	32.7	6.00
norfloxacin	24.5	3.78	clindamycin	24.0	4.40
clarithromycin	23.3	3.59	SMX/TMP*	14.6	2.68

*SMX/TMP, sulfamethoxazole and trimethoprim.

In addition, smoking increases infection risk for digestive, reproductive, and other systems, which could lead to slightly higher antibiotic use in Hungarian elderly than in Swedish (Jiang et al., 2020). The annual number of hospital discharges due to malignant neoplasm of the respiratory tract (trachea, bronchus, and lung) in 2017 was also higher in Hungarian elderly (13,115 patients) than in its Swedish counterparts (4,966 patients) (Eurostat, 2017a). Prescribers may have a lower threshold for initiating antibiotic use in patients with cancer because antibiotics have positive side effects, such as cancer apoptosis promotion, cancer growth inhibition, and cancer metastasis prevention, e.g., lung cancer (Gao et al., 2020).

The population's low health literacy and health-related knowledge can contribute to patients' attitudes, beliefs, perceptions, and behaviors related to antibiotic use and can result in higher overall antibiotic use (Salm et al., 2018). The Eurobarometer public survey from 2018 revealed that the Hungarian public's knowledge of antibiotics was worse than Swedish because only 37% of respondents gave entirely correct answers for all four antibiotic knowledge-related questions in Hungary, while 74% in Sweden (WHO, 2018).

The Eurostat statistics from 2017 revealed that the proportion of Hungarian elderly with >10 GP visits per year was 20.0% (65–74 years) and 29.5% (≥75 years), while this rate was only 3.7% (65–74 years) and 5.8% (≥75 years or more) in Sweden, suggesting that GP visits have a lower threshold in the Hungarian elderly population, which can contribute to higher antibiotic use (Tyrstrup et al., 2017). In addition, of the surveyed people in Hungary in the Eurobarometer study, 25% stated antibiotic prescription for sore throat and 17% for fever, while 9% for sore throat and 2% for fever in Sweden (European Commission, 2016). Data suggests that initiating antibiotic treatment is less judicious among Hungarian doctors although this data is based on patient recalls. Misleading advertising can be partly responsible for this. Over-the-counter dorithricin-containing lozenges, a local antibiotic, were heavily advertised on TV as a "throat saver antibiotic" in earlier years in Hungary, sending the incorrect message both to patients and doctors that antibiotics are required to relieve sore throats.

Physicians are primarily responsible for the decision to use antibiotics; thus, ensuring the optimal attitudes and knowledge that underlie their prescribing habits is a prerequisite for improving prescription quality (Gonzalez et al., 2015). A recent study revealed a 20% proportion of final-year medical students who want more education on prudent antibiotic use in Sweden, while >71% in Hungary. This means that medical students in Sweden feel prepared for prudent antibiotic prescription in much higher percentages than final-year students in Hungary (Dyar et al., 2018).

Moreover, antibiotic use is influenced by the existence of a national antibiotic policy (WHO, 2011). Sweden implemented the WHO recommendations for antibiotic stewardship in the form of a national strategic program to combat antibiotic resistance (Medical Products Agency and Strama, 2008), which is a continuously evolving collaboration that has been in place since 1995 (Mölstad et al., 2017). In contrast, a national antibiotic policy is not implemented with clear targets, responsibilities, and dedicated funding in Hungary (WHO, 2018).

Market forces and manufacturers' marketing activity can also largely influence prescription practices in Hungary (WHO, 2018). The number of generics is very high in Hungary because they aim to reduce the price as much as possible (MacKenzie et al., 2006; Wouters et al., 2017), which might promote higher antibiotic use.

Overall, our study revealed that elderly females were prescribed more antibiotics than males in both

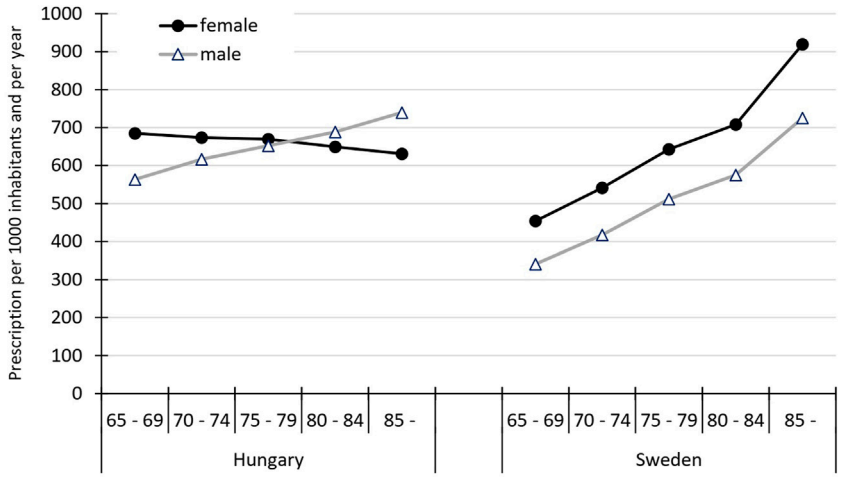

FIGURE 2
Sex-specific use of antibiotics in ambulatory care presented by age subgroups in the elderly population in Hungary and Sweden (2017).

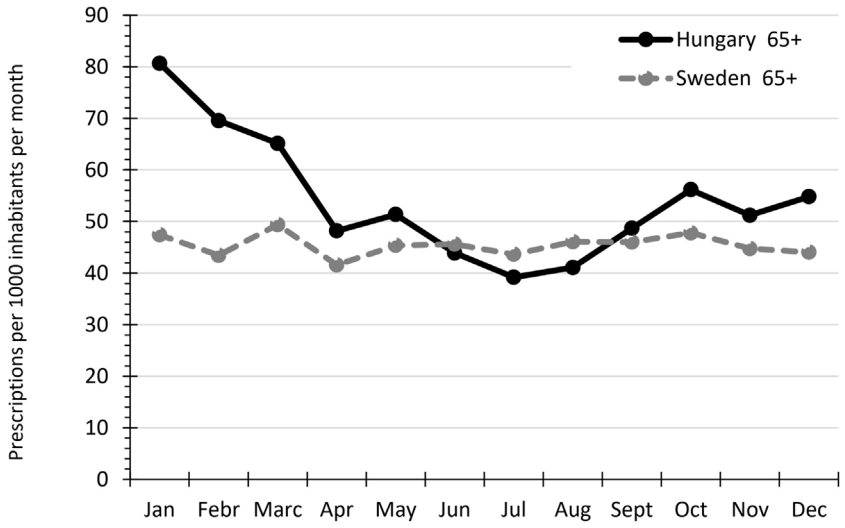

FIGURE 3
Seasonal variation of antibiotic use among the elderly population in Hungary and Sweden in 2017.

countries. This can be partly explained by the sex differences in GPs visiting rates, wherein the rate of Hungarian elderly with >10 GP visits per year was 17.7% and 28.6% for males aged 65–74 years and >75 years, respectively, while 21.5% and 30.0% in the same age groups for females.

The sex gap in antibiotic prescription can partly be explained by consultation behavior differences (Smith et al., 2018). Males and females communicate differently with healthcare professionals, and prescribers may have gender biases that affect their willingness to prescribe antibiotics, resulting in higher antibiotic use in females (Smith et al., 2018). Males in the oldest two age groups were prescribed more antibiotics in Hungary due to the higher prevalence of risk factors among males, such as smoking and excessive alcohol consumption (WHO, 2018). The number of elderly male smokers is double compared to elderly female smokers aged 65–74 years and is five times higher in >75 years old in Hungary. Meanwhile, both sexes are equally smokers in each age subgroup in Sweden (Eurostat, 2014).

Pattern of use

We found that the absolute and relative ambulatory care use of different antibacterial subgroups differed greatly in the elderly population between Hungary and Sweden. In Hungary, penicillin beta-lactamase combinations, such as co-amoxiclav were preferred, compared to Sweden where it was marginally used (19.08% vs 1.83%). The high use of co-amoxiclav has been estabilished in previous research as a drug of choice for RTI in Hungary (Matuz et al., 2013). Swedish policy recommends prescribing narrow-spectrum penicillins in ambulatory care for RTI (Aspevall et al., 2020) and our data indirectly indicate good adherence to this guideline. Surveillance report from the European Antimicrobial Resistance Surveillance Network (EARS-Net) showed that percentages of penicillin-resistant pneumococci (PRP) were similar in Hungary (6.9%) and Sweden (6.1%) (ECDC, 2017). Clavulanic acid use is not necessary for PRP because the resistance mechanism is not connected to the bacteria's capability to produce beta-lactamase enzymes; hence, the addition of clavulanic acid to aminopenicillin will not help to overcome this resistance (Huttner et al., 2020). Co-amoxiclav is dominantly used compared to amoxicillin alone in Hungary because co-amoxiclav was placed on the market earlier than amoxicillin alone; thus, doctors became used to it (Benko, 2016). The use of broad-spectrum antibiotics, such as co-amoxiclav can compromise the host microbiome. Even short-term antibiotic exposure alters the gut microbiota and bacterial diversity recover after weeks or months after (Elvers et al., 2020). Disruption of the human microbiom by antibiotic use can lead to AMR infections and several diseases such as allergia, asthma, obesity or vitamin K deficiency (Langdon et al., 2016).

Quinolone was also more frequently used in Hungary than in Sweden (34.53% vs. 9.98% of total ambulatory use in the elderly, respectively). Previous research showed that fluoroquinolones were commonly used in ambulatory care to treat urinary tract infections and also RTIs in Hungary (Juhasz et al., 2013; Matuz et al., 2015; Benkő et al., 2020). Contrarily, pivmecillinam and nitrofurantoin were proved to be the first-line antibiotics to treat community-acquired UTIs in Sweden (Kornfält et al., 2019). The consequences of high fluoroquinolone use can be various. The Food and Drug Administration has placed a boxed warning on fluoroquinolone antibiotics which highlights older adults as being at an elevated risk of serious side effects, including tendon rupture, delirium, peripheral neuropathy, blood sugar disturbances, and aortic dissection (U.S. Food and Drug Administration, 2018). Fluoroquinolones also increase the risk of CDI (*Clostridioides difficile* infection) (Kabbani et al., 2018). Fluoroquinolone can cause QT interval prolongation and subsequently increase the risk of *torsades de pointes (TdP) type arrhythmias*. Given that heart failure and other risk factors such as uncorrected hypokalaemia, hypomagnesaemia might be present more frequently in the elderly, they are more vulnerable to potentially fatal cardiac arrhythmias such as TdP (Stahlmann & Lode, 2010). The 2017 annual report of the EARS-Net showed a difference in the percentage of fluoroquinolone-resistant *Escherichia coli* between Hungary and Sweden (30.6% vs 15.8%, respectively) that could be due to differences in the quinolone use in the two countries (ECDC, 2017).

The results of this comparison between the two countries are essential for Hungary since they need to optimize antibiotic use in the elderly to prevent serious adverse effects, more rapid resistance development, and higher costs (WHO, 2018). The availability of therapeutic guidelines might contribute to the observed pattern of antibiotic use in both countries. Up-to-date diagnostic and treatment guidelines have been unavailable for most community-associated infections for several years in Hungary, but Sweden continuously updates the guidelines every 3 years (Government Offices of Sweden, 2020).

Seasonal antibiotic use

The Hungarian antibiotic use in the elderly was very similar to Sweden in the summer months, but we detected substantially higher antibiotic use in the Hungarian elderly in the winter months. Seasonal fluctuation of outpatient antibiotic use in the general population across European countries has been previously described (Elseviers et al., 2007) and linked to an increased prevalence of RTI during the winter months, resulting in higher antibiotic prescription rates during this time (Elseviers et al., 2007).

Viral RTI and influenza-like syndromes were the most frequent infections in winter in both countries (Folkhälsomyndigheten, 2017; Kovács and Pakot, 2020); thus, antibiotics were possibly prescribed for self-limiting viral infections. The close correlation between viral respiratory infections, such as influenza and antibiotic prescriptions (Ryu et al., 2018), suggests that reducing the incidence of influenza through vaccination efforts in elderly people (Smetana et al., 2018) could help decrease the overprescription of antibiotics. The Eurostat in 2017 reported that Sweden has a higher vaccination rate against influenza in the population aged ≥65 years (49.8%) than in Hungary (26.8%) (Eurostat, 2017b), which might result in lower influenza illness rates in Sweden.

Study strengths and limitations

The strength of this study is the nearly 100% population and drug coverage in both countries. However, some limitations need to be acknowledged. Firstly, this research only uses 1-year data from the two countries, which precludes analysis of annual trends in antibiotic use. Secondly, data is not stratified by specific indications. However, these limitations do not affect our aims and conclusions. Finally, we have to highlight, that systemic antibiotic use (WHO: J01) includes methenamine (urinary disinfectant) with considerable use in Sweden (sixth place on the top list). Excluding methenamine would result in even higher differences in the antibiotic utilization of the two countries.

Conclusion

The scale and pattern of elderly ambulatory antibiotic use differed between Hungary and Sweden. Some of the observed differences could be explained by the different health statuses between the two populations; however, data suggest that interventions are needed to optimize antibiotic use in the elderly in Hungary.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: Aggregated datasets (without age, gender) is publicly available, while more detailed should be requested from the National Health Fund (NEAK). Requests to access these datasets should be directed to www.neak.gov.hu.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

Conceptualization: MM, RB, MH, IK, RB; methodology, formal analysis, software, RB and MM; investigation, RB and MM, data curation, validation, MH, EH, and AV; writing—original draft preparation, IK; writing—review and editing, IK, MM, RB, and MB; and funding acquisition, DC. writing: RB, RR, IK, writing, review, editing: MM, RB, EH, ÁV, PD, MB, EZ, DC. All authors have read and approved the final version of the manuscript.

Funding

This work has been implemented with the support provided by the Ministry of Innovation and Technology of Hungary from the National Research, Development and Innovation Fund, financed supported by ITM NKFIA TKP2021-EGA-32. RB was supported by The János Bolyai Research Scholarship of the Hungarian Academy of Science.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 01 December 2022
DOI 10.3389/fphar.2022.1047387

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Drugs Outcomes Research and Policies, a section of the journal Frontiers in Pharmacology

RECEIVED 18 September 2022
ACCEPTED 22 November 2022
PUBLISHED 01 December 2022

CITATION
Choi E, Kim S and Suh HS (2022), Exploring the prevalence and characteristics of adverse drug events among older adults in South Korea using a national health insurance database. *Front. Pharmacol.* 13:1047387. doi: 10.3389/fphar.2022.1047387

Exploring the prevalence and characteristics of adverse drug events among older adults in South Korea using a national health insurance database

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Background: Adverse drug events (ADEs) in the elderly frequently occur because of their multiple chronic diseases and complexity of drug therapy. To better understand adverse drug events, the prevalence and characteristics of adverse drug events in elderly South Korean patients were assessed.

Methods: The National Health Insurance databases for 2015 and 2016 were used for the analysis. We included patients aged ≥65 years that had at least one claim with the diagnosis codes 'drug-induced,' 'poisoning by drug,' and 'vaccine-associated' each year for the base-case analysis. To minimize the underestimation of adverse drug event prevalence, we also used an extended definition analysis by adding the 'adverse drug event very likely' codes. We estimated the prevalence of adverse drug events by sex, age group, and type of insurance and examined the frequent types of adverse drug events in 2015 and 2016.

Results: In the base-case analysis, adverse drug event prevalence in individuals aged 65 years and older was 2.75% in 2015 and 2.77% in 2016. With advanced age, the prevalence of adverse drug event tended to increase, peaking in the age group of 75–79 years. In addition, the adverse drug event prevalence was higher in females and Medical Aid enrollees. The most frequently occurring adverse drug event was 'allergy, unspecified,' followed by 'other drug-induced secondary parkinsonism,' and 'generalized skin eruption due to drugs and medicaments.' When we examined the extended definition analysis, the prevalence of adverse drug events was 4.47% in 2015 and 4.52% in 2016, which significantly increased from those estimated in the base-case analysis.

Conclusion: Among the older adults, the prevalence of adverse drug event was higher in advanced age, females, and Medical Aid enrollees. In particular, allergy and drug-induced secondary parkinsonism frequently occurred. This study provides evidence that health policies addressing the prevention and management of adverse drug events should be a priority for the most vulnerable elderly patients.

KEYWORDS

adverse drug event, prevalence, drug safety, elderly, female, diagnosis codes

Introduction

Adverse drug events (ADE) are untoward complications that may occur during drug therapy (Nebeker et al., 2004). Bates et al. defined an ADE as any injury resulting from drug-related medical interventions, including medication errors (Bates et al., 1997). ADE is a broad spectrum of definitions compared with an adverse drug reaction (ADR), which is harmful and unintended consequences, occurring at appropriate use of drugs (Nebeker et al., 2004). Because nearly half of ADEs come from medication errors and can be prevented, only considering the effect of medications normally used underestimates the problem (Bates et al., 1995; Lghoul-Oulad Saïd et al., 2020).

ADEs are an essential public health issue that contribute to morbidity and a considerable economic burden on healthcare resources (Bates et al., 1995; Bates et al., 1997; Classen et al., 1997). According to a review of forty-seven European studies, hospital admissions due to ADRs, a subset of ADEs, were 3.6%, and the occurrence of ADRs during the hospital stay was 10.1% (Bouvy et al., 2015). The costs associated with ADEs in two tertiary care hospitals were estimated at $5.6 million annually, even in the late 1990s (Bates et al., 1997).

In particular, elderly patients are at high risk of ADEs because they have altered drug metabolism, have more chronic diseases, and take several medications (Field et al., 2004; Pedrós et al., 2014). For example, in South Korea, 86.4% of those aged 65 years or above had polypharmacy, defined as the concurrent use of six or more medications per person (Kim H. et al., 2014). Furthermore, a large meta-analysis reported that hospital admission related to ADR in the elderly was four times higher than in younger adults (Beijer and de Blaey, 2002). Therefore, efforts to improve patient safety in the elderly by reducing ADEs are a public health priority (Bates et al., 2009).

Despite the widespread recognition that ADEs are common in elderly patients and extensive epidemiological studies being conducted in Western countries (Field et al., 2004; Passarelli et al., 2005; Alhawassi et al., 2014; Friedman et al., 2015), the prevalence of ADEs and their characteristics have not been well described in the Asian population, including those in South Korea (Leendertse et al., 2010). Moreover, although a few studies have estimated the prevalence of ADEs in South Korea using medical chart reviews and spontaneous reporting (Koo, 2009; Shin et al., 2009; Yu et al., 2015), these studies lack generalizability because the study populations were limited. Several studies have suggested that claims data provide a complementary and alternative method for detecting ADEs with other monitoring systems, such as chart reviews, voluntary reporting, and computerized surveillance (Hougland et al., 2006; Miguel et al., 2013; Kuklik et al., 2017; Digmann et al., 2019). South Korea has a single National Health Insurance program; all populations are covered under this program, approximately 50 million people. The Health Insurance Review and Assessment (HIRA) database contains not only individual insurance information but various health information, including diseases, symptoms, and prescribed medication (Kim et al., 2017). It provides healthcare coverage to all outpatient and inpatient services. Therefore, we conducted this population-based study using a National Health Insurance database to assess the prevalence of ADEs in elderly patients and identify the types of ADEs that occurred in South Korea. We compared the annual prevalence of ADEs and examined patterns of prevalence by sex, age group (65–69, 70–74, 75–79, and ≥80 years), and type of insurance.

Materials and methods

Data source

We conducted a descriptive, retrospective study using Health Insurance Review and Assessment Service-National Patient Sample (HIRA-NPS) claims data from 2015 to 2016. The HIRA-NPS claims data are available from the Health Insurance Review and Assessment Service through a formal request for research purposes (Kim et al., 2017). The HIRA-NPS data are designed to approximate a 3% stratified sample (approximately 1,400,000 persons) of the entire population enrolled in the National Health Insurance (NHI) or Medical Aid (MA) program each year (Kim H et al., 2014). The Patient Sample data was generated systematically by probabilistic sample extraction method using stratified sampling with a total of 32 strata based on sex (2 strata) and age (16 strata) (Kim H et al., 2014). South Korea has a government-run mandatory national health security program consisting of NHI and MA program enrollees. The NHI program is a wage-based, contributory insurance program covering approximately 96% of the population, while the MA program is a government-subsidized public assistance program for low-income and medically indigent individuals (Song, 2009). The patient sample database confirmed the representativeness of the entire South Korean population through a validity test (Kim et al., 2013).

The HIRA-NPS data are cross-sectional, and different patients were selected for the sample data each year for their privacy; therefore, it is not possible to follow an individual over the years (Kim et al., 2017). The data contain each patient's unique encrypted identification number, age, sex, type of

TABLE 1 Definitions of diagnosis codes and examples of adverse drug events.

Classification	Definition	Examples of diagnosis codes[1)]	
		ICD-10 code	Description
Drug-induced	The ICD-10 code description includes 'induced by drug'	G25.1	Drug-induced tremor
	The ICD-10 code description includes 'induced by drug or other causes'	I42.7	Cardiomyopathy due to drugs and other external agents
Poisoning by drug	The ICD-10 code description includes 'poisoning by drug'	T36	Poisoning by systemic antibiotics
	The ICD-10 code description includes 'poisoning by or harmful use of a drug or other causes'	F55	Abuse of non-dependence-producing substances
Vaccine-associated	Vaccine-associated adverse event	A80.0	Acute paralytic poliomyelitis, vaccine-associated
ADE very likely	Adverse drug event deemed to be very likely although the ICD-10 code description does not refer to a drug	A04.7	Enterocolitis due to *Clostridium difficile*

ADE, adverse drug event; ICD-10, *International Classification of Diseases, 10th Revision*.
[1]A full list of diagnosis codes is listed in Supplementary Material.

insurance, diagnosis, and prescription drugs, which provide valuable resources for healthcare service research (Kim L et al., 2014b). Diagnoses were encoded in accordance with the *International Classification of Diseases, 10th Revision* (ICD-10).

Study participants and definition of adverse drug events

To be included in this study, participants with ADEs needed to be aged ≥65 years and have at least one NHI or MA claim record of outpatient, inpatient, or emergency department services with an ADE diagnosis code from the HIRA-NPS in 2015–2016. According to the prevalence-based approach, patients had both new and pre-existing cases of ADEs each year (Kim Y et al., 2013).

We selected diagnosis codes for ADEs from a previous systematic review to identify ADEs in the claims data (Hohl et al., 2014). The ADE diagnosis codes include the phrase or meaning 'drug-induced,' 'poisoning by drug,' and 'vaccine-associated.' These codes directly describe the drug's relevance to a symptom or disease.

Furthermore, to minimize the underestimation of the prevalence of ADEs, we added 'ADE very likely' codes to comprehensively capture ADEs from the claim records (Hohl et al., 2014). Diagnosis codes associated with 'ADE very likely' do not refer to a drug in the diagnosis code description. However, they are probably associated with drug use, according to a causality assessment by clinical experts in a previous study (Hohl et al., 2014). For the analyses, 586 codes, together with sub-codes, were used to identify ADEs, including 'drug-induced,' 'poisoning by drug,' 'vaccine-associated,' and 'ADE very likely.' The diagnosis codes and descriptions of the ADEs are presented in Table 1 and Supplementary Table S1, respectively.

Statistical analysis

We estimated the annual prevalence of ADE as the number of patients with ADEs divided by the number of the entire HIRA-NPS population each year. The results were expressed as frequency and percentage (%). To evaluate whether the ADE prevalence had changed annually, the differences in the prevalence of ADEs between 2015 and 2016 were analyzed using the Cochran–Armitage trend test.

To better understand patient characteristics associated with the occurrence of ADEs, we also calculated the age-and sex-specific prevalence in each year and compared the prevalence stratified by sex (male, female), age group (65–69, 70–74, 75–79, and ≥80), and type of insurance (NHI, MA) between 2015 and 2016. In order to compare the sex differences, we calculated the female-to-male ratio of prevalence by age group. Chi-square tests were used to compare differences in prevalence between the sexes.

Additionally, we identified the characteristics of ADE each year and compared the differences between the sexes. To determine the frequent types of ADEs, the frequency of each diagnosis code to define ADEs was calculated annually in 2015 and 2016. If a diagnosis code was given repeatedly to a patient, the code was considered to be claimed only once.

Sensitivity analysis was performed to compare the two approaches in defining the patients with ADE. The patients in the base-case group have the diagnosis codes of 'drug-induced,' 'poisoning by drug,' and 'vaccine-associated.' The patients in the extended definition group included base-case patients and those who have the diagnosis codes of 'ADE very likely.' The chi-square test was used to compare the results of the base-case and extended definition analyses.

Statistical analysis was performed using the SAS software (version 9.4; SAS Institute Inc., Cary, NC, United States). Statistical significance was set at $p \leq 0.05$.

TABLE 2 Prevalence of adverse drug events by sex, age group, and type of insurance.

	2015			2016			*p*-value[1)]
	Male	Female	Overall	Male	Female	Overall	
No. Claims	6,914	12,311	19,225	7,359	11,809	19,168	
No. Events	2,112	3,388	5,500	2,253	3,495	5,748	
No. Patients	2,012	3,245	5,257	2,171	3,344	5,515	
Prevalence (%)							
Overall	2.53	2.91	2.75	2.61	2.89	2.77	0.6460
Age group							
65–69	2.18	2.88	2.54	2.43	2.94	2.69	0.1015
70–74	2.69	2.93	2.82	2.64	2.92	2.80	0.8088
75–79	2.86	3.35	3.15	2.79	3.26	3.07	0.4899
≥80	2.63	2.51	2.55	2.74	2.49	2.57	0.8556
Type of insurance							
NHI program	2.49	2.84	2.69	2.57	2.84	2.72	0.5054
MA program	3.28	3.68	3.56	3.29	3.45	3.40	0.4548

NHI, national health insurance; MA, medical aid.
[1]*p*-value from Cochrane-Armitage test for trend of overall prevalence.

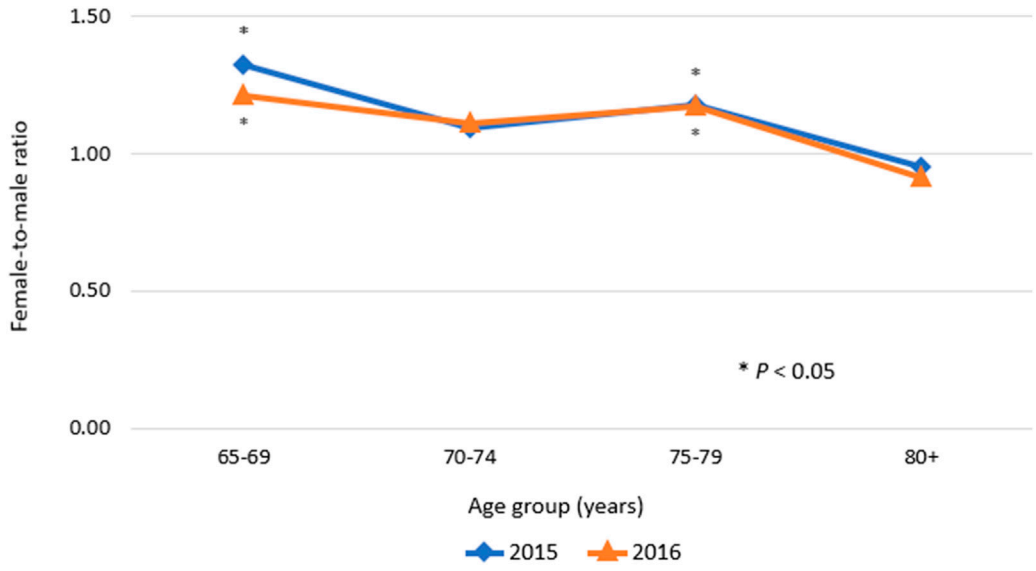

FIGURE 1
Female-to-male ratio of prevalence of adverse drug event.

Results

Based on the base-case analysis, 5,257 and 5,515 patients aged 65 years and older were identified as having ADEs in 2015 and 2016, respectively (Table 2). The number of adverse events identified in the claims records was 5,500 and 5,748 in 2015 and 2016, respectively.

The prevalence of ADEs was 2.75% and 2.77% in 2015 and 2016, respectively. There was no significant difference in overall prevalence between calendar years. In all age groups and types of insurance, the trends in the annual prevalence were quite similar. In both 2015 and 2016, a higher prevalence was observed with increasing age, with the peak prevalence observed in the age group of 75–79 years and a higher

TABLE 3 Most frequent type of adverse drug events in 2015–2016.

ICD-10 codes	Code description	No. Events (%)			
		2015		2016	
T78.4	Allergy, unspecified	2,156	(39.20)	2,261	(39.34)
G21.1	Other drug-induced secondary parkinsonism	333	(6.05)	391	(6.80)
L27.0	Generalized skin eruption due to drugs and medicaments	312	(5.67)	343	(5.97)
L23.3	Allergic contact dermatitis due to drugs in contact with skin	247	(4.49)	239	(4.16)
T88.7	Unspecified adverse event of drug or medicament	178	(3.24)	183	(3.18)
E27.3	Drug-induced adrenocortical insufficiency	164	(2.98)	163	(2.84)
L27.1	Localized skin eruption due to drugs and medicaments	148	(2.69)	166	(2.89)
E24.2	Drug-induced Cushing's syndrome	146	(2.65)	151	(2.63)
Y45.3	Drugs, medicaments and biological substances causing adverse effects in therapeutic use - Analgesics, antipyretics and anti-inflammatory drugs	133	(2.42)	132	(2.30)
T78.2	Anaphylactic shock, unspecified	121	(2.20)	140	(2.44)
T78.3	Angioneurotic oedema	113	(2.05)	125	(2.17)
L27.9	Dermatitis due to unspecified substance taken internally	108	(1.96)	114	(1.98)
G25.1	Drug-induced tremor	106	(1.93)	104	(1.81)
M81.4	Drug-induced osteoporosis without pathological fracture	92	(1.67)	102	(1.77)
L27.8	Dermatitis due to other substances taken internally	79	(1.44)	87	(1.51)
L24.4	Irritant contact dermatitis due to drugs in contact with skin	58	(1.05)	70	(1.22)
Others		1,006	(18.29)	977	(17.00)
Total		5,500	(100)	5,748	(100)

ICD-10, *International Classification of Diseases, 10th Revision*.

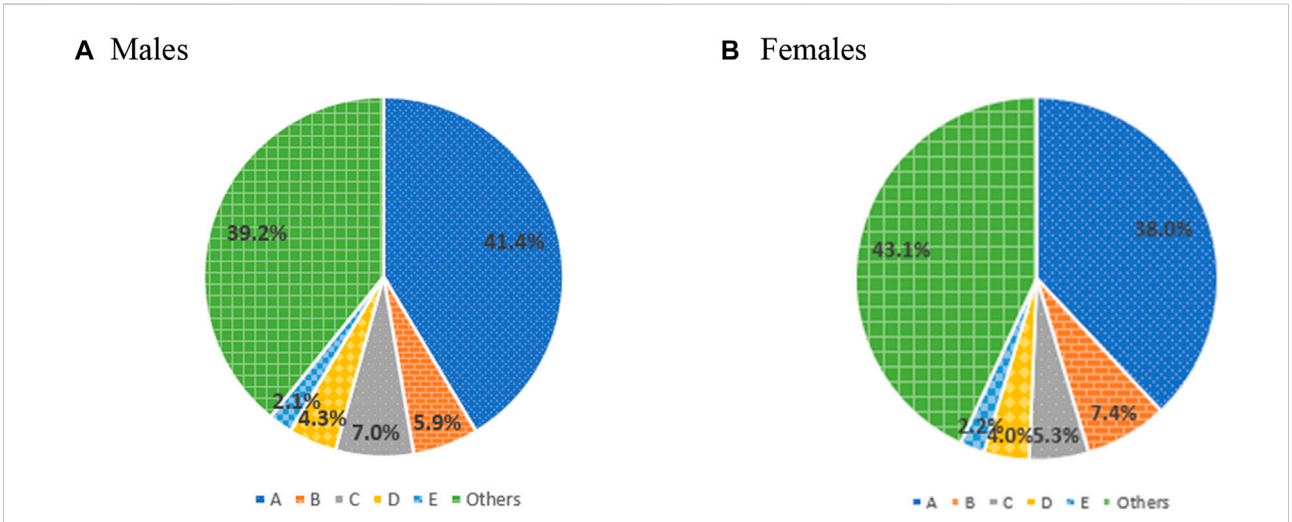

FIGURE 2
Prevalence of frequent type of adverse drug events by sex. A, allergy, unspecified; B, other drug-induced secondary parkinsonism; C, generalized skin eruption due to drugs and medicaments; D, allergic contact dermatitis due to drugs in contact with skin; E, unspecified adverse event of drug or medicament.

prevalence in females. The female-to-male ratio of prevalence of ADEs was significantly higher than 1.0 in the age group of 65–69 years and the age group of 75–79 years ($p < 0.05$; Figure 1). In contrast, in the over-80 age group, a higher prevalence of ADEs was observed in males compared with females. In addition, in both men and women, the prevalence

TABLE 4 Prevalence of adverse drug events by definition study population.

	Base-case		Extended definition		*p*-value[1)]
	2015	2016	2015	2016	
No. Claims	19,225	19,168	27,878	28,401	
No. Events	5,500	5,748	9,156	9,607	
No. Patients	5,257	5,515	8,556	8,991	
Prevalence (%)	2.75	2.77	4.47	4.52	<0.0001

[1]*p*-value from chi-square test between base-case and extended-definition estimates.

of ADEs was higher in MA program enrollees compared with NHI program enrollees.

During the study period, the most common ADEs were 'allergy, unspecified,' followed by 'other drug-induced secondary parkinsonism,' and 'generalized skin eruption due to drugs and medicaments' (Table 3). The patterns in the characteristics and frequencies of ADEs were comparable to 2015 and 2016. Notably, 'other drug-induced secondary parkinsonism,' the second most common ADE, illustrated a higher distribution in females than in males (Figure 2).

Using the extended definition of ADEs to minimize underestimation, the prevalence of ADEs increased significantly ($p < 0.0001$; Table 4). According to the extended definition analysis, the prevalence of ADE was 4.47% and 4.52% in 2015 and 2016, respectively, which increased by approximately 60% compared to the estimates of base-case analysis.

Discussion

In this study, we estimated the prevalence of ADEs in people aged 65 years or older in South Korea using the nationally representative claims data. We also examined whether the prevalence of ADEs changed by comparing the prevalence each year and identified the types of ADEs that occurred during the study period.

Based on the HIRA-NPS database, the base-case analysis in our study found that the estimated prevalence of ADEs for those aged 65 years or above in 2015 and 2016 were relatively lower than those reported in other countries. A study using data from a national survey in the United States reported that visits to emergency departments and outpatient clinics related to ADEs were 48.8 per 1,000 persons between 2001 and 2005 (Bourgeois et al., 2010). A systematic review that included fourteen observational studies reported that the prevalence of ADR, a subset of ADE, was 11.0%, ranging from 5.8% to 46.3% (Alhawassi et al., 2014). However, our estimates are significantly higher compared with a previous study that reported ADE prevalence among patients aged 65 years and older who visit an emergency department in a tertiary-care hospital in South Korea was 0.45% (Lee, 2015).

Based on a previous systematic review of sixty-eight studies (Beijer and de Blaey, 2002), our results supported that the prevalence of ADEs increases with age. This is in line with a recent systematic review of thirty-three studies that reported patients aged ≥65 years showed the highest prevalence of ADEs (Insani et al., 2021). Because elderly patients usually have many underlying diseases leading to polypharmacy, they are at risk of ADEs (Hajjar et al., 2007; Atella et al., 2019; Khezrian et al., 2020). According to a previous study, the potential preventability of hospital admission related to medication in elderly patients was approximately twice that in younger patients (Lghoul-Oulad Saïd et al., 2020). Therefore, elderly patients are imperative target populations for effective intervention strategies to prevent ADEs.

Concerning sex differences, we observed that females had a significantly higher prevalence of ADEs than males. This finding is consistent with the results of several other studies (Martin et al., 1998; Zopf et al., 2008; Bourgeois et al., 2010; Kane-Gill et al., 2010; Hofer-Dueckelmann et al., 2011; Wu et al., 2012). For example, an observational study including all patients admitted to an internal hospital in Austria over 6 months reported that more females than males experienced ADEs, particularly elderly (10% vs 6%, $p < 0.005$) (Hofer-Dueckelmann et al., 2011). The potential reasons for the differences in ADE prevalence by sex can be explained by differences in pharmacokinetics, pharmacodynamics, and drug utilization patterns (Tran et al., 1998; Zucker and Prendergast, 2020).

Patients enrolled in the MA program had a higher prevalence of ADEs than those in the NHI program. This might be related to excessive healthcare resource use and polypharmacy among MA program enrollees (Kim H. et al., 2014; Suh et al., 2014). Previous studies comparing individuals with NHI coverage and those with MA coverage for healthcare utilization revealed that MA program enrollees showed more frequent outpatient visits and hospital admissions (Lee et al., 2020). In addition, Kim et al. reported significant associations between polypharmacy and the lower-income MA population (Kim L et al., 2014). A possible reason for the excessive use of medical services and polypharmacy in the MA program enrollment is that they are not required to provide co-payments for almost all healthcare utilization (Suh et al., 2014; Lee et al., 2020). Furthermore, previous studies have reported that polypharmacy is a significant risk factor for ADEs because of the increased possibility of drug-drug interactions and inappropriate drug use (Onder et al., 2002; Field et al., 2004; Steinman et al., 2006; Rashed et al., 2012). Therefore, quality improvement, such as drug utilization review programs, is recommended to prevent meaningful drug-drug interactions and duplicate prescriptions (Aparasu et al., 2005).

In the present study, allergy and skin manifestations were the most frequent ADEs identified in the claims data. This finding is consistent with a previous result based on a spontaneous report

conducted in South Korea (Shin et al., 2009). However, the characteristics of ADEs in our study differed from those in other countries. For example, in a retrospective study examining ADR-related hospital admissions at a single hospital in Thailand, 'drug-induced neutropenia' was the most common (Siltharm et al., 2017). Another study conducted in England, Germany, and the United States revealed that 'Enterocolitis due to *Clostridium difficile*' was the most frequent type of ADEs (Stausberg, 2014).

Notably, the second most common ADE was 'other drug-induced secondary parkinsonism,' which more frequently occurred in females. An observational study in South Korea reported that females and the elderly showed a high prevalence and incidence of drug-induced secondary parkinsonism (Han et al., 2019). Antipsychotics and gastrointestinal motility drugs are frequently associated with drug-induced secondary parkinsonism (Shin and Chung, 2012; López-Sendón et al., 2013; Kim et al., 2019; Kim and Suh, 2019). It is essential to bear in mind that physicians and other healthcare providers frequently overlook the presence of drug-induced parkinsonism because it is challenging to differentiate drug-induced parkinsonism from idiopathic Parkinson's disease (Hansen et al., 1992). Recovery after the withdrawal of causal drugs may take several years, and clinical deficits might be progressive and persistent in some cases. Therefore, based on our results, effective intervention to prevent drug-induced secondary parkinsonism would be a critical component of ADE management for the elderly.

Because ADEs are expressed as various signs, symptoms, or diseases, it is difficult to identify an ADE based on the diagnosis codes from the claims record. Therefore, to improve the detection of ADE cases, two approaches by different ADE definitions were used in this study: the base-case and extended definition groups. From the base-case analysis of patients, the number of patients identified according to the extended definition of ADEs increased significantly. In a previous study, the reported prevalence of ADEs varied depending on the operational definition of events, as well as specific aspects such as the study setting, study population, and data collection methods (Leendertse et al., 2010). Stausberg and Hasford studied the prevalence of ADEs using more broad definitions of diagnosis codes, including 'ADE likely' and 'ADE possible,' which were less associated with drug use than 'ADE very likely.' According to their definitions of ADEs, the prevalence of drug-related hospital admission and hospitalization considerably differed, ranging from less than 1%–37.6% (Stausberg and Hasford, 2011). However, data estimates are possibly uncertain because validity and reliability could not be assessed owing to limited information from the claims data; thus, careful interpretation is needed to understand these results.

To the best of our knowledge, this study provides the first comprehensive estimate of the prevalence of ADEs in the elderly in the Asian population using claims data. Our results are representative because the HIRA-NPS claims data provide reliability, and valid information for the entire population of South Korea. Furthermore, various ADEs are identified through the broader focus of adverse events, including the consequences of inappropriate drug use, even though our results are conservative because study participants are limited due to our operational definitions of ADEs.

This study had several limitations, including the potential underestimation of ADEs. First, not all ADEs could be identified due to the limitations of the diagnosis codes. Not all ADEs can be searched using the codes, including the phrases 'drug-induced,' 'poisoning by drug,' 'vaccine-associated,' or even 'ADE very likely,' because ADE codes could not cover all potential illnesses or symptoms caused by drugs. Moreover, patient-reported adverse events or abnormalities in laboratory results related to drugs were not recorded because of the limited clinical information available in the claims data. Second, physician under-reporting could account for the low estimate of ADE prevalence. Although physicians are obligated to monitor patients' ADEs during their practice, a significant proportion do not report ADEs (Dormann et al., 2003). Several reasons for not reporting ADEs include a lack of time due to stressful environments, uncertainty about the drug causing the ADE, difficulty in accessing reporting systems, and lack of awareness of the need to record that ADEs have occurred (Hazell and Shakir, 2006). Third, we included only study participants with at least one claim-encoded ADE diagnosis code. However, most ADEs are mild; thus, a substantial number of patients may not seek medical care for minor signs or symptoms caused by drugs. Fourth, the possible drugs associated with ADEs could not be determined using claims data because of the limited clinical information available and the retrospective study design. Fifth, the 2-year study period may be insufficient to understand any trends in ADE prevalence. Sixth, we did not analyze ADE prevalence in different clinical settings. Further studies are needed to understand the prevalence of ADE in outpatient, inpatient, and emergency departments. Lastly, it was not recent data that we used in this study. Therefore, our study results may not reflect current estimates. However, after 2016, several diagnosis codes classified as sensitive information were not provided in the HIRA-NPS database. Therefore, we used the 2015 and 2016 database, the most recent database that we could fully identify all diagnosis codes.

Conclusion

This study using the representative claims data provided comprehensive estimates of ADE prevalence and

characteristics among the elderly in South Korea. Due to the extended life expectancy, the prevalence of ADEs is expected to grow continuously. The results of our study suggest that more efforts will be needed to prevent ADE in the elderly. National healthcare policy, such as regulatory intervention for polypharmacy and educational program, is required to reduce ADE for vulnerable people, especially in MA program enrollees. To effectively prevent and manage ADEs, further studies are needed to explore potential drugs that cause ADEs.

Data availability statement

The datasets presented in this article are not readily available because this study used the Health Insurance Review and Assessment Service-National Patient Sample (HIRA-NPS) 2015 and 2016 database in South Korea. Data were obtained from the HIRA with permission.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Board of the Pusan National University (PNU IRB/2020_152_HR). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

Conceptualization, EC, SK, and HS; methodology, EC, SK, and HS; software, EC and SK; validation, EC and SK; formal analysis, EC and SK; investigation, EC, SK, and HS; resources, EC and HS; data curation, EC and SK; writing—original draft preparation, EC, SK, and HS; writing—review and editing, SK and HS; visualization, EC, SK, and HS; supervision, HS; project administration, HS; funding acquisition, HS All authors have read and agreed to the published version of the manuscript.

Funding

This research was supported by a grant (21153MFDS601) from Ministry of Food and Drug Safety in 2022. This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (No. 2020R1F1A1069526).

Acknowledgments

We used Health Insurance Review and Assessment Service-National Patient Sample 2015 (HIRA-NPS-2015-0199) and 2016 (S20211228748); however, we declare that the results do not reflect the positions of either the Health Insurance Review and Assessment Service or the Ministry of Health and Welfare in Korea.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.1047387/full#supplementary-material

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frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 13 January 2023
DOI 10.3389/fphar.2022.1029067

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Drugs Outcomes Research and Policies, a section of the journal Frontiers in Pharmacology

RECEIVED 26 August 2022
ACCEPTED 23 December 2022
PUBLISHED 13 January 2023

CITATION
Cahir C, Curran C, Walsh C, Hickey A, Brannigan R, Kirke C, Williams DJ and Bennett K (2023), Adverse drug reactions in an ageing PopulaTion (ADAPT) study: Prevalence and risk factors associated with adverse drug reaction-related hospital admissions in older patients. *Front. Pharmacol.* 13:1029067. doi: 10.3389/fphar.2022.1029067

Adverse drug reactions in an ageing PopulaTion (ADAPT) study: Prevalence and risk factors associated with adverse drug reaction-related hospital admissions in older patients

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Background: Older people experience greater morbidity with a corresponding increase in medication use resulting in a potentially higher risk of adverse drug reactions (ADRs).

Objectives: The aim of this study was to; 1) determine the prevalence and characteristics of ADR-related hospital admissions among older patients (≥65 years) in Ireland; and 2) identify the risk factors associated with ADR-related hospital admissions.

Methods: A cross-sectional study of ADR prevalence in patients aged ≥65 years admitted acutely to hospital in Ireland over a 8 month period (November 2016- June 2017). A multifaceted review of each hospital admission was undertaken to assess the likelihood of an ADR being a reason for admission (cause of admission or contributing to admission) in the context of the patient's medication, clinical conditions, comorbidities and investigations. A number of decision aids were applied by two independent reviewers to assess ADR causality, avoidability and severity. A random sample of patients, determined not to have a suspected ADR on screening, were assigned to a non-ADR control group. Multivariable logistic regression was used to assess the association between potential risk factors for ADR-related admissions compared with non-ADR-related admissions.

Results: In total, 3,760 hospital admission episodes (in 3,091 patients) were screened and 377 admissions were considered ADR-related (10.0%, 95% CI 9.1%, 11.0%). 219 (58.1%) ADR-related admissions were caused by an ADR, while ADRs contributed to 158 (41.9%) admissions. 268 (71.1%) of all ADR-related admissions were deemed definitely or possibly preventable/avoidable. 350 (92.8%) ADRs were classified as being of moderate severity, with 27 (7.2%) classified as severe. Antithrombotic agents, mainly aspirin and warfarin, were the drugs most frequently associated with ADR-related admissions (gastrointestinal and vascular haemorrhagic disorders). In

multivariable analysis, immobility, frailty, having delirium or ulcer disease and taking anticoagulant and antiplatelet medication on admission were significantly associated with an ADR-related hospital admission.

Conclusion: One in ten hospital admissions, among those aged 65 + years, were considered ADR-related, with approximately 70% potentially avoidable. Reliable and validated ADR detection and prediction tools are needed to develop prevention strategies.

KEYWORDS

adverse drug reaction, older people, hospital admission, medication, risk factors

Introduction

An adverse drug reaction (ADR) is defined as 'an appreciably harmful or unpleasant reaction resulting from an intervention relating to the use of a medicinal product' (Edwards and Aronson, 2000). Older people experience greater morbidity, increased medication utilisation and a variety of physiological changes affecting the pharmacokinetics and pharmacodynamics of medications and are therefore at an increased risk of ADR-related hospital admissions (Franceschi et al., 2008; Lehnert et al., 2011). Two systematic reviews have suggested a median ADR-related hospital admission rate of 10% and 11%, respectively, in those aged ≥65 years (Kongkaew et al., 2008; Alhawassi et al., 2014). A meta-analysis of observational studies measuring hospitalisations due to ADRs found one in ten hospital admissions of older patients to be due to an ADR (Oscanoa et al., 2017). However both reviews and the meta-analysis have reported wide variation in ADR prevalence rates, ranging from 5% to 50%, with heterogeneity in how ADRs are defined and identified given as the principle reason for much of this variability (Alhawassi et al., 2014).

ADRs are difficult to identify in older populations and hospital reporting systems significantly under-report the incidence of ADRs resulting in unreliable estimates of ADR-related hospital admissions in older populations (Waller et al., 2004; Sari et al., 2007). A prospective review classified 15% of medical admissions to be ADR-related in older people, compared with 2.7% in the same patient cohort using administrative coding (Parameswaran Nair et al., 2017). To accurately detect ADRs, a number of methods are required including an in-depth medical record review and a causality assessment between the drug and the adverse clinical event (Williams et al., 2008).

While studies have been performed in the United Kingdom, Europe and the United States, there is limited data published on the prevalence and characteristics of ADR-related hospital admissions in older people in Ireland (Kongkaew et al., 2008; Alhawassi et al., 2014; Osanlou et al., 2022). A 4-week study of ADR-related hospital admissions in the general adult population reported a prevalence rate of 8.8%, with over half deemed preventable (Ahern et al., 2014). Internationally studies have indicated that more than half of ADR-related hospital admissions in older patients are preventable with only 19%–28% of ADRs considered unavoidable (Pirmohamed et al., 2004; Franceschi et al., 2008). Identifying the characteristics of ADR-related hospital admissions, including the types of drugs involved and the nature of the harm represents an important gap in knowledge in preventing ADR-related hospital admissions.

Another approach to preventing ADR-related hospital admissions in older patients is to identify those who are most at risk of ADR-related admissions. Previous risk prediction tools have mainly focused on ADRs occurring within the hospital setting and few have been developed for use in community settings (Onder et al., 2010). A systematic review identified age, female gender, increasing comorbid burden and number of medications to be associated with an increased ADR risk in older people in the acute care setting (Alhawassi et al., 2014). However, the list of risk factors investigated was not comprehensive and other factors, such as functional and social factors, may contribute to ADR-related hospitalisation. The aims of our study were to; 1) determine the prevalence and characteristics of ADR-related hospital admissions among older patients (≥65 years) in Ireland; and 2) identify the risk factors associated with ADR-related hospital admissions.

Methods

Study design

This was a cross-sectional study of ADR prevalence in all patients aged ≥65 years admitted acutely to a large tertiary referral hospital in Ireland over a 8 month period (November 2016-June 2017). The study protocol has previously been published (Cahir et al., 2017). Ethical approval was obtained from Beaumont Hospital Ethics Committee (REC 16/49).

ADR screening

All admitted patients were screened for a suspected ADR-related hospital admission within the first 36 h of admission by the research team (Consultant Geriatrician (CCu), two hospital pharmacists (CW, CB)) and a research nurse (ML)) using a previously validated screening process (Pirmohamed et al., 2004; Hopf et al., 2008). Patients were excluded if they were transferred from other hospitals, were elective non-acute admissions or aged under 65 years. The screening approach incorporated a multifaceted review of each hospital admission to assess the likelihood of the ADR being a reason for admission (cause of admission or contributing to admission) in the context of the patient's medication, clinical conditions, medical history, comorbidities and investigations. A number of independent sources were consulted to verify the patient's medication history, including the patient's self-reported medication list, pharmacist medication list and general practitioner (GP) medication list. The medication list included recently discontinued or short-course medications, over-the-counter (OTC) medications and herbal preparations as part of the medication reconciliation process. A random sample of patients, who were determined not to have a suspected ADR on screening, were

assigned to a non-ADR control group for comparative purposes. These patients were randomised to the non-ADR control group from the hospital admission list, which detailed patients' chronological order of hospital admission on each day for those aged ≥65 years, using randomisation software http://www.randomization.com.

ADR characteristics

Two members of the research team (CCu and CW or CB) independently applied a number of decision aids and validated algorithms to assess the causality, preventability and severity of each ADR. ADR causality was determined using the World Health Organisation (WHO) criteria, the Naranjo criteria and the Liverpool Algorithm (Naranjo et al., 1981; WHO, 2005; Gallagher et al., 2011). The Hallas criteria were used to categorise the avoidability/preventability of the ADRs (Hallas et al., 1990). ADR severity was classified using the Hartwig severity assessment scale (Hartwig et al., 1992). Differences in causality, preventability and severity between the two reviewers were reviewed by an independent third reviewer (DW; Clinical Pharmacologist). The nature of the reaction was reported using the Medical Dictionary for Regulatory Activities (MedDRA) terminology (WHO, 2005). The details of all medications involved in the ADR-related hospital admission were recorded using the WHO Anatomical Therapeutic Chemical (ATC) codes.

Risk factors associated with ADR-related hospital admissions

A number of potential risk factors for an ADR-related hospital admission were measured as part of the ADR screening process on hospital admission. They were categorised as (Edwards and Aronson, 2000); sociodemographic-related risk factors (Franceschi et al., 2008); functional ability-related risk factors (Geriatric syndromes) (Lehnert et al., 2011); disease-related risk factors and (Kongkaew et al., 2008); medication-related risk factors. Sociodemographic risk factors included age, gender and medical card status (Yes/No). Medical card eligibility is means-tested and entitles the individual to free or substantially-subsidised healthcare (Sinnott et al., 2017). Functional ability-related risk factors (Geriatric syndromes) included measures of mobility, functional impairment, falls, frailty, delirium, urinary incontinence (Yes/No), unintentional weight loss in the previous 6 months (Yes/No) and nursing home residency (Yes/No) (Cahir et al., 2017). Patients self-reported if they were immobile (Yes/No), their level of mobility (use of walking aids when crossing a room and when outside), if they had a functional impairment and their falls history (fallen previously, fallen in the last year, fallen more than once). Frailty was assessed using the Triage Risk Screening Tool (Fan et al., 2006) and the PRISMA-7 (Hebert et al., 2010). Delirium was assessed using the 4AT (De et al., 2016) and DSM4 criteria (American Psychiatric Association, 1994). Disease-related risk factors included certain diagnoses (e.g. chronic lung disease, cerebrovascular disease) and comorbidity burden was measured using the Charlson co-morbidity index (Charlson et al., 1987). Medication-related risk factors included number and types of medications, polypharmacy, use of blister packs (Yes/No) and self-reported adherence (Yes/No). Polypharmacy was defined as greater than five medications and excessive polypharmacy as greater than 10 (Dwyer et al., 2016).

Data analysis

Prevalence and characteristics of ADR-related hospital admissions

Descriptive statistics, including median (inter-quartile range (IQR), percentages and frequencies, as appropriate, with 95% confidence intervals (CIs), were used to summarise the results of the prevalence of ADRs, their various classifications (e.g., preventability, severity) and the drug classes involved in ADRs. Cohen's Kappa statistics (κ) were used to measure inter-rater reliability between the two reviewers, on the measures of causality, preventability and severity of each ADR, with interpretation as follows; poor (<0.20), fair (0.20–0.40), moderate (0.41–0.60), good (0.61–0.80), and very good (0.81–1.00). (Altman, 1991). The primary presenting complaint in ADR-related and non-ADR related hospital admissions were compared using chi-square tests for categorical variables, with Bonferroni corrections ($p < 0.003$).

Risk factors associated with ADR-related hospital admissions

Descriptive statistics including means (standard deviation, SD), medians (IQR) and proportions, were calculated for all risk factors. The associations between all risk factors and ADR-related hospital admissions *versus* non-ADR-related admissions were assessed using a multivariable logistic regression model. Adjusted ORs with 95% CIs are presented. The data was analysed using SAS Version 9.4 statistical package and Stata Version 17.0 (StataCorp, College Station, TX, United States). Adjusted ORs with 95% CIs are presented. Significance at $p < 0.05$ is assumed. The data was analysed using SAS Version 9.4 statistical package and Stata Version 17.0 (StataCorp, College Station, TX, United States). Significance at $p < 0.05$ is assumed.

Results

Prevalence and characteristics of ADR-related hospital admissions

A total of 3,760 hospital admission episodes (in 3,091 eligible patients), were screened for an ADR and 377 were determined to be ADR-related (10.0%, 95% CI 9.1%, 11.0%); 41 (10.9%) of these ADR-related admissions were related to ≥2 ADRs ($n = 424$ total ADRs). Of the 377 ADR-related admissions, 219 (58.1%) admissions were caused by an ADR, while ADRs contributed to 158 (41.9%) admissions. For the majority of the ADRs (N = 229, 54.0%) there was no other known acute medical issue that may have contributed to the ADR.

There was moderate agreement between the two reviewers as per the WHO criteria ($\kappa = 0.54$) and good agreement as per the Naranjo criteria (κ = 0.65) and Liverpool Algorithm ($\kappa = 0.71$). There was also good agreement regarding preventability as per the Hallas criteria (κ = 0.73) and very good agreement for severity as per the Hartwig severity assessment scale ($\kappa = 0.98$). Table 1 presents the overall causality of the ADRs according to the three sets of criteria. The majority of ADRs were deemed possible ADRs (66%–77%), with approximately one-fifth

TABLE 1 Classification of ADR causality per the WHO criteria, Naranjo criteria and Liverpool Algorithm (*n* = 424).

	Possible ADR	Probable/likely ADR	Certain/Definite ADR	Unlikely/doubtful ADR
	N (%)	N (%)	N (%)	N (%)
WHO criteria	309 (72.9)	87 (20.5)	26 (6.1)	2 (0.5)
Naranjo criteria	328 (77.4)	87 (20.5)	9 (2.1)	0 (0)
Liverpool Algorithm	281 (66.3)	99 (23.4)	44 (10.4)	0 (0)

TABLE 2 The main classes of drugs associated with ADR-related hospital admissions and the nature of the reaction (*n* = 424).

Therapeutic group (ATC)	N (%)	Main drug substances	N (%) of therapeutic group[a]	Nature of the ADR[b]	N (%) of therapeutic group[a]
Antithrombotic agents (B01)	141 (33)	Aspirin	77 (55)	Gastrointestinal –haemorrhage and inflammatory conditions	70 (50)
		Warfarin	28 (20)	Vascular- haemorrhagic disorders	45 (32)
		Aspirin and Warfarin	19 (13)		
Diuretics (C03)	134 (32)	Furosemide	65 (49)	Renal disorders	62 (46)
		Hydrochlorothiazide	21 (16)	Electrolyte and fluid balance conditions	48 (36)
		Bumetanide	21 (16)	Hypotension and non-specific blood pressure disorders and shock	23 (17)
Agents acting on the renin-angiotensin-aldosterone system (C09)	127 (30)	Ramipril	37 (29)	Renal disorders	56 (44)
		Perindopril	27 (21)	Hypotension and non-specific blood pressure disorders and shock	33 (26)
		Valsartan	18 (14)	Electrolyte and fluid balance conditions	32 (25)
Calcium channel blockers (C08)	28 (7)	Amlodipine	17 (61)	Hypotension and non-specific blood pressure disorders and shock	18 (64)
Beta-blocking agents (C07)	26 (6)	Bisoprolol	18 (69)	Hypotension and non-specific blood pressure disorders and shock	12 (46)
				Cardiac arrhythmia	11 (42)
Psychoanaleptics (N06)	25 (6)	Escitalopram	6 (24)	Electrolyte and fluid balance conditions	13 (52)

[a]Number and percentage of ADRs, associated with a drug substance as a proportion of the overall number of ADRs, associated with the therapeutic drug group during the study period.
[b]The nature of the reaction is reported using Medical Dictionary for Regulatory Activities (MedDRA) terminology and refers to the therapeutic group.

classified as probable/likely ADRs. Forty-three (11.4%) ADRs were deemed definitely preventable/avoidable, 225 (59.7%) possibly preventable/avoidable and 109 (28.9%) unavoidable. In total, 350 (92.8%) ADRs were classified as being of moderate severity, with 27 (7.2%) classified as severe.

Table 2 identifies the most frequent classes of drugs associated with the ADR-related hospital admissions and the nature of the reaction. Antithrombotic agents, mainly aspirin and warfarin, were the drugs most frequently associated with ADR-related hospital admissions with 33% of ADR-related hospital admissions citing gastrointestinal haemorrhage and vascular haemorrhagic disorders as the main adverse reactions. A number of cardiovascular system drugs were associated with ADR-related hospital admissions including diuretics, agents acting on the renin-angiotensin-aldosterone system, calcium channel blockers and beta-blocking agents (ranging from 32% to 6% of ADR-related admissions respectively). These drugs were associated with the adverse reactions of hypotension and non-specific blood pressure disorders, and shock and electrolyte and fluid balance conditions. Psychoanaleptics (6% of ADR-related hospital admissions) were associated with the adverse reactions of electrolyte and fluid balance conditions. Supplementary Table 1 provides further detail on the diagnostic categories associated with ADR-related hospital admissions.

Table 3 compares the primary presenting complaint in ADR-related and non-ADR related hospital admissions. In ADR-related hospital admissions, there was a significantly higher

TABLE 3 Primary presenting complaint at hospital admission (*n* = 814).

Primary presenting complaint at hospitalisation	Total (*n* = 814)	Non-ADR admissions (*n* = 437)	≥1 ADR admissions (*n* = 377)	*p*-value[a]
	N (%)	N (%)	N (%)	
Respiratory disorders	173 (21.3)	110 (25.2)	63 (16.7)	$p < 0.003$[a]
Bleeding disorders	128 (15.7)	12 (2.8)	116 (30.8)	$p < 0.003$[a]
Gastrointestinal disorders	124 (15.2)	36 (8.2)	88 (23.3)	$p < 0.003$[a]
Falls and syncope Syncope	115 (14.1) 57 (9.5)	65 (14.9) 19 (4.4)	50 (13.3) 38 (10.1)	$p = 0.51$ $p < 0.003$[a]
Cardiac disorders Bradycardia Hypotension	107 (13.1) 7 (.9) 17 (2.1)	87 (19.9) 2 (.5) 3 (.7)	20 (5.3) 5 (1.3) 14 (3.7)	$p < 0.003$[a] $p = 0.18$ $p < 0.003$[a]
Renal and urinary disorders	87 (10.7)	45 (10.3)	42 (11.1)	$p = 0.15$
Neurological disorders Stroke	53 (6.5) 12 (1.5)	35 (8.0) 10 (2.3)	18 (4.8) 2 (0.5)	$p = 0.06$ $p = 0.04$
Muscoskeletal disorders	32 (3.9)	27 (6.2)	5 (1.3)	$p < 0.003$[a]
Skin and soft tissue disorders	20 (2.5)	17 (3.9)	3 (0.8)	$p = 0.004$
Endocrine disorders Hypoglycaemia	9 (1.1) 6 (0.7)	1 (.2) 0 (0.0)	8 (2.1) 6 (1.6)	$p = 0.01$ $p = 0.01$
Electrolyte imbalance	9 (1.1)	1 (0.2)	8 (2.1)	$p = 0.01$
Hepatobiliary	8 (1.0)	6 (1.4)	2 (0.5)	$p = 0.88$
Psychiatric disorders	4 (0.5)	2 (0.5)	2 (0.5)	$p = 0.88$
Vascular disorders	4 (0.5)	2 (0.5)	2 (0.5)	$p = 0.88$

[a]Chi-squared test for categorical data with Bonferonni adjustment ($p < 0.003$). Sub-categories of primary presenting complaints at hospitalisation are the more frequent complaints within that category e.g. stroke within neurological disorders.

proportion of bleeding disorders, gastrointestinal disorders and syncope and hypotension compared to non-ADR hospital admissions. There was a significantly higher proportion of respiratory, cardiac and muscoskeletal disorders in the non-ADR group ($p < 0.003$).

There was no significant difference in falls and syncope as a primary presenting issue between ADR-related hospital admissions ($n = 50$, 13.3%) and non-ADR related hospital admissions ($n = 65$, 14.9%) (p = 0.51). Further analysis found that 179 (22.0%) hospital admissions had a fall as a contributing factor (not a primary presenting issue), but again there was no significant difference between ADR-related hospital admissions ($n = 88$, 23.3%) and non-ADR related hospital admissions ($n = 91$, 20.8%) (p = 0.39).

Risk factors associated with ADRs (per patient)

Of the 3,091 patients screened, 361 (11.7% 95% CI 10.5%, 12.8%) patients had an ADR-related admission and 47 (13.0%) of these patients experienced ≥1 ADR-related admission. Table 4 shows the main patient characteristics for the ADR and non-ADR admissions groups. In the unadjusted analysis, factors associated with an ADR-related hospital admission were having a comorbidity of cerebrovascular disease, myocardial infarction or diabetes and anticoagulant, antiplatelet, diuretic or antihypertensive medication use. Increasing age, adherence to medication and patients with a comorbidity of chronic lung disease were less likely to have an ADR-related hospital admission. In the adjusted analysis being immobile or frail, having delirium or ulcer disease and taking anticoagulant and antiplatelet medication on hospital admission were significantly associated with an ADR-related hospital admission. While older age, having state-subsidised healthcare and prescriptions (medical card), having fallen previously and having chronic lung disease were significantly associated with not having an ADR-related hospital admission.

Discussion

Summary of main findings

This study found that 10.0% of hospital admissions in older patients (≥65 years) in a large tertiary referral hospital in Ireland were ADR-related, with 58.1% of these admissions caused by an ADR and ADRs contributing to the remaining admissions. Furthermore, approximately 71% of ADR-related admissions were deemed definitely or possibly preventable/avoidable. Antithrombotic agents,

TABLE 4 Unadjusted and adjusted odds ratios (OR) and 95% CI for risk factor associations with ADR-related hospital admissions and non-ADR admissions (N = 798).

Risk factors	Non-ADR admissions (*n* = 437)	ADR admissions ≥1 (*n* = 361)	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Sociodemographics (N, %)				
Age (mean, SD)	81.6 (7.7)	79.9 (7.3)	0.97 (0.95, 0.99)*	0.96 (0.94, 0.98)*
Age >85 years	153 (35.0)	103 (28.5)	0.74 (0.55, 1.00)	—
Gender- Female	233 (53.1)	184 (51.0)	0.91 (0.69, 1.20)	1.03 (0.73, 1.44)
Medical card (Yes/No)	167 (38.2)	116 (32.1)	0.77 (0.57, 1.03)	0.66 (0.47, 0.92)*
Functional ability -Geriatric syndromes (N, %)				
Immobility (Yes/No)	188 (47.4)	167 (47.9)	1.02 (0.76, 1.36)	2.33 (1.01, 5.38)*
Use of walking aids (inside) (Yes/No)	169 (42.9)	130 (37.3)	1.26 (.94, 1.69)	—
Use of walking aids (outside) (Yes/No)	192 (48.7)	163 (46.8)	1.08 (0.81, 1.44)	—
Functional impairment (Yes/No)	210 (52.9)	168 (48.1)	0.83 (0.62, 1.10)	0.71 (0.44, 1.15)
Falls history				
Fallen- previously (Yes/No)	203 (51.1)	169 (48.4)	0.90 (0.67, 1.20)	0.25 (0.10, 0.64)*
Fallen –in the last year (Yes/No)	132 (30.2)	111 (30.8)	1.08 (0.79, 1.46)	—
Fallen more than once (Yes/No)	61 (15.5)	50 (14.4)	1.09 (0.73, 1.64)	—
Frailty- TRS	224 (56.4)	217 (62.4)	1.28 (0.95, 1.72)	2.51 (1.39, 4.53)*
Frailty- Prisma 7	241 (60.7)	199 (57.0)	0.86 (0.64, 1.15)	—
Delirium (4AT)-Unlikely	143 (35.9)	125 (35.1)	—	—
Possible cognitive impairment	150 (37.7)	120 (33.7)	0.92 (0.65, 1.29)	
Possible delirium ± cognitive impairment	105 (26.4)	111 (31.2)	1.21 (0.84, 1.73)	
Delirium (DSM 4)	100 (25.1)	105 (29.5)	1.25 (0.90, 1.72)	1.63 (1.06, 2.50)*
Urinary incontinence (Yes/No)	4 (1.0)	26 (7.5)	—	—
Unintentional weight loss (Yes/No)	107 (27.0)	74 (21.2)	0.73 (0.52, 1.02)	0.84 (0.57, 1.24)
Nursing home resident (Yes/No)	40 (10.1)	23 (6.6)	0.63 (0.37, 1.07)	0.65 (0.34, 1.25)
Disease-related				
Co-morbidities vs. none				
Chronic lung disease	76 (17.4)	33 (19.1)	0.48 (0.31, 0.74)*	0.51 (0.28, 0.94)*
Heart failure	45 (10.3)	51 (14.1)	1.43 (0.93, 2.20)	1.17 (0.63, 2.16)
Myocardial infarction	38 (8.7)	52 (14.4)	1.77 (1.13, 2.75)*	1.34 (0.73, 2.47)
Diabetes mellitus	7 (1.6)	15 (4.2)	2.66 (1.07, 6.60)*	1.85 (0.63, 5.48)
Chronic liver disease	1 (0.2)	2 (0.6)	—	—
Cancer	3 (0.7)	4 (1.1)	—	—
Dementia	37 (8.5)	25 (6.9)	0.80 (0.47, 1.36)	1.09 (0.53, 2.25)
Cerebrovascular	38 (8.7)	48 (13.3)	1.61 (1.03, 2.52)*	1.48 (0.80, 2.73)
Chronic kidney disease	23 (5.3)	14 (3.9)	0.73 (0.37, 1.43)	0.74 (0.32, 1.71)
Connective tissue disease	18 (4.1)	12 (3.3)	0.80 (0.38, 1.68)	0.92 (0.36, 2.35)
Ulcer disease	8 (1.8)	13 (3.6)	2.00 (0.82, 4.89)	2.94 (1.04, 8.28)*

(Continued on following page)

TABLE 4 (*Continued*) Unadjusted and adjusted odds ratios (OR) and 95% CI for risk factor associations with ADR-related hospital admissions and non-ADR admissions (N = 798).

Risk factors	Non-ADR admissions (*n* = 437)	ADR admissions ≥1 (*n* = 361)	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Charlson weights- 0	81 (18.6)	57 (15.8)	—	—
Charlson weights- 1 and 2	183 (42.0)	152 (42.1)	1.18 (0.79, 1.76)	1.15 (0.64, 2.07)
Charlson weights- ≥3	172 (39.5)	152 (42.1)	1.26 (0.84, 1.88)	0.97 (0.54, 1.76)
Medication-related				
No of medications (IQR)	10	10	1.02 (0.99, 1.05)	—
Polypharmacy				
Non-polypharmacy (≤4 drugs)	64 (14.7)	46 (12.7)	—	—
Polypharmacy (5–9 drugs)	211 (48.3)	164 (45.4)	1.08 (0.70, 1.66)	0.65 (0.37, 1.15)
Excessive polypharmacy (≥10 drugs)	162 (37.1)	151 (41.8)	1.30 (0.84, 2.01)	0.75 (0.38, 1.44)
Types of medication on admission (vs. none)				
Anticoagulants	105 (24.3)	131 (36.3)	1.80 (1.32, 2.45)*	2.00 (1.35, 2.97)*
Antiplatelets	227 (52.0)	227 (62.9)	1.57 (1.18, 2.08)*	1.64 (1.13, 2.38)*
NSAIDs	31 (7.1)	17 (4.7)	0.65 (0.35, 1.19)	0.61 (0.30, 1.24)
Diuretics	99 (22.7)	119 (33.0)	1.68 (1.23, 2.30)*	1.38 (0.95, 1.99)
Anti-hypertensives	318 (72.8)	297 (82.3)	1.74 (1.23, 2.45)*	1.41 (0.93, 2.15)
Sedatives	85 (19.5)	71 (19.7)	1.01 (0.71, 1.44)	1.18 (0.77, 1.78)
Neuroleptics	41 (9.4)	30 (8.3)	0.88 (0.53, 1.43)	0.90 (0.50, 1.64)
Antidepressants	114 (26.1)	98 (27.2)	1.06 (0.77, 1.45)	0.99 (0.66, 1.50)
Anxiolytics	52 (11.9)	35 (9.7)	0.79 (0.51, 1.25)	1.07 (0.60, 1.92)
Use of medications				
Blister pack usage (Yes/No)	155 (35.6)	134 (37.4)	0.92 (0.69, 1.23)	0.93 (0.64, 1.33)
Self-reported adherence (Yes)	436 (100)	336 (93.3)	0.77 (0.67, 0.89)	-

*p-value < 0.05. Use of walking aids, fallen in previous year or more than once, delirium (4AT), number of medications and self-reported adherence were omitted from the multivariable analysis because of collinearity. Urinary incontinence, chronic liver disease and cancer were omitted from the analysis as n < 5 in ADR, or non-ADR, group. 737 patients were included in the multivariable analysis (data were missing at random for 61 patients).

mainly aspirin and warfarin, were the drugs most frequently associated with ADR-related hospital admissions. A number of cardiovascular system drugs and psychoanaleptics were also associated with ADR-related hospital admissions. There was a significantly higher proportion of bleeding disorders, syncope, gastrointestinal disorders and hypotension in ADR-related hospital admissions, compared to non-ADR hospital admissions. Immobility, frailty, delirium, having a comorbidity of ulcer disease and taking anticoagulant and antiplatelet medication on hospital admission were independently associated with an ADR-related hospital admission.

The prevalence of ADR-related hospital admissions, as observed in our study, is higher than that of a previous Irish study (Ahern et al., 2014) but is consistent with other studies, which have reported that approximately 10% of admissions are ADR-related (Kongkaew et al., 2008; Alhawassi et al., 2014). Almost three-quarters of the ADR-related hospital admissions were deemed potentially avoidable which suggests a considerable opportunity to reduce healthcare burden and costs due to ADRs (Pirmohamed et al., 2004). There was good agreement on the assessment of ADR causality among the review panel using three algorithms. Higher inter-rater agreement has been reported when using algorithms *versus* clinical judgement, but no one measure is universally accepted (Agbabiaka et al., 2008).

Medicines which have been particularly implicated in ADR-related hospital admissions include antiplatelets, anticoagulants, NSAIDs, cytotoxics, immunosuppressants, diuretics, antidiabetics and antibiotics (Howard et al., 2007; Coleman and Pontefract, 2016). These medications have a high innate toxicity, particularly in older populations (Howard et al., 2007). A previous study of adverse drug events (ADE) in primary care in Ireland found that 86% of patients prescribed aspirin and warfarin reported bruising, bleeding, and indigestion (Cahir et al., 2019). In the current study, of ADR-related hospital admissions these drugs were associated with gastrointestinal and vascular haemorrhage. In a US study of older adults, gastrointestinal haemorrhage was one of the most frequently reported ADRs (Budnitz et al., 2011), while in the United Kingdom, 20 out of 28 deaths in ADR-related hospital

admissions were due to gastrointestinal or intracranial bleeding (Pirmohamed et al., 2004). Antithrombotic agents such as warfarin need to be carefully monitored and titrated according to the international normalised ratio (INR) in older people to reduce ADR-related hospital admissions (Bloomfield et al., 2011). Consistent with previous studies, cardiovascular and psychotropic drugs contributed to a large number of ADR-related hospital admissions, most commonly renal impairment and electrolyte disturbances (Pedrós et al., 2014; Lucenteforte et al., 2017). In Italy, 39.5% of suspected ADE-related hospitalisations in the older population were related to cardiovascular medications, including beta-blockers, diuretics and renin-angiotensin system inhibitors (Crescioli et al., 2021). To avoid hypotensive episodes, guidelines recommend adopting an individualised holistic approach in deciding on blood pressure targets, particularly in those aged ≥80 years and with significant postural hypotension (Benetos et al., 2019; Kulkarni et al., 2020).

A number of risk factors have previously being identified as associated with ADRs in older populations, including female sex, advanced age, increased disease burden, number of medications and polypharmacy (Alhawassi et al., 2014). In the current study these factors were not significantly associated with ADR-related hospital admissions. Differences in this study in identified risk factors may be due to the cohort comprising of older, frail patients with multiple comorbidities who were prescribed on average ten or more medications. Identifying independent risk factors for ADR-related hospital admissions is particularly challenging as both risk factors and ADRs can present as non-specific symptoms and syndromes that are highly prevalent in older people (e.g. delirium, falls, ulcer disease) (Davies and O'Mahony, 2015). In a US study of long-term care residents, delirium was identified as one of the most common indications of a potential ADE and a trigger for medication rationalisation (Wierenga et al., 2012). On the other hand, polypharmacy has been identified as a risk factor for delirium, but it is unclear which medications or medication combinations are implicated. (Clegg and Young, 2011).

Strengths and limitations

This study is one of the first large scale studies on ADR-related hospital admissions in Ireland. The large sample size enabled the study to establish detailed information on the characterisation of ADRs and related drugs, patient morbidity and functional status from a number of sources. A gold-standard medication reconciliation list was completed, where the patients' medication list was verified by a pharmacist against two alternative sources (Almanasreh et al., 2016). Nearly all consecutive hospitalisations in older people due to acute illnesses were included, reducing selection bias. The causality, preventability and severity of each ADR and the contribution of the ADR to hospitalisation were independently investigated by two investigators based on standard criteria.

However, there are a number of limitations. The study was conducted in a single large hospital and the results may, therefore, not be generalizable to other settings. While, the determination of ADR prevalence included a multifaceted review of each suspected ADR including clinical judgement and chart review, and the application of a number of validated algorithms, there is a potential risk of misclassification, particularly as the study population had several comorbidities and disabilities and were prescribed a large number of medications.

Implications

The prevalence of ADR-related hospital admissions is high in older populations and many of these ADRs are deemed preventable. ADRs should be considered as a potential diagnosis in older complex patients, especially where symptom presentation is non-specific (Davies and O'Mahony, 2015). Not recognising an ADR in clinical practice may lead to a prescribing cascade whereby a new drug is prescribed to treat the adverse effects of an existing drug, potentially leading to further adverse health outcomes for the patient (Lavan and Gallagher, 2016). There is a lack of reliable and valid ADR detection and prediction tools developed for use in community settings. Current ADR causality tools are difficult to apply in everyday practice and inter-rater reliability amongst the tools is not robust (Agbabiaka et al., 2008). Predictive factors for ADR-related hospital admissions are still poorly understood. While some ADR risk prediction tools have been developed (e.g. ADRROP, GerontoNet), their predictive validity is low, and they are not universally accepted or used routinely in clinical practice (Lavan and Gallagher, 2016; Stevenson et al., 2014; O'Mahony et al., 2018). The focus to date has mainly being on investigating patient factors and further research needs to be completed to tease out the complex relationship between particular high-risk drug classes, multimorbidity, frailty and ADR-related hospital admissions (Jennings et al., 2019). The tools also need to be practical and efficient to use in clinical practice and the focus may need to be narrowed to specific high-risk drugs or drug class combinations.

Reliable, valid and user-friendly methods to detect and predict ADRs in community settings are necessary in order to develop interventions to reduce ADR-related hospital admissions. Improved therapeutic monitoring and pharmacotherapeutic adjustments, appropriate deprescribing and medication reviews have all being identified as interventions to minimise ADR-related admissions in older populations (Angamo et al., 2016; Gray et al., 2018). Empowering older patients through health education and literacy may also reduce the burden of ADR-related hospital admissions (Cahir et al., 2019). Literature reviews have highlighted the importance of patient involvement and shared decision-making in medication reviews and deprescribing but acknowledge that their implementation in clinical practice is complex and challenging (Reeve et al., 2014; Scott et al., 2015).

In conclusion, ADR-related hospital admissions in older people are a common clinical problem resulting in significant morbidity, healthcare consumption and costs (Wu et al., 2012). They are largely preventable through improved pharmacological management and education. Future research needs to focus on developing community-based tools and skills to enable healthcare providers and older patients detect and differentiate adverse effects of medication from symptoms of chronic disease or frailty and to identify those most at risk of medication-related harm. This may ultimately reduce ADR-related hospital admissions in the ever increasing population of older multi-morbid adults.

Data availability statement

The dataset presented in this article is not publicly available for use. Requests to access the dataset should be directed to caitrionacahir@rcsi.ie.

Ethics statement

This study was reviewed and approved by Beaumont Hospital Ethics Committee (REC 16/49). The patients/participants provided their written informed consent to participate in this study.

Author contributions

KB, DW, AH, CC, CK and CCu conceived and designed this study. CCu and CW managed the data collection process. CC analysed the data. KB, DW, AH, CCu, CW, RB, CK and CC contributed to the interpretation of the analysis and writing of the manuscript.

Funding

This work is independent research funded by the Health Research Board (RL-15-1579 and SDAP-2021-020) and the RCSI StAR MD programme.

Acknowledgments

We wish to thank Catherine Byrne and Margaret Large who supported the data collection in this study. We also wish to thank Sarah Tecklenborg and Catherine Waldron in RCSI and all the hospital staff in Beaumont Hospital who helped to facilitate this study.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.1029067/full#supplementary-material

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frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 02 February 2023
DOI 10.3389/fphar.2023.1088900

OPEN ACCESS

EDITED BY
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SPECIALTY SECTION
This article was submitted to Drugs Outcomes Research and Policies, a section of the journal Frontiers in Pharmacology

RECEIVED 03 November 2022
ACCEPTED 19 January 2023
PUBLISHED 02 February 2023

CITATION
Očovská Z, Mařík ová M and Vlček J (2023), Potentially clinically significant drug-drug interactions in older patients admitted to the hospital: A cross-sectional study. *Front. Pharmacol.* 14:1088900. doi: 10.3389/fphar.2023.1088900

Potentially clinically significant drug-drug interactions in older patients admitted to the hospital: A cross-sectional study

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Background: An international consensus list of potentially clinically significant drug-drug interactions (DDIs) in older people has been recently validated. Our objective was to describe the prevalence and characteristics of drug combinations potentially causing clinically significant DDIs identified in the medication history of older patients admitted to the hospital and the prevalence and characteristics of manifest DDIs—DDIs involved in adverse drug events present at hospital admission, DDIs that contributed to ADE-related hospital admissions, and DDIs involved in drug-related laboratory deviations.

Methods: The data were obtained from our previous study that examined the drug-relatedness of hospital admissions to University Hospital Hradec Králové *via* the department of emergency medicine in the Czech Republic. Patients ≥ 65 years old were included. Drug combinations potentially causing clinically significant DDIs were identified using the international consensus list of potentially clinically significant DDIs in older people.

Results: Of the 812 older patients admitted to the hospital, 46% were exposed to drug combinations potentially causing clinically significant DDIs. A combination of medications that affect potassium concentrations accounted for 47% of all drug combinations potentially causing clinically significant DDIs. In 27 cases, potentially clinically significant DDIs were associated with drug-related hospital admissions. In 4 cases, potentially clinically significant DDIs were associated with ADEs that were present at admissions. In 4 cases, the potentially clinically significant DDIs were associated with laboratory deviations. Manifest DDIs that contributed to drug-related hospital admissions most frequently involved antithrombotic agents and central nervous system depressants.

Conclusion: The results confirm the findings from the European OPERAM trial, which found that drug combinations potentially causing clinically significant DDIs are very common in older patients. Manifest DDIs were present in 4.3% of older patients admitted to the hospital. In 3.3%, manifest DDIs contributed to drug-related hospital admissions. The difference in the rates of potential and manifest DDIs suggests that if a computerized decision support system is used for alerting potentially clinically significant DDIs in older patients, it needs to be contextualized (e.g., take concomitant medications, doses of medications, laboratory values, and patients' comorbidities into account).

Abbreviations: ACE; Angiotensin-converting enzyme, ADE; Adverse drug event, ADR; Adverse drug reaction, ARB; Angiotensin II receptor blockers (AT1 receptor antagonists), ASA; Acetylsalicylic acid, CNS; Central nervous system, DDI; Drug-drug interaction, NSAID; Non-steroidal anti-inflammatory drug, OR; Odds ratio, SSRI; Selective serotonin reuptake inhibitors, SNRI; Serotonin and norepinephrine reuptake inhibitors, SRI; Serotonin reuptake inhibitors.

KEYWORDS
hospitalization, Czech Republic, adverse drug event, drug drug interaction, older patients

Introduction

Multimorbidity is highly prevalent in our aging societies, and it often leads to the use of multiple medications in older patients. Following recommendations for prescription in clinical guidelines will result in several potentially serious drug-drug interactions (DDIs) (Dumbreck et al., 2015). Drug regimens are increasingly complex and potentially harmful, and people with polypharmacy need regular review and prescribing optimization (Guthrie et al., 2015). Polypharmacy might represent either appropriate polypharmacy or problematic polypharmacy. Appropriate polypharmacy is the concurrent use of multiple medications by one individual when medication use has been optimized and when the medications are prescribed according to the best evidence. Problematic polypharmacy is the concurrent use of multiple medications by one individual when medications are prescribed inappropriately or when the intended benefit of the medication is not realized (McCarthy et al., 2019).

Older patients are at higher risk of adverse drug events (ADEs) from DDIs due to age-related changes in pharmacokinetics and pharmacodynamics and a higher number of comorbidities and medications. Several population-based studies have reported significant harm associated with DDIs in older patients (Hines and Murphy, 2011).

Our findings suggest that more than two-thirds of patients admitted to the hospital *via* the emergency department have at least one potential DDI in their medication history (Očovská et al., 2021). Fortunately, only a few of these combinations potentially causing DDIs are contraindicated or require drug dosage adjustments (Očovská et al., 2022b). The most common management strategies suggested by DDI databases all concern monitoring (Očovská et al., 2022b). Moreover, for many potential DDIs, there is a theoretical potential for an adverse interaction to occur based on the known pharmacological properties of the administered drugs, but no clinically relevant adverse effect (Pirmohamed, 2010). As a consequence, potential DDIs far outnumber actual DDIs (Pirmohamed, 2010; Magro et al., 2012; Očovská et al., 2021). Concerns about DDIs for which no clinical outcome evidence exists might lead to the underuse of safe and effective medications (Bykov and Gagne, 2017). It would mean that the evidence-based benefits of the medications are ignored in the face of a theoretical potential for harm (Pirmohamed, 2010). Just as harm associated with DDIs is usually avoidable, suboptimal patient outcomes due to the underuse of evidence-based medications are also usually avoidable (Bykov and Gagne, 2017). The omission of recommended drug therapy is associated with negative health outcomes, including reduced quality of life and a greater risk of hospitalizations or death. In comparison to younger populations, older patients are more likely to suffer adverse consequences from both action and inaction (Sloane and Niznik, 2022).

Tukukino et al. have shown that interaction alerts are of questionable value as indicators of problematic prescribing. Most alerts are either already being addressed or are not relevant in the clinical setting. The identification of DDIs using DDI databases thus results in many DDIs which might not be clinically significant (Tukukino et al., 2022). Recently, an international consensus list of potentially clinically significant DDIs in older people has been validated (Anrys et al., 2021). However, the association of DDIs listed in the international consensus list with clinical manifestations has never been examined.

Therefore, our objective was not only to describe the prevalence and characteristics of potentially clinically significant DDIs recorded in medication history but also to describe the prevalence and characteristics of manifest/actual DDIs (DDIs associated with ADE-related hospital admissions, ADEs that were present at hospital admissions and laboratory deviations).

Methods

This is a sub-study of our previous observational study, which has been described earlier (Očovská et al., 2022a). The study examined the drug-relatedness of hospital admissions to the University Hospital Hradec Králové *via* the department of emergency medicine in August–November 2018. The number of hospital admissions *via* the department of emergency medicine of the University Hospital Hradec Králové is approximately 450 per month. The exclusion criteria included visits to the department of emergency medicine without inpatient hospitalization, hospitalizations for diagnostic or elective surgical procedures for pre-existing conditions, hospitalizations with missing medical records, and hospitalizations taking less than 24 h. We have not applied any exclusion criteria related to the type of medical ward. Most of the patients were admitted to the departments of internal medicine (49%), surgery (26%), neurology (10%), pneumology (4%), anesthesiology, resuscitation and intensive medicine (3%), oncology and radiotherapy (3%), orthopedics (2%), infectious diseases (1%), and psychiatry (1%). In this sub-study, we analyzed only hospital admissions of older patients (≥ 65 years old).

The design of the original study was cross-sectional–we have examined each patient's medical record only at one point in time (we have not followed the patients in time). The data collection was performed retrospectively during 2018–2021. Data were obtained from electronic medical records and entered into a Microsoft Access database. The collected data included demographic characteristics, medication history, medical history, presenting complaint, admission diagnosis, laboratory values, results of clinical investigations, documented ADRs and information on medication adherence. Medications stated in medication history were counted as active substances.

Identification of potentially clinically significant DDIs

Potentially clinically significant DDIs were identified using the international consensus list of potentially clinically significant DDIs in older people (Anrys et al., 2021). Potential harms resulting from these DDIs were classified according to Zerah et al. (2021) into the following categories: serious cardiovascular adverse effects; serious neurological adverse effects; bleeding; deterioration of renal function and/or hyperkalemia (including severe myopathy and rhabdomyolysis, which may lead to acute renal failure); hematologic toxicity; and miscellaneous others.

Potentially clinically significant DDIs should be interpreted as drug combinations potentially causing clinically significant DDIs.

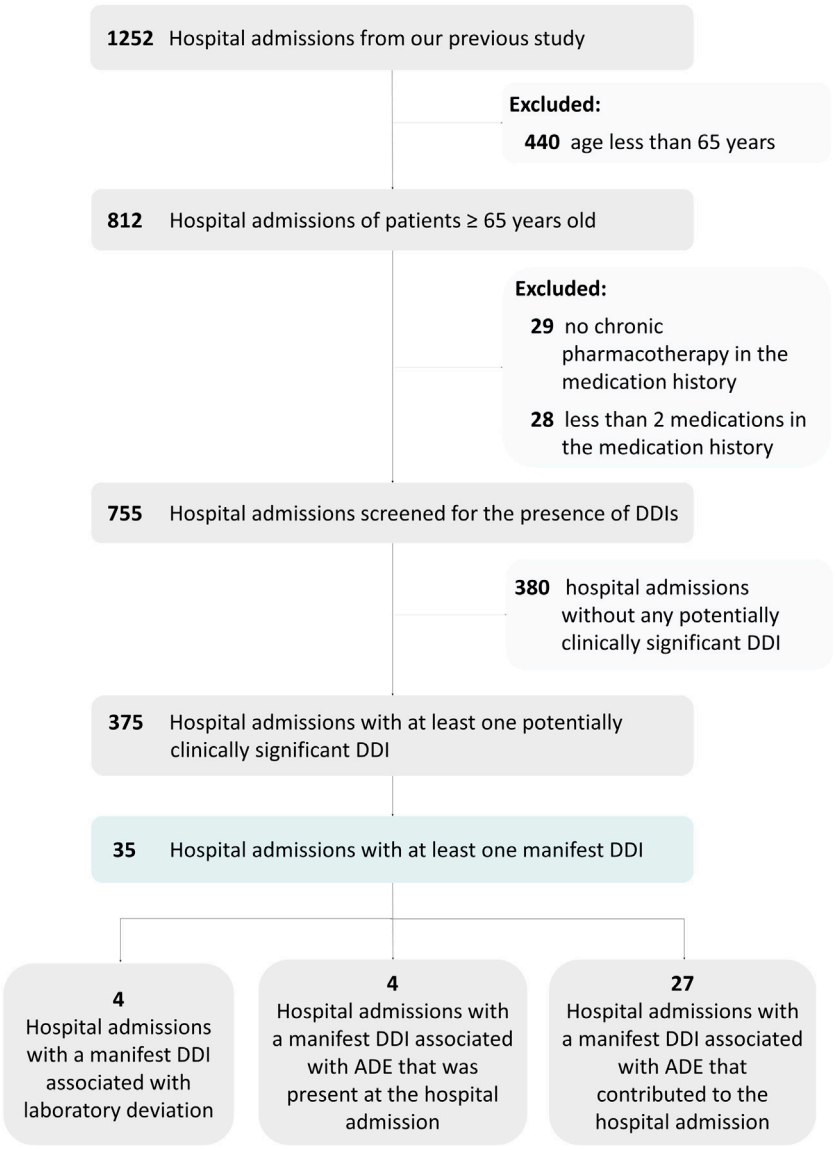

FIGURE 1
Flow chart showing the number of hospital admissions in each step.

Outcome measures

The prevalence of hospital admissions with a potentially clinically significant DDI was calculated as the number of hospital admissions with at least one potentially clinically significant DDI according to the international consensus list (Anrys et al., 2021) divided by the total number of hospital admissions of older patients.

The prevalence of hospital admissions with a manifest DDI was calculated as the number of hospital admissions with at least one DDI according to the international consensus list (Anrys et al., 2021) that was associated with laboratory deviation, ADE that was present at hospital admission, or drug-related hospital admissions divided by the total number of hospital admissions of older patients.

Manifest DDIs included potentially clinically significant DDIs with potential harms that corresponded with observed clinical manifestations of ADE or laboratory deviations. The clinical adjudication process of drug-related hospital admissions has already been described in detail in our previous study (Očovská et al., 2022a). Drug-related hospital admissions were identified using the OPERAM drug-related hospital admissions adjudication guide (Thevelin et al., 2018). The process of drug-related hospital admissions identification consisted of data abstraction, screening for potential ADEs causing or contributing to hospital admission, causality assessment (using modified WHO-UMC criteria) and assessment of contribution to hospital admission.

Statistical analysis

Data were analyzed using Microsoft Excel and IBM SPSS Statistics version 28. Descriptive statistics was performed in Microsoft Excel and multiple logistic regression was performed in IBM SPSS Statistics. We considered a p-value less than 0.05 as statistically significant.

Results

Figure 1 shows the number of hospital admissions in each step of the study. Of 812 older patients admitted to the hospital, 375 patients (46%) had at least one drug combination potentially causing clinically significant DDI according to the international consensus list (Anrys et al., 2021) in the medication history. In 35 cases, potentially clinically significant DDIs were associated with clinical manifestations. The prevalence of hospital admissions with at least one manifest clinically significant DDI according to the international consensus list was 4.3%.

Descriptive characteristics of the study sample can be found in Supplementary Tables S1–S3. Polypharmacy (≥5 medications) was present in 597 (74%) patients and hyperpolypharmacy (≥ 10 medications) was present in 228 (28%) patients.

Drug combinations potentially causing clinically significant DDIs

The most common medications involved in potentially clinically significant DDIs according to the international consensus list (Anrys et al., 2021) included furosemide, hydrochlorothiazide, fenoterol, amiodarone, acetylsalicylic acid, warfarin, amiloride, formoterol, spironolactone, ramipril, perindopril, potassium chloride, escitalopram, theophylline, atorvastatin, citalopram, tramadol, sertraline, ibuprofen, digoxin, diclofenac, and meloxicam. Supplementary Table S4 shows the most common potentially clinically significant DDIs according to the international consensus list (Anrys et al., 2021) that were listed in the medication history of older patients. Supplementary Table S5 shows medication classes involved in potentially clinically significant DDIs according to the international consensus list (Anrys et al., 2021). The most common medication classes involved in potentially clinically significant DDIs included Diuretics (C03), Drugs for obstructive airway diseases (R03), Antithrombotic agents (B01), Agents acting on the renin-angiotensin system (C09), Antiinflammatory and antirheumatic products (M01), Cardiac therapy (C01) and Psychoanaleptics (N06).

Potential harms of potentially clinically significant DDI according to the international consensus list (Anrys et al., 2021) included hypokalemia (n = 240), bleeding (n = 148), hyperkalemia (n = 139), CNS depression (n = 63), additive adverse effects on renal function (n = 52), hyponatremia (n = 45), myopathy (n = 42), digoxin toxicity (n = 26), serotonin syndrome (n = 24), bradycardia (n = 7), and anticholinergic effects (n = 6). Table 1 shows the overview of potentially clinically significant DDIs categorized to potential harms according to Zerah et al. (2021) and Table 2 shows the proportion of patients with the corresponding potential harm of potentially clinically significant DDIs according to Zerah et al., 2021. Potentially clinically significant DDIs involving drugs that affect potassium concentrations accounted for 47% of all potentially clinically significant DDIs according to the international consensus list (Anrys et al., 2021).

184 (23%) patients had at least one potentially clinically significant DDI related to the deterioration of renal function or hyperkalemia. 146 (18%) patients had at least one potentially clinically significant DDI related to serious cardiovascular adverse effects. 116 (14%) patients had at least one potentially clinically significant DDI related to bleeding. 72 (9%) patients had at least one potentially clinically significant DDI related to serious neurologic adverse effects. 42 (5%) patients had at least one potentially clinically significant DDI related to hyponatremia.

Manifest clinically significant DDIs

Table 3 shows the overview of manifest DDIs that were associated with drug-related hospital admissions. Manifest DDIs were involved in 27 drug-related hospital admissions. The most common clinical presentation of manifest DDIs was bleeding (especially gastrointestinal bleeding). Medication classes most frequently involved in manifest DDIs included antithrombotics (antiplatelets, anticoagulants) and CNS depressants.

Table 4 shows the lists of manifest DDIs that were associated with ADEs that were present at hospital admission but did not contribute to drug-related hospital admission (n = 4) and DDIs that were associated with drug-related laboratory deviations (n = 4). Medications with hyperkalemic effects–spironolactone, amiloride, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II receptor blockers (ARBs) were involved in DDIs that were associated with laboratory deviations (hyperkalemia).

In addition, there were ten additional cases with manifest DDIs that were not included in the international consensus list of potentially clinically significant DDIs in older people (Anrys et al., 2021).

Discussion

Prevalence of drug combinations potentially causing clinically significant DDIs

We have found that almost half of the patients (46%) admitted to the hospital were exposed to potentially clinically significant DDIs according to the international consensus list (Anrys et al., 2021). This prevalence is lower than the prevalence of 54% found in the OPERAM trial (Zerah et al., 2021). However, if we restricted our sample only to similar patients as in the OPERAM trial (≥70 years, with ≥ 3 chronic conditions) and polypharmacy (≥ 5), we would find a slightly higher prevalence of potentially clinically significant DDIs (58%) (303/523).

If we looked at the prevalence of any potential DDIs (not only potentially clinically significant DDIs in older people), the prevalence of potential DDIs would be 85%. Only in 63 cases with at least two medications in the medication history, there was no DDI identified either by Lexicomp, Micromedex, or Stockley drug interaction databases.

Therefore, limiting the identification of DDIs to those listed in the international consensus list of potentially clinically significant in older people has almost halved the prevalence of potential DDIs.

Medications involved in drug combinations potentially causing clinically significant DDIs

In the OPERAM trial, 80% of all potentially clinically significant DDIs involved drugs that reduce potassium (diuretics, inhaled beta2-agonists, systemic corticosteroids),

TABLE 1 The number of drug combinations potentially causing clinically significant DDIs with corresponding potential harm category according to Zerah et al., 2021.

Potential harm category	N of DDIs	% of DDIs
Serious cardiovascular adverse effect	**273**	**34.1**
hypokalemia	240	30.0
digoxin toxicity	26	3.3
bradycardia	7	0.9
Deterioration of renal function or hyperkalemia	**233**	**29.1**
hyperkalemia	139	17.4
additive adverse effects on renal function, antagonist effects on blood pressure	33	4.1
myopathy	42	5.3
deterioration of renal function, hyperkalemia, altered blood pressure control	19	2.4
Bleeding	**156**	**19.5**
bleeding	148	18.5
gastrointestinal ulceration or bleeding	8	1.0
Serious neurologic adverse effects	**93**	**11.6**
excessive sedation and prolonged hypnotic effects	6	0.8
increased risk of falls and fractures, impaired cognition	57	7.1
serotonin syndrome	24	3.0
anticholinergic effects including cognitive decline	6	0.8
Others	**45**	**5.6**
hyponatremia	45	5.6
Total	**800**	**100**

DDI: Drug-drug interaction.
Note: These drug-drug interactions should be interpreted as drug combinations potentially causing clinically significant DDIs, according to the international consensus list (Anrys et al., 2021).

TABLE 2 The proportion of patients with drug combinations potentially causing clinically significant DDIs with the corresponding potential harm category according to Zerah et al., 2021.

Potential harm category	N of patients	% of patients
Deterioration of renal function or hyperkalemia	184	23
Serious cardiovascular adverse effect	146	18
Bleeding	116	14
Serious neurologic adverse effects	72	9
Hyponatremia	42	5
Any harm category	375	46

n = 812 (100%).
Note: These drug-drug interactions should be interpreted as drug combinations potentially causing clinically significant DDIs, according to the international consensus list (Anrys et al., 2021).

centrally acting drugs (psychotropics, antidepressants, opioids, antiepileptics), potassium-sparing drugs (ACE inhibitors, ARBs, spironolactone) and antithrombotics (Zerah et al., 2021).

In our study, DDIs most frequently included a combination of medications that reduce potassium (DDI No. 65), a combination of medications that increase potassium (DDI No. 21 + 22 + 23), a combination of an oral anticoagulant with an antiplatelet drug (DDI No. 12), and concomitant use of ≥ 3 centrally-acting drugs (DDI 36). In 70 cases, both DDIs involving drugs that reduce potassium and DDIs involving drugs that increase potassium were

TABLE 3 List of manifest DDIs that were associated with drug-related hospital admissions (n = 27).

Actual harm category	Manifest drug-drug interaction
Bleeding	apixaban + ASA
	ASA + warfarin + clopidogrel + escitalopram
	ASA + clopidogrel + rivaroxaban
	ASA + warfarin
	ASA + nimesulide
	ASA + warfarin + sertraline
	ASA + rivaroxaban
	NSAID + warfarin
	clopidogrel + warfarin
	ASA + ibuprofen
	ASA + diclofenac
	ASA + dabigatran etexilate + meloxicam
	clopidogrel + warfarin
	ibuprofen + rivaroxaban
	diclofenac + prednisone
	ASA + warfarin
	dabigatran etexilate + meloxicam
	clopidogrel + warfarin + ASA
	ASA + warfarin
CNS depression	pregabalin + tramadol + zolpidem
	baclofen + pregabalin + tramadol
	buprenorphine + gabapentin + trazodone
	dosulepin + tapentadol + tramadol + trazodone + pregabalin
	fentanyl + gabapentin + haloperidol + morphine
Hyperkalemia	perindopril + potassium chloride + spironolactone
	amiloride + telmisartan
	perindopril + spironolactone

ASA: acetylsalicylic acid, CNS: central nervous system, NSAID: non-steroidal anti-inflammatory drug.

present at the same time, which highlights the need for contextualization of DDIs alerts.

The most common potential harm of drug combinations potentially causing clinically significant DDIs

Hypokalemia represented the most common potential harm of potentially clinically significant DDIs according to the international consensus list (Anrys et al., 2021). Manifestations of hypokalemia include muscle weakness, constipation, cardiac arrhythmias, kidney abnormalities, and glucose intolerance. Although hypokalemia represented the most common type of potential harm of potentially clinically significant DDIs in our study, we have not detected any ADEs associated with hypokalemia. Thiazide diuretics were often prescribed in fixed combination with ACE inhibitors, ARBs, or amiloride. The risk was further minimized by using lower doses of thiazide diuretics. Spironolactone and ACE inhibitors were often prescribed in patients with heart failure (heart failure represented the most common admission diagnosis in our study). In addition, medications frequently implicated in potential DDIs associated with hypokalemia included inhaled beta 2 agonists, which do not have a high potential to cause hypokalemia.

Due to the hospital setting of our study, we could only identify cases of hypokalemia with severe types of manifestations (e.g., arrhythmias) as we did not prospectively look for the patient's

TABLE 4 List of other manifest DDIs (*n* = 8).

Manifest drug-drug interaction	Adverse drug event or laboratory deviation
DDIs involved in adverse drug events that were present at hospital admission (n = 4)	
ASA + rivaroxaban	gastroduodenal hemorrhage
gabapentin + trazodone + zolpidem	abnormal dreams
olanzapine + solifenacin	constipation
clonazepam + quetiapine + trazodone	CNS depression
DDIs involved in drug-related laboratory deviations (n = 4)	
spironolactone + telmisartan	hyperkalemia 7.5 mmol/L
perindopril + spironolactone	hyperkalemia 5.4 mmol/L
amiloride + perindopril + spironolactone	hyperkalemia 9.0 mmol/L
furosemide + hydrochlorothiazide	hypokalemia 2.9 mmol/L

ASA: acetylsalicylic acid, CNS: central nervous system, DDI: drug-drug interaction.

reported symptoms (e.g., muscle weakness) outside of the hospital setting. There were very few cases of hypokalemia in our study, and they were mostly related to vomiting, diarrhea, or excessive alcohol use.

Prevalence of manifest DDIs

In our study, the prevalence of hospital admissions with at least one manifest DDIs according to the international consensus of potentially clinically significant DDIs was 4.3%. This prevalence is higher compared to the median DDI prevalence of 1.1% from the latest systematic review (Dechanont et al., 2014).

However, there are also a few studies with a higher prevalence of DDI-related hospital admissions. In a study from Australia, DDIs were potentially involved in 8.1% of all hospital admissions and 43% of ADR-related admissions (Parameswaran Nair et al., 2017). In a study from Italy, an actual DDI was found in 5.5% of emergency department admissions (Marino et al., 2016). A study from the USA reported that DDIs were the cause of 57% of ADR-related admissions and 4.3% of all hospital admissions. (Rivkin, 2007). The latest systematic review indicated that in ADR patients, the median DDI prevalence rate for hospital admissions is 22.2%. (Dechanont et al., 2014). A recent study (Osanlou et al., 2022) found that 29.4% of ADRs are possibly or probably caused by DDIs.

The prevalence of hospital admissions associated with DDIs ranges from 0% (Hohl et al., 2001) to 18% (De Paepe et al., 2013). The prevalence of hospital admissions related to manifest DDIs is influenced by various factors such as characteristics of the studied population (e.g., age, number of comorbidities, number of medications), the definition of manifest DDI, the method used to identify DDIs, the method of causality assessment, the selected causality threshold, the assessment of contribution to hospital admission, and the emergence of new evidence of ADEs associated with DDIs.

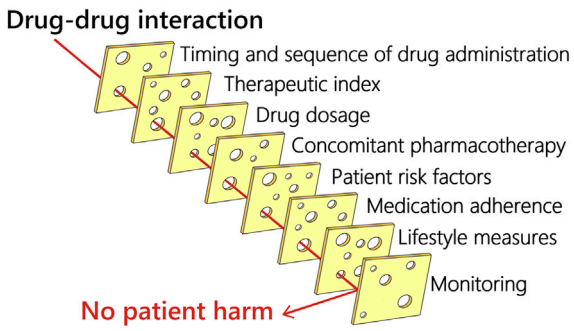

FIGURE 2
Factors that might influence whether potential DDI will lead to patient harm.

Factors that influence the manifestation of potential DDIs

Several factors influence the manifestation of potential DDIs. These factors can be related to the medication (e.g., therapeutic index, drug dosage or duration of treatment, other concomitant pharmacotherapy), patient characteristics (e.g., genetic polymorphism, the status of eliminating organs and comorbidities), drug administration (route, sequence, and correct way of drug administration), and patient behavior (medication adherence, self-monitoring, lifestyle measures). Lifestyle measures such as consumption of certain foods and beverages, hydration, smoking, and alcohol consumption also represent a source of variability. Last but not least, healthcare professionals minimize the risk of DDIs by monitoring (e.g., monitoring drug levels, potassium levels, kidney functions, blood pressure, heart rate, QTc interval, and symptoms of ADEs). Figure 2 shows the various factors that might influence whether potential DDI will lead to patient harm.

DDIs not included in the international consensus list

DDIs that were not listed in the international consensus list of potentially clinically significant DDIs in older patients but were associated with drug-related hospital admissions in our study included the combinations of selective serotonin reuptake inhibitors (SSRIs) with antithrombotic agents (both anticoagulant and antiplatelets), the combination of two antiplatelet agents (acetylsalicylic acid and clopidogrel), the combinations of beta-blockers with amiodarone or digoxin and the combinations of several medications with hypotensive effect.

Considering that bleeding represents the most common clinical manifestation of DDI-related hospital admissions, additional DDIs related to increased risk of bleeding should be considered during the development of an updated list of potentially clinically significant DDI in older adults. Gastrointestinal hemorrhage represented the most common ADE also in our previous study focused on older patients admitted to the geriatric ward (Maříková et al., 2021). A combination of two antiplatelet agents was frequently implicated in serious ADRs associated with DDIs identified *via* a spontaneous reporting database from Italy (Magro et al., 2020). In a pharmacovigilance study from China (Jiang et al., 2022), acetylsalicylic acid represented the most common medication implicated in ADRs caused by actual DDIs. The inclusion of a combination of antidepressants belonging to the SSRI and SNRI class with antithrombotics should also be considered. In the meta-analysis of 32 non-randomized studies (Nochaiwong et al., 2022), serotonin reuptake inhibitor (SRI) antidepressants among patients treated with antithrombotic therapy (either anticoagulant or antiplatelet) were associated with a higher risk of bleeding complications. The combination of vitamin K antagonist with SSRI/SNRI is also included in the Ghent Older People's Prescriptions Community Pharmacy Screening list of DDIs especially relevant in older people (Foubert et al.,2021).

In the current version of the international consensus list of potentially significant DDIs, most DDIs affecting CNS were only included when patients were taking three or more centrally-acting drugs. Nevertheless, the list could also include the combination of opioids with benzodiazepines and the combination of opioids with gabapentinoids as recommended by AGS Beers criteria (AGS, 2019). In addition, the combination of skeletal muscle relaxants with opioids and benzodiazepines is not included in the international consensus list. Concomitant use of specific muscle relaxants (e.g., baclofen), benzodiazepines, and gabapentinoids might increase the risk of opioid overdose (Li et al., 2020; Khan et al., 2021; Khan et al., 2022) and the risk of injuries (Leonard et al., 2020).

Moreover, compared to younger patients, older patients do not require too tight blood pressure and glycemic control. Fortunately, due to the development of new oral antidiabetics, the combinations of antidiabetics with the risk of hypoglycemia are not common in clinical practice. However, the combination of oral antidiabetics with a risk of hypoglycemia (sulphonylureas) or insulin with beta-blockers might result in masking the first symptoms of hypoglycemia (tachycardia, tremor). On the other hand, the combinations of several medications with hypotensive effects are common in clinical practice. Hypotension caused by multiple blood pressure-lowering agents was reported in a study from Australia (Parameswaran Nair et al., 2017). Conversely, medications that antagonize the effect of ACE inhibitors/ARBs or diuretics (e.g., NSAIDs) might contribute to heart failure exacerbations (Page et al., 2016; Swart et al., 2020).

Risk minimization of adverse drug events

Since gastrointestinal bleeding represented the most common ADE associated with manifest DDIs in our study, DDIs that increase the risk of bleeding or gastrointestinal ulceration deserve attention. Risk minimization measures should target inappropriate prescriptions of antiplatelet agents and NSAIDs. Low-dose acetylsalicylic acid use is not recommended for the primary prevention of cardiovascular disease. Since the risk of major bleeding from acetylsalicylic acid increases in older patients, initiation of low-dose acetylsalicylic acid for primary prevention of cardiovascular disease should be avoided and deprescribing should be considered in older patients already taking low-dose acetylsalicylic acid for primary prevention. (2022 AGS Annual Scientific Meeting). For patients with atrial fibrillation on anticoagulation who underwent percutaneous coronary intervention, the use of direct oral anticoagulants is preferred over a vitamin K antagonist when appropriate. Clinical decision-making regarding the duration of antiplatelet therapy should be based on a balanced assessment of three competing risks: cardioembolic stroke, coronary ischemic events, and bleeding. In patients with a low risk of thrombotic events or a high risk of bleeding, early omission of aspirin therapy and treatment with a direct oral anticoagulant plus clopidogrel is entirely warranted (Mehta, 2019). In general, the use of triple therapy (dual antiplatelet therapy plus anticoagulation) is not recommended for most patients due to an increased risk of bleeding. If triple therapy is needed, a short duration (e.g., no more than 30 days) is recommended (Kumbhani et al., 2021). A screening tool for cardiovascular pharmacotherapy in geriatric patients (RASP_CARDIO list) states that triple therapy (dual antiplatelet therapy and one anticoagulant) longer than 1 month after a percutaneous coronary intervention is potentially inappropriate. Treatment duration is preferably limited to 1 week (with mostly stepping down to dual antithrombotic therapy upon discharge from the hospital) (De Schutter et al., 2022). For patients taking two antithrombotic agents, starting or continuing a proton pump inhibitor and avoiding NSAIDs should be employed to reduce gastrointestinal bleeding risk. However, while proton pump inhibitors reduce the risk of upper gastrointestinal bleeding, the risk of lower gastrointestinal bleeding is not reduced. In addition, proton pump inhibitors might be implicated in ADRs that lead to hospital admissions, e.g., due to *C. difficile* enterocolitis (Osanlou et al., 2022).

Risk minimization of CNS adverse events should focus on off-label prescription of psychotropic drugs–particularly the use of benzodiazepines and antipsychotics should be avoided except in approved evidence-based indications. Non-pharmacologic treatment of insomnia and depression should be promoted. Deprescribing opioids and gabapentinoids might be complicated by the lack of safe and effective alternatives for pain control in older adults. Paracetamol dosages should be checked and possibly increased (up to 1,000 mg) in patients with inadequate pain management. In our study, paracetamol doses of 325–650 mg (paracetamol in fixed combinations with tramadol) or 500 mg were often used. Perhaps, the use of metamizole (dipyrone) for chronic pain could be reevaluated in some countries in light of the high burden of ADRs associated with NSAIDs, opioids, and gabapentinoids. Start low and go slow dosing of many CNS medications is recommended in older patients. Furthermore, CYP2D6 activity affected by genotype and drug exposure (including DDIs) might influence the CNS's vulnerability to ADRs (Just et al., 2021). In the future, the use of pharmacogenetics might increase drug safety by optimizing individual drug treatment (Evans and Relling, 2004).

Risk minimization of hyperkalemia should focus on slow titration of ACE inhibitors/ARBs and spironolactone during the initiation of the treatment of heart failure (start low and go slow approach). In addition,

kidney function and potassium levels should be closely monitored, and medication reconciliation should be in place to avoid situations in which patients are being discharged with potassium chloride once hypokalemia has resolved. A recent study from the United States found a high incidence of loop diuretic-potassium supplementation prescribing cascade, with up to one-third of patients continuing to receive potassium supplementation despite loop diuretic discontinuation (Wang et al., 2022).

Future studies

First of all, future studies on DDIs should assess the evidence of clinical outcomes of DDIs. An absence of evidence about whether a drug-drug interaction affects clinical outcomes not only contributes to DDI alert overload but can also result in suboptimal patient outcomes due to the underutilization of safe and effective medications (Bykov and Gagne, 2017). Bykov and Gagne have highlighted the urgent need for more and better pharmacoepidemiologic studies to understand the clinical impact, or lack thereof, of pharmacologically demonstrated DDIs (Bykov and Gagne, 2017). The evidence of clinical outcomes would benefit from more studies with a self-controlled design (particularly self-controlled case series) which is suited for the evaluation of transient effects of drug-drug interactions and controls for confounders that are stable over the observational period (Bykov et al., 2019).

Furthermore, studies should also focus on higher-order interactions. Drug-drug-drug signal detection using pharmacoepidemiologic screening of health insurance data could have broad applicability across drug classes and databases (Acton et al., 2022).

Most importantly, there is a need to contextualize DDI alerts so that computerized systems alert those DDIs that are relevant to the patient's clinical situation. Clinical decision support systems tools need to be contextualized by taking clinical, user, and institutional factors into consideration (Chou et al., 2021). Warnings for DDIs are frequently overridden because they are often irrelevant for specific patients. Alerting systems for DDIs should incorporate patients' comorbidities (e.g., chronic kidney disease, history of gastrointestinal bleeding), laboratory results (e.g., potassium, blood pressure, QTc values), drug dosages, duration and route of administration, and most importantly concomitant pharmacotherapy (particularly the presence of various DDIs affecting potassium). Concomitant pharmacotherapy can either reduce the clinical relevancy of a DDI by antagonistic effect (simultaneous presence of DDIs that reduce and increase serum potassium level) or further increase the clinical relevancy by synergistic effect (high-order drug interactions involving antithrombotic agents, antiplatelet agents, NSAIDs, and serotonin reuptake inhibitor antidepressants). A problematic issue related to DDI databases is generalizing evidence to members of a drug class and not distinguishing the clinical relevancy between different members of the same drug class. For example, metamizole (dipyrone) generates theoretical DDIs that affect blood pressure and kidney functions due to being listed among other NSAIDs. Recently Wasylewicz et al. have shown that contextualized DDI management can considerably decrease the number of irrelevant DDI alerts and thereby increase the time available to interpret relevant DDI alerts (Wasylewicz et al., 2022). Although it may be difficult to operationalize certain factors to reduce unnecessary alerts, these factors can provide useful information for clinicians to decide whether to override an alert (Reese et al., 2022).

Strengths

The key strength of this study is the assessment of clinical manifestations associated with potentially clinically significant DDIs–laboratory deviations, ADEs that were present at admission, and drug-related hospital admissions. The second strength is the use of electronic health records as a data source. Compared to administrative claims data or spontaneous reporting systems, electronic health records are more likely to capture ADEs associated with DDIs. Electronic health records include presenting complaints, hospital discharge summaries, patient history, results of investigations, and various free text notes which are not available in other data sources. The third strength of this study is the use of the OPERAM drug-related hospital admissions adjudication guide for the identification of drug-related hospital admissions. This standardized guide provides comprehensive information on the definition, screening, and adjudication of drug-related hospital admissions (including ADE causality assessment and assessment of ADE contribution to hospital admission).

In addition, the study was not limited to specific hospital wards or a specific subgroup of older adults, thereby increasing its generalizability. However, since the study was focused on older adults acutely admitted to the hospital *via* the department of emergency medicine, we do not have any information on ADEs that did not result in hospital admissions of older patients. Although the study was single-centered, we have identified almost the same prevalence and characteristics of potentially clinically significant DDIs as the four medical centers from the OPERAM trial (Bern, Brussels, Cork, Utrecht). This study, therefore, contributes to existing knowledge on DDIs in older adults by providing information on the prevalence and characteristics of potentially clinically significant DDIs (medications involved in DDIs, potential harms of DDIs) from a different country.

The study provides additional evidence concerning actual clinical manifestations associated with potentially clinically significant DDIs in older adults. This is the first time that the international consensus list of potentially clinically significant DDIs in older adults has been used to explore drug-related hospital admissions. The information on manifest DDIs has extended our knowledge of the clinical relevance of potentially clinically significant DDIs in older adults. The identified difference between the prevalence of potentially clinically significant DDIs and the prevalence of manifest DDIs adds to a growing body of literature on the need to contextualize DDI alerts.

Limitations

The main limitation of this study is the cross-sectional design. Since we were not able to follow patients in time, we did not have precise information on the time of initiation of each medication. In a prospective cohort study from Ireland, the authors were able to classify identified DDIs as chronic and acute (Hughes et al., 2021). Certain pharmacokinetic DDIs are only relevant when the object drug is initiated, discontinued, or dosage changes are made. Due to a lack of information on the duration of treatment, we were not able to assess the causality of amiodarone + warfarin DDI. Other DDIs were either pharmacodynamic or not associated with any relevant clinical manifestation.

The second limitation concerns the absence of patient interviews. Due to missing patient interviews, we do not have precise information on medication adherence and the use of over-the-counter medications and supplements. The imprecise information on NSAID use represents a major drawback of the study since gastrointestinal bleeding is the most frequent cause of drug-related hospital admissions. Although we have identified some

cases of DDIs that involved the combination of NSAIDs with anticoagulants and antiplatelets, the magnitude of gastrointestinal bleeding associated with NSAIDs is likely greater. According to the systematic review, NSAIDs represent the most common drugs involved in hospital admissions associated DDIs (Dechanont et al., 2014). In addition, the adverse impact of DDIs on the quality of life remains unknown.

Moreover, fixed combinations consisting of two active ingredients were coded as two different active ingredients. The prevalence of hypokalemia is overestimated because the combination of hydrochlorothiazide and amiloride was also implicated in DDIs that potentially lead to hypokalemia.

Conclusion

The results confirm the findings from the European OPERAM trial, which found that drug combinations potentially causing clinically significant DDIs are very common in older patients. Manifest DDIs were present in 4% of older patients admitted to the hospital. In 3%, manifest DDIs contributed to drug-related hospital admissions. The difference in the prevalence of potential and manifest DDIs suggests that if a computerized decision support system is used for alerting potentially clinically significant DDIs in older patients, it needs to be contextualized (e.g., take concomitant medications, doses of medications, laboratory values, and patients' comorbidities into account).

Manuscript contribution to the field

This is the first study that applied the International Consensus List of Potentially Clinically Significant Drug-Drug Interactions in Older People outside of the OPERAM trial. The results confirm the findings from the European OPERAM trial, which found that potentially clinically significant DDIs are very common in older patients. This study has identified potentially clinically significant drug-drug interactions that were missed in the consensus list (the combination of anticoagulants with SSRI antidepressants, the combination of two antiplatelet agents, and the combination of opioids with gabapentinoids). Therefore, this study could serve as an important guide for the development of the updated version of the international consensus list of potentially clinically significant drug-drug interactions in older people.

The strengths of this study include the assessment of clinical manifestations associated with drug-drug interaction in older patients (particularly drug-related hospital admissions) as well as laboratory deviations and adverse drug events that were present at hospital admission. The assessment of drug-related hospital admissions was performed using a standardized drug-related hospital admission adjudication guide developed during the European OPERAM trial.

The paper also proposed possible risk minimization measures for the most common ADEs associated with drug-drug interactions (bleeding, CNS depression, hyperkalemia), highlighted the factors that influence the manifestation of drug-drug interactions, and the importance of contextualization (e.g., taking concomitant medications, doses of medications, laboratory values, and patients' comorbidities into account).

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of the University Hospital Hradec Králové and Ethics Committee of the Faculty of Pharmacy in Hradec Králové. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

ZO conceived and designed the study. ZO created a Microsoft Access database for data analysis and performed data analysis. ZO, MM, and JV were involved in clinical adjudication of adverse drug events. ZO, MM, and JV were involved in the interpretation of data. JV supervised the study and critically revised the manuscript for important intellectual content. ZO drafted the manuscript, and all co-authors contributed to and approved the final manuscript.

Funding

This work was supported by the EFSA-CDN project (Reg. No. CZ.02.1.01/0.0/0.0/16_019/0000841) co-funded by the European Union, by Charles University (project SVV 260 551), by Charles University Grant Agency (project GA UK 14120).

Acknowledgments

We are grateful to pharmacy students (Kateřina Holmanová, Daniela Mašková) for the screening for potential drug-drug interactions via drug interaction databases during their master's thesis research.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1088900/full#supplementary-material

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frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 07 February 2023
DOI 10.3389/fphar.2023.1080073

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Drugs Outcomes Research and Policies, a section of the journal Frontiers in Pharmacology

RECEIVED 25 October 2022
ACCEPTED 20 January 2023
PUBLISHED 07 February 2023

CITATION
Lunghi C, Rochette L, Massamba V, Tardif I, Ouali A and Sirois C (2023), Psychiatric and non-psychiatric polypharmacy among older adults with schizophrenia: Trends from a population-based study between 2000 and 2016.
Front. Pharmacol. 14:1080073.
doi: 10.3389/fphar.2023.1080073

Psychiatric and non-psychiatric polypharmacy among older adults with schizophrenia: Trends from a population-based study between 2000 and 2016

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Background: Schizophrenia is a severe psychiatric disorder associated with multiple psychiatric and non-psychiatric comorbidities. As adults with schizophrenia age, they may use many medications, i.e., have polypharmacy. While psychiatric polypharmacy is well documented, little is known about trends and patterns of global polypharmacy. This study aimed to draw a portrait of polypharmacy among older adults with schizophrenia from 2000 to 2016.

Methods: This population-based cohort study was conducted using the data of the Quebec Integrated Chronic Disease Surveillance System of the National Institute of Public Health of Quebec to characterize recent trends and patterns of medication use according to age and sex. We identified all Quebec residents over 65 years with an ICD-9 or ICD-10 diagnosis of schizophrenia between 2000 and 2016. We calculated the total number of medications used by every individual each year and the age-standardized proportion of individuals with polypharmacy, as defined by the usage of 5+, 10+, 15+, and 20+ different medications yearly. We identified the clinical and socio-demographic factors associated with polypharmacy using robust Poisson regression models considering the correlation of the responses between subjects and analyzed trends in the prevalence of different degrees of polypharmacy.

Results: From 2000 to 2016, the median number of medications consumed yearly rose from 8 in 2000 to 11 in 2016. The age-standardized proportion of people exposed to different degrees of polypharmacy also increased from 2000 to 2016: 5+ drugs: 76.6%–89.3%; 10+ drugs: 36.9%–62.2%; 15+: 13.3%–34.4%; 20+: 3.9%–14.4%. Non-antipsychotic drugs essentially drove the rise in polypharmacy since the number of antipsychotics remained stable (mean number of antipsychotics consumed: 1.51 in 2000 vs. 1.67 in 2016). In the multivariate regression, one of the main clinically significant factor associated with polypharmacy was the number of comorbidities (e.g., Polypharmacy-10+: $RR_{[2\ vs.\ 0-1]}$ = 1.4; 99% IC:1.3–1.4, $RR_{[3-4]}$ = 1.7 (1.7–1.8); $RR_{[5+]}$ = 2.1 (2.1–2.2); Polypharmacy-15+: $RR_{[2\ vs\ 0-1]}$ = 1.6; 99% IC:1.5–1.7, $RR_{[3-4]}$ = 2.5 (2.3–2.7); $RR_{[5+]}$ = 4.1 (3.8–4.5).

Conclusion: There was a noticeable increase in polypharmacy exposure among older adults with schizophrenia in recent years, mainly driven by non-antipsychotic

medications. This raises concerns about the growing risks for adverse effects and drug-drug interactions in this vulnerable population.

KEYWORDS

polypharmacy, drug utilization, administrative databases, trends, older adults, elderly, schizophrenia

Introduction

Schizophrenia is a severe disease characterized by hallucinations, delusions, disorganized speech, and abnormal thinking, which significantly impact the ability of patients to function in their daily lives and quality of life (Marder and Cannon, 2019). It is among the top 10 global causes of disability (Fleischhacker et al., 2014; Charlson et al., 2018), with an estimated worldwide prevalence that can reach up to 1% (Saha et al., 2005). Schizophrenia patients are more often sedentary, higher cigarette smokers and drug users (Fleischhacker et al., 2014). They have frequent physical comorbidities such as cardiovascular diseases (Fleischhacker et al., 2014), obesity (Mamakou et al., 2018), type two diabetes (Fleischhacker et al., 2014), metabolic syndrome (Jeon and Kim, 2017), and dementia (Stroup et al., 2021). Mental comorbidities such as depression (Remington et al., 2017), alcohol or substance abuse (Buchanan et al., 2010), and insomnia (Stummer et al., 2018) are also common in these patients. It is also hypothesized that the aging process is accelerated in schizophrenia patients (Nguyen et al., 2018).

On the other hand, patients with schizophrenia are underdiagnosed with physical conditions and, when the diagnosis arrives, these conditions are often at an advanced stage, requiring more intensive treatment and more medications (Fleischhacker et al., 2014). In the general older population, multimorbidity (Gontijo Guerra et al., 2019), is often associated with polypharmacy [i.e., taking multiple medications (Sirois et al., 2019a)]. Polypharmacy is a genuine concern in older individuals due to the higher risk for adverse drug events, drug-drug interactions, adherence problems, and potentially inappropriate prescriptions (Kojima et al., 2020; Lin, 2020). In recent years, polypharmacy has been studied in different populations of older individuals with chronic conditions, such as heart failure (Campeau Calfat et al., 2022), chronic obstructive pulmonary disease (COPD) (Sirois et al., 2019b), or diabetes (Oktora et al., 2021). These studies have shown an increase in polypharmacy in the last decades. Nevertheless, polypharmacy has not been studied in older patients with schizophrenia, despite this concern similarly exists for these patients because of their elevated risk of multimorbidity (Buchanan et al., 2010; Fleischhacker et al., 2014; Jeon and Kim, 2017; Remington et al., 2017; Mamakou et al., 2018; Nguyen et al., 2018; Stummer et al., 2018; Stroup et al., 2021).

The cornerstone of schizophrenia treatment is antipsychotic medications (Marder and Cannon, 2019). Antipsychotic drugs usually must be taken lifelong (Remington et al., 2017; Marder and Cannon, 2019). Antipsychotic polypharmacy (Jeon and Kim, 2017), namely the use of more than one antipsychotic at the same time, is frequent in clinical practice either to achieve reasonable control of psychosis or to treat specific symptoms such as insomnia (Stummer et al., 2018) or other side effects (Baandrup, 2020). In a recent study on hospitalized patients with schizophrenia-spectrum disorders, 28.1% of patients took four or more psychotropic drugs before hospitalization, with a mean number of 2.8 medications. Still, the number of non-psychotropic drugs was not mentioned (Gaudiano et al., 2018). We can hypothesize that global polypharmacy is significant, especially in older patients with schizophrenia, given multimorbidity, as age is a predictor of polypharmacy in psychiatric patients (Viola et al., 2004; Paudel et al., 2020).

Even if global polypharmacy may be frequent in older patients with schizophrenia, studies on this topic have focused only on the psychiatric polypharmacy (Zink et al., 2010), with the main emphasis on the antipsychotic combination therapy (Gaudiano et al., 2018; Baandrup, 2020; Lin, 2020). Considering the potential burden that polypharmacy may impose on these patients, it is important to quantify the problem and to identify factors associated with polypharmacy that may help identify those at higher risk of adverse consequences of polypharmacy. To the best of our knowledge, no study has investigated the trends and patterns of global polypharmacy in older adults with schizophrenia.

The objectives of this study were thus to draw a portrait of polypharmacy among Quebec older adults with schizophrenia from 2000 to 2016 and to identify factors associated with different degrees of polypharmacy.

Materials and methods

Data source and population

We performed a population-based observational study of annual cohorts (one cohort for each year under study) using the data of the Quebec Integrated Chronic Disease Surveillance System (QICDSS) of the National Institute of Public Health of Quebec (*Institut National de Santé Publique du Québec*–INSPQ) (Blais et al., 2014). The QICDSS database is composed of five different sources of medico-administrative data: information on the insurance plan of its members (i.e., starting and end date of eligibility), on hospitalizations (i.e., primary and secondary diagnostic codes according to the ninth and tenth revisions of the International classification of diseases–ICD-9 and ICD-10, respectively), on physician visits (primary ICD-9 diagnostic codes), on reimbursed drugs (i.e., drug name, dispensing date, days' supply, the specialty of the prescriber) and on deaths. More than 90% of the Quebec population aged 65 years and above is covered by the public drug plan, and their information is in the QICDSS (Blais et al., 2014). Older adults in long-term care and those with a private drug plan are not covered by the public drug plan and are thus excluded.

This study identified all Quebec residents over 65 with an ICD-9 or ICD-10 diagnostic inpatient or outpatient code for schizophrenia (ICD-9: 295.0 to 295.9; ICD-10: F20.0 to F21.9, F23.2, F25.0 to F25.9) between April 1st, 2000 and March 31st, 2017. We constructed 17 cohorts (one for each year under study) which included both incident and prevalent cases of schizophrenia.

Definition of polypharmacy and medication use

We assessed the number of different medications used by each individual in every fiscal year, with the fiscal year beginning on April 1st and ending on March 31st. We included all the patients covered by the public drug insurance plan and alive for the year under investigation to assess the total number of medications used that year. Medications were classified according to the American Hospital Formulary Service (AHFS) classification (Francke, 1963) and common drug denomination (chemical name of the medication).

There is no consensus on the definition of polypharmacy, with the most common definitions used in the literature having a threshold of 5 or 10 medications (Sirois et al., 2019a). Considering the population of older adults with multimorbidity, we decided to use different thresholds to define polypharmacy. Thus, in this study, polypharmacy was referred to as the presence of prescription claims for at least 5, 10, 15, or 20 different medications in a fiscal year. We, therefore, assessed different degrees of polypharmacy for the time frame of a fiscal year, for every fiscal year in the study period. In accounting for the sum of medications claimed in each fiscal year, we considered only medications reimbursed by the public drug plan. Thus, over-the-counter drugs or other non-reimbursed medications (e.g., z-drugs) were not included. Medications used as needed ("prn") and those for acute illnesses (e.g., antibiotics), if reimbursed by the public drug plan, were included.

Socio-demographic and clinical characteristics

Socio-demographic characteristics of individuals in each cohort included age, sex, material and social deprivation index (in quintiles) and residence area [based on the Quebec census geographical areas: Montreal (> 1,000,000 inhabitants), other census metropolitan (100,000 to 1,000,000 inhabitants), agglomerations (10,000 to 100,000 inhabitants), and rural (< 10,000 inhabitants)]. Material and social deprivation indexes represent a proxy of the socioeconomic status of the individual (Pampalon et al., 2009). These indexes, which are ecological indexes based on the census dissemination area, are divided into quintiles, with the first quintile including the least deprived and the fifth quintile the most deprived individuals (Pampalon et al., 2009). We also calculated a global deprivation index combining social and material deprivations according to five classes (most deprived, deprived, mostly socially deprived, mostly materially deprived, least deprived), as explained in Supplementary Figure S1. We identified the annual number of hospitalizations and the number of physician visits recorded in the QIDSS for each individual and each year under study. ICD-9 and ICD-10 codes were used to identify comorbid conditions according to validated QICDSS algorithms for Alzheimer's disease, asthma, chronic obstructive pulmonary disease (COPD), diabetes, hypertension, mood disorders, osteoporosis, stroke, mood disorders, and dementia (Blais et al., 2014) during 5 years (the current year and the four preceding years). We used the combined Charlson-Elixhauser comorbidity index to calculate a score of the burden of comorbidities of each patient (Simard et al., 2018).

Statistical analysis

We used descriptive statistics to describe the subjects included in each cohort. For each subject, we assessed the number of different drugs claimed in every fiscal year by using the drug's common denomination (identifying the chemical entity). We calculated the proportion of individuals exposed to different degrees of polypharmacy and then estimated the age-standardized annual prevalence of polypharmacy with the reference population of Quebec in 2011. We further identified the clinical and socio-demographic factors associated with polypharmacy using robust Poisson regression analyses, modeling the number of individuals who claimed at least 5, 10, 15, or 20 different medications in a fiscal year, depending on the model and considering the correlation of the responses between subjects. Thus, we calculated unadjusted and adjusted prevalence ratios (PRs) and their 99% confidence intervals (CIs). We also tested the trends of change in the mean annual prevalence of polypharmacy with the same models. We performed all the analyses using SAS Enterprise Guide 7.1.

Results

Cohorts comprised 2,566 individuals in 2000 and up to 4,634 in 2016 (Table 1). Female patients were the large majority (about two-third of each cohort), as for those in the 66–75 age group (about 70%), with some changes in the age distribution depending on the cohort. Indeed, the proportion of older individuals (>85 years) slightly increased from 4.2% to 5.9% over time. Between 2000 and 2016, the proportion of individuals with mood disorders decreased by 26% (from 40.3% to 30.0%), but those with diabetes, hypertension and osteoporosis largely increased, with relative changes of 104%, 54%, and 124%, respectively. Indeed, as expected, with the aging of the individuals being part of the annual cohorts from 2000 to 2016, the population was composed of older individuals with more physical comorbidities in more recent years.

As reported in Figure 1, the number of different medications claimed increased over the 16 years, with the mean number of drugs claimed rising from 8.76 [standard deviation (SD) 5.29] in 2000 to 12.3 (SD 6.78) in 2016. Accordingly, the age-standardized prevalence of different degrees of polypharmacy also increased over time, with 36.9% of individuals being exposed to 10 drugs and above in 2000, increasing to 62.2% in 2016. Similarly, the prevalence of polypharmacy defined as 5 medications and above, as 15 medications and above, and as 20 medications and above went from 76.6%, 13.3%, and 3.9% in 2000 to 89.3%, 34.4%, and 14.4% in 2016, respectively (Figure 1). The trend analyses showed that the age-adjusted proportion of individuals exposed to different degrees of polypharmacy increased in the study period. Over the 17 years under investigation, the yearly mean increases of individuals exposed to varying degrees of polypharmacy were 0.8% (99% CI = 0.7%–0.9%) for 5 and more medications, 2.6% (99% CI = 2.4%–2.9%) for 10 medications and above, 4.5% (99% CI = 4.0%–4.9%) for 15 medications and above, and 5.2% (99% CI = 4.4%–5.9%) for 20 medications and above.

The rise in medication use was essentially driven by non-antipsychotic drugs, as presented in Table 2. The number of antipsychotics remained stable, with a mean number of antipsychotics consumed of 1.51 ± 0.75 in 2000 and 1.67 (±0.84) in 2016. When analyzing the prevalence of the main medication classes claimed, different patterns emerged. Some classes increased over the study period, such as cardiovascular medications, gastrointestinal

10.3389/fphar.2023.1080073

TABLE 1 Characteristics of the population studied from selected cohorts (2000; 2004; 2008; 2012 and 2016).

Characteristics	2000		2004		2008		2012		2016	
	n = 2,566		*n* = 2,947		*n* = 3,467		*n* = 4,100		*n* = 4,634	
	N	%	N	%	N	%	N	%	N	%
Age (years)										
66–75	1,832	71.4	2,037	69.1	2,326	67.1	2,849	69.5	3,283	70.9
76–85	627	24.4	773	26.2	960	27.7	1,020	24.9	1,079	23.3
86+	107	4.2	137	4.7	181	5.2	231	5.6	272	5.9
Sex										
Female	1,780	69.4	1,971	66.9	2,284	65.9	2,652	64.7	2,846	61.4
Male	786	30.6	976	33.1	1,183	34.1	1,448	35.3	1,788	38.6
Material deprivation (quintile)										
1 (least deprived)	380	14.8	347	11.8	458	13.2	524	12.8	586	12.7
2	407	15.9	433	14.7	530	15.3	562	13.7	628	13.6
3	455	17.7	526	17.9	619	17.9	628	15.3	721	15.6
4	448	17.5	588	20.0	670	19.3	794	19.4	868	18.7
5 (most deprived)	585	22.8	620	21.0	740	21.3	879	21.4	1,012	21.8
Missing	291	11.3	433	14.7	450	13.0	713	17.4	819	17.7
Social deprivation (quintile)										
1 (least deprived)	275	10.7	260	8.8	328	9.5	372	9.1	425	9.2
2	309	12.0	359	12.2	399	11.5	422	10.3	513	11.1
3	407	15.9	448	15.2	527	15.2	575	14.0	574	12.4
4	521	20.3	590	20.0	715	20.6	874	21.3	998	21.5
5 (most deprived)	763	29.7	857	29.1	1,048	30.2	1,144	27.9	1,305	28.2
Missing	291	11.3	433	14.7	450	13.0	713	17.4	819	17.7
Comorbidity										
Alzheimer	247	9.6	333	11.3	495	14.28	629	15.34	606	13.1
Asthma	144	5.6	223	7.6	332	9.58	424	10.34	499	10.8
COPD	533	20.8	725	24.6	901	25.99	1,107	27.00	1,348	29.1
Diabetes	405	15.8	612	20.8	883	25.5	1,175	28.7	1,492	32.2
Heart Failure	191	7.4	234	7.9	270	7.8	345	8.4	389	8.4
Hypertension	946	36.9	1,388	47.1	1799	51.9	2,316	56.5	2,638	56.9
Mood disorders	1,034	40.3	1,150	39.0	1,352	39.0	1,372	33.5	1,390	30.0
Osteoporosis	305	11.9	508	17.2	777	22.4	1,098	26.8	1,235	26.7
Stroke	171	6.7	238	8.1	323	9.3	350	8.5	404	8.7
Number of comorbidities[a]										
0–1	615	24.0	688	23.4	761	22.0	923	22.5	1,143	24.7
2	623	24.3	650	22.1	773	22.3	893	21.8	901	19.4
3–4	779	30.4	907	30.8	1,045	30.1	1,052	25.7	1,223	26.4
5+	549	21.4	702	23.8	888	25.6	1,232	30.1	1,367	29.5
Combined comorbidity score[b]										

(Continued on following page)

TABLE 1 (*Continued*) Characteristics of the population studied from selected cohorts (2000; 2004; 2008; 2012 and 2016).

Characteristics	2000		2004		2008		2012		2016	
	n = 2,566		*n* = 2,947		*n* = 3,467		*n* = 4,100		*n* = 4,634	
	N	%	N	%	N	%	N	%	N	%
0	183	7.1	206	7.0	1,607	46.4	1,848	45.1	2,106	45.5
1	1,144	44.6	1,294	43.9	424	12.2	464	11.3	495	10.7
2	324	12.6	360	12.2	434	12.5	491	12.0	505	10.9
3+	915	35.7	1,087	36.9	1,002	28.9	1,297	31.6	1,528	33.0
Number of hospitalizations[c]										
0	1,567	61.1	1,862	63.2	2,233	64.4	2,660	64.9	3,055	65.9
1	642	25.0	684	23.2	774	22.3	899	21.9	984	21.2
2+	357	13.9	401	13.6	460	13.3	541	13.2	595	12.8
Number of physician visits[c]										
0	227	8.9	289	9.8	266	7.7	276	6.7	318	6.9
1–4	742	28.9	989	33.6	1,327	38.3	1,677	40.9	2027	43.7
5–9	629	24.5	702	23.8	849	24.5	1,023	25.0	1,088	23.5
10+	968	37.7	967	32.8	1,025	29.6	1,124	27.4	1,201	25.9

[a]Number of physical and psychiatric comorbidities in a 5-years period (the current year and the 4-years before).
[b]Charlson—Elixhauer combined comorbidity score measured in a 5-years period (the current year and the 4-years before).
[c]Number of physician visits and hospitalizations in the current year.

TABLE 2 Number of different antipsychotic medications claimed during one year-period by older people with schizophrenia from 2000 to 2016.

Number of antipsychotic medications	2000		2004		2008		2012		2016	
	n = 2,566		*n* = 2,947		*n* = 3,467		*n* = 4,100		*n* = 4,634	
	N	%	N	%	N	%	N	%	N	%
Mean ± SD	1.51 ± 0.75		1.52 ± 0.74		1.54 ± 0.75		1.62 ± 0.77		1.67 ± 0.84	
0	419	16.3	387	13.1	398	11.5	664	16.2	642	13.9
1	1,321	51.5	1,552	52.7	1,791	51.7	1,836	44.8	2,060	44.5
2	607	23.7	748	25.4	964	27.8	1,168	28.5	1,360	29.4
3+	219	8.5	260	8.8	314	9.1	432	10.5	572	12.3

SD: standard deviation

medications (mainly driven by proton pump inhibitors–PPIs), and osteoporosis medications (Figure 2). Other classes, such as anxiolytics, showed an important decrease overtime. The more impacting diseases were cardiovascular and respiratory comorbidities, such as heart failure, stroke, asthma, and COPD.

In the multivariable robust Poisson regressions, women were more likely to be exposed to polypharmacy with adjusted prevalence ratios (PR) ranging from 1.05 for 5 to 1.22 for 20 medications and above (Table 3). Older individuals were slightly more likely to be exposed to lower degrees of polypharmacy (5+ and 10+ medications), while age was not a statistically significant factor for higher levels of polypharmacy (15+ and 20+). The only clinically significant factor statistically associated with polypharmacy was the number of comorbidities, with prevalence ratios increasing with the number of comorbidities and the degree of polypharmacy (see Table 3).

Discussion

The main result of this study is that polypharmacy has been increasing steadily over the last few years for older patients with schizophrenia. To the best of our knowledge, this study is the first one that has evaluated polypharmacy and not only psychiatric polypharmacy (e.g., the use of more than one psychotropic medication) in older individuals with schizophrenia. Some studies have evaluated psychotropic medication use and psychiatric polypharmacy in this population. In a study on schizophrenia-spectrum disorder patients, the authors found that, at hospitalization, 28.1% of patients received four or more psychotropic drugs with a mean number of 2.8 (Gaudiano et al., 2018). Those with four or more psychotropic drugs were older (43.0 vs. 38.6 years) and had more medical comorbidities, including metabolic conditions (Gaudiano

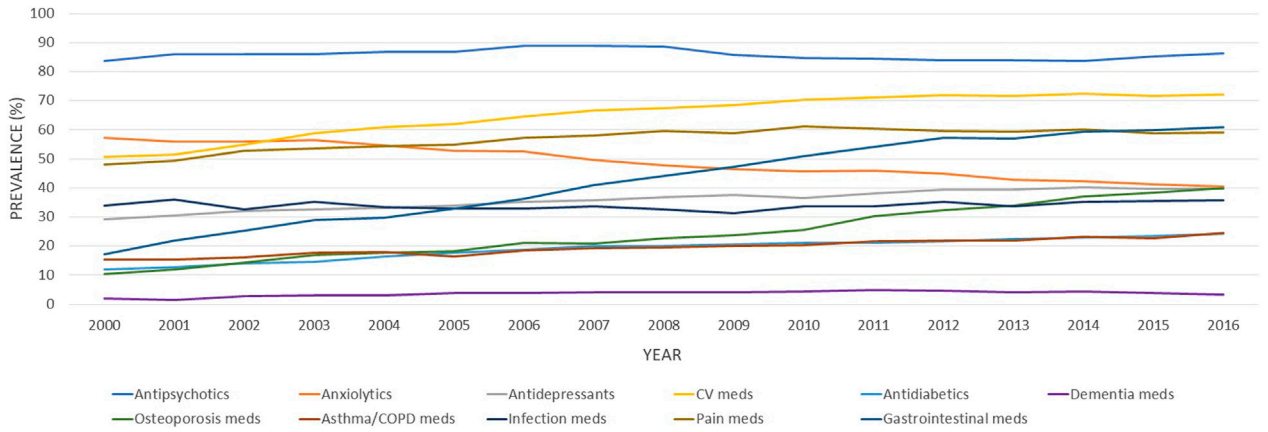

FIGURE 1
Age-standardized proportions of older adults with schizophrenia exposed to different degrees of polypharmacy (≥5, ≥10, ≥15, and ≥20 medications), between 2000 and 2016. Bars represent the age-adjusted prevalence of different degrees of polypharmacy and the line is the mean number of different medications claimed in the current fiscal year.

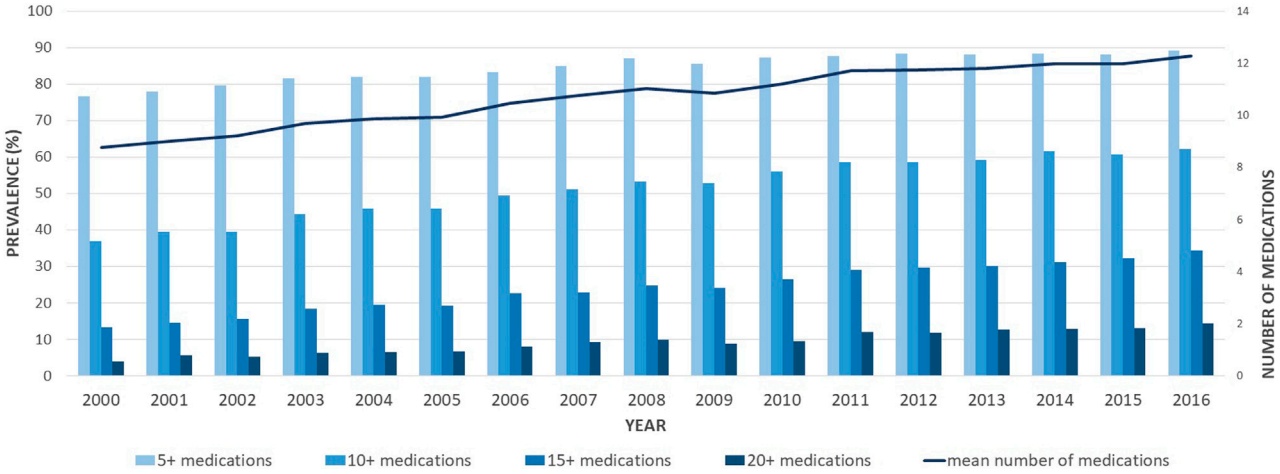

FIGURE 2
Age-standardized proportions of older adults with schizophrenia exposed to different classes of medications between 2000 and 2016. CV, cardiovascular; COPD, chronic obstructive pulmonary disease; Meds, medications.

et al., 2018). Even if the number of non-psychotropic drugs was not estimated in that study, we could hypothesize that global polypharmacy was significantly higher. A study analyzing prescriptions from office-based physicians in the United States to treat schizophrenia patients showed that 29% of them received at least two medications and 18% three or more (Dussias et al., 2010). Moreover, 58% of patients received one or more antipsychotic medications, and the others received a combination of antipsychotics and other psychiatric medications (20% antidepressants, 15% mood stabilizers, 7% anxiolytics, and 6% treatment for extrapyramidal symptoms) (Dussias et al., 2010). In another study evaluating central nervous system (CNS) medication prescriptions trends in patients with schizophrenia-related conditions between 2004 and 2012 (Heald et al., 2017), the authors found an increase in psychotropic polypharmacy over the study period. This rise corresponded to increased body mass index (BMI) and fasting blood glucose (Heald et al., 2017), conditions requiring additional pharmacological treatments. Despite the lack of studies on global pharmacology in older patients with schizophrenia, the cited studies evaluating psychotropic medications indicate that the pharmacological burden on these patients is significant. Psychiatric polypharmacy could indeed increase the burden of medication load leading to an increase in medications used for both mental and somatic conditions.

In the context of the lack of studies evaluating the global pharmacological burden affecting these patients, our study underlines the high prevalence of polypharmacy, with more than a third of patients having claimed at least 15 different medications in the last year under study. This study should be a starting point in the research on older patients with schizophrenia. Indeed, the long-term

TABLE 3 Multivariable robust Poisson regressions of the factors associated with polypharmacy, defined as the claim of at least five, ten, fifteen, or twenty different medications in 1 year during the study period.

Characteristics	Polypharmacy definition															
	5+ medications				10+ medications				15+ medications				20+ medications			
	aPR	99% CI		*p* value	aPR	99% CI		*p* value	aPR	99% CI		*p* value	aPR	99% CI		*p* value
Year	**1.01**	**1.01**	**1.01**	**<0.0001**	**1.03**	**1.02**	**1.03**	**<0.0001**	**1.04**	**1.04**	**1.05**	**<0.0001**	**1.06**	**1.05**	**1.06**	**<0.0001**
Age																
66-75	1	-	-	-	**1**	-	-	-	1	-	-	-	1	-	-	-
76-85	**1.03**	**1.01**	**1.04**	**<0.0001**	**1.03**	**1.01**	**1.06**	**0.0009**	1.02	0.98	1.07	0.1702	0.98	0.90	1.06	0.4985
86+	**1.03**	**1.01**	**1.05**	**<0.0001**	**1.07**	**1.03**	**1.12**	**<0.0001**	1.02	0.95	1.11	0.4517	0.88	0.76	1.03	0.0335
Sex																
Female	**1.05**	**1.04**	**1.07**	**<0.0001**	**1.12**	**1.08**	**1.15**	**<0.0001**	**1.17**	**1.11**	**1.23**	**<0.0001**	**1.22**	**1.11**	**1.33**	**<0.0001**
Male	1	-	-	-	**1**	-	-	-	1	-	-	-	1	-	-	-
Combined social and material deprivation																
Least deprived	1	-	-	-	1	-	-	-	1	-	-	-	1	-	-	-
Deprived	1.10	0.98	1.02	0.7063	1.01	0.96	1.05	0.7555	1.05	0.96	1.15	0.1562	1.05	0.90	1.24	0.4046
Mostly social deprived	1.00	0.98	1.02	0.7462	1.01	0.96	1.06	0.6198	1.04	0.95	1.13	0.2441	1.09	0.93	1.28	0.1394
Mostly material deprived	1.01	0.99	1.03	0.4503	1.02	0.97	1.06	0.3460	1.09	1.00	1.19	0.0076	1.06	0.90	1.24	0.3587
Least deprived	1.00	0.98	1.02	0.8444	1.01	0.97	1.06	0.4450	1.10	1.01	1.19	0.0036	1.10	0.95	1.29	0.0974
Missing	1.01	0.99	1.03	0.2489	1.04	1.00	1.10	0.0176	**1.16**	**1.06**	**1.28**	**<0.0001**	1.17	0.99	1.38	0.0126
Number of comorbidities[a]																
0-1	1	-	-	-	**1**	-	-	-	**1**	-	-	-	**1**	-	-	-
2	**1.16**	**1.14**	**1.18**	**<0.0001**	**1.36**	**1.31**	**1.42**	**<0.0001**	**1.60**	**1.47**	**1.74**	**<0.0001**	**1.92**	**1.61**	**2.30**	**<0.0001**
3-4	**1.24**	**1.22**	**1.27**	**<0.0001**	**1.74**	**1.67**	**1.81**	**<0.0001**	**2.51**	**2.31**	**2.72**	**<0.0001**	**3.90**	**3.29**	**4.62**	**<0.0001**
5+	**1.30**	**1.27**	**1.32**	**<0.0001**	**2.14**	**2.06**	**2.23**	**<0.0001**	**4.12**	**3.80**	**4.45**	**<0.0001**	**9.28**	**7.86**	**10.95**	**<0.0001**
Residence area																
Urban																
> 1,000,000 inhab	1	-	-	-	**1**	-	-	-	**1**	-	-	-	**1**	-	-	-
≥ 100,000 inhab	**1.04**	**1.02**	**1.05**	**<0.0001**	**1.10**	**1.06**	**1.13**	**<0.0001**	**1.17**	**1.10**	**1.24**	**<0.0001**	**1.19**	**1.08**	**1.33**	**<0.0001**
≥ 10,000 inhab	**1.05**	**1.03**	**1.07**	**<0.0001**	**1.13**	**1.09**	**1.18**	**<0.0001**	**1.23**	**1.15**	**1.32**	**<0.0001**	**1.20**	**1.05**	**1.36**	**0.0003**

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TABLE 3 (*Continued*) Multivariable robust Poisson regressions of the factors associated with polypharmacy, defined as the claim of at least five, ten, fifteen, or twenty different medications in 1 year during the study period.

Characteristics	Polypharmacy definition															
	5+ medications			10+ medications			15+ medications			20+ medications						
	aPR	99% CI		*p* value	aPR	99% CI		*p* value	aPR	99% CI		*p* value	aPR	99% CI		*p* value
Rural																
<10,000 inhab	**1.04**	**1.03**	**1.06**	**<0.0001**	**1.13**	**1.09**	**1.17**	**<0.0001**	**1.24**	**1.16**	**1.32**	**<0.0001**	**1.31**	**1.17**	**1.47**	**<0.0001**
Missing	**1.05**	**1.02**	**1.09**	**<0.0001**	**1.08**	**1.01**	**1.16**	**0.0056**	0.95	0.82	1.10	0.3417	0.89	0.68	1.16	0.2535

Inhab, inhabitants; aPR, Adjusted prevalence ratio.
[a]Number of physical and psychiatric comorbidities in a 5-years period (the current year and the 4-years before).
Items in bold indicate statistically significant factors.

pharmacological treatment of these patients should be considered globally in a holistic point of view. The pharmacological treatment should thus be re-evaluated when the patient becomes older. Polypharmacy is a well-known risk factor for many adverse outcomes (Davies et al., 2020; Zaninotto et al., 2020; Franchi et al., 2021; Li et al., 2022). The high proportion of individuals exposed to this potential risk should raise concerns and stimulate new studies on this vulnerable population.

In our population, the rise in polypharmacy was mainly driven by non-antipsychotic medications, for which the use rested stable over time. Some classes, such as medications for osteoporosis or gastrointestinal and cardiovascular drugs, showed an increased use over time. These increases are due to the aging population during the study period and the presence of effective medications on the market (i.e., PPIs). Other classes, such as anxiolytics, showed a significant decrease over time, driven by the changes in clinical guidelines as reported also from a recent population-based study in Quebec (Gosselin et al., 2022). The most used medication classes were those for cardiovascular and respiratory comorbidities, such as heart failure, stroke, asthma, and COPD. Chronic somatic diseases are more frequent among schizophrenia patients than in the general older population. In a review including 25,692 schizophrenia patients, the prevalence of metabolic syndrome was estimated at 32.5%, increasing to 51.9% for patients treated with clozapine (Mitchell et al., 2013). Among older patients with schizophrenia, diabetes is highly prevalent (about 25% of patients), especially among women (Annamalai et al., 2017; Huo et al., 2021), with a 2 to 5-fold increased risk than in the general population (Annamalai et al., 2017; Mamakou et al., 2018). Similarly, these patients are at higher risk for hypertension (Meszaros et al., 2011; Mamakou et al., 2018), obesity (Allison et al., 2009; Annamalai et al., 2017), and dyslipidemia (Mamakou et al., 2018). The higher risk of schizophrenia patients for these comorbidities can be explained by the physiopathology of the disease itself and the utilization of psychotropic medications (Mitchell et al., 2013; Abosi et al., 2018; Mamakou et al., 2018). Antipsychotic medications are indeed associated with an important side effect burden, including metabolic side effects (Jeon and Kim, 2017). Antipsychotic side effects are common, and they may easily reach an intensity requiring another pharmacological treatment, such as benztropine for extrapyramidal side effects (Marder and Cannon, 2019), benzodiazepines, propranolol, or mirtazapine for akathisia, (Zink et al., 2010; Marder and Cannon, 2019), metformin or liraglutide for weight control (de Silva et al., 2016; Grigg et al., 2017), aripiprazole or hormone therapy for hyperprolactinemia (Myles et al., 2017), hormonal therapy for sexual dysfunctions (Grigg et al., 2017; Marder and Cannon, 2019), or laxatives for constipation (De Berardis et al., 2018).

We observed that the number of comorbidities increased over time and contributed to the burden of polypharmacy. This was confirmed by the multivariate regression models analyzing the factors associated with different degrees of polypharmacy. In those analyses, no matter the definition of polypharmacy used, multimorbidity was a statistically and clinically significant factor associated with polypharmacy. The American Psychiatric Association (APA) practice guidelines for managing patients with schizophrenia (Keepers et al., 2020) highlight the importance of addressing integrated medical care to prevent and treat comorbidities. They address weight management, smoke cessation, cardiovascular risk factors (metabolic syndrome, hypertension, dyslipidemia, or heart failure), and renal and liver function. Moreover, these guidelines recommend identifying optimal approaches to prevent and treat specific side effects of antipsychotic medications (i.e., weight gain, metabolic syndrome, cardiovascular

toxicity) (Areas for Further Research in Individuals With Schizophrenia, 2021), with particular attention to older individuals for their higher risk for side effects of antipsychotic medications, and potential renal and hepatic impairment (Keepers et al., 2020). Nevertheless, the risks and benefits of exposure to many medications (e.g., polypharmacy) to treat comorbid conditions in older patients with schizophrenia are not well defined yet.

Polypharmacy is a real concern in all older individuals because it has been associated with negative health outcomes such as non-adherence (Franchi et al., 2021), drug-drug interactions (Davies et al., 2020), potentially inappropriate medications (Davies et al., 2020), falls (Zaninotto et al., 2020), hospitalizations (Davies et al., 2020), and mortality (Li et al., 2022), also in COVID-19 patients (Sirois et al., 2022). In this schizophrenia patients, the use of antipsychotic medications, which are necessary to control the symptoms of the disease, can increase the risk for physical comorbidities, especially cardiovascular and metabolic ones (Jeon and Kim, 2017). Older patients with schizophrenia represent a real challenge because of the high number of medications they receive for schizophrenia itself and the frequent comorbidities they are diagnosed with. Future studies should identify the effect of polypharmacy on the risk of negative health outcomes and mortality. They should also focus on which combinations of medications can provide the greatest benefits with the lowest risks for better integrated medical care, considering not only the control of schizophrenia and the management of its treatment with antipsychotics and psychiatric medications but also non-psychiatric comorbidities, their prevention and treatment.

This study highlighted how polypharmacy is frequent in older adults with schizophrenia, even when more restrictive thresholds as 15 or 20 medications and above are used to define it. These patients are indeed at elevated risk for drug-drug interactions, adverse drug effects interactions, and drug-disease interactions compared to their peers without schizophrenia because of the frequency of physical comorbidities and the already impacting burden of antipsychotic treatments.

We believe this study has the main strength of well highlighting the burden of global polypharmacy among older individuals with schizophrenia. Medico-administrative databases allowed us to access annual large cohorts of patients with schizophrenia throughout Québec, as well as all the reimbursed medications they claimed, the diagnoses they received, and their resource utilization. With this approach, we could observe the pharmacological burden of older patients with schizophrenia, putting the antipsychotic treatment in the context of the global treatment of the older individual. Moreover, we could analyze trends and patterns of different pharmacological classes over a period of almost 20 years, highlighting changes and practices.

The results of this study should, nevertheless, be considered in light of some limitations. First, because of the use of administrative databases, we could not clinically assess the diagnosis of schizophrenia or the presence of comorbidities. However, the algorithms used for the identification of such diagnoses are routinely used by the INSPQ for surveillance purposes and the QICDSS (Blais et al., 2014). We could also have overestimated polypharmacy. To measure polypharmacy, we used claims of prescribed medications during a 1-year time frame. This means that the medications considered could not have been used simultaneously, as happens when treatments are switched because of side effects or inefficacy. On the contrary, we could consider only prescribed medications reimbursed by the public drug plan. This could have thus led to an underestimation of polypharmacy since over-the-counter medications, such as anti-inflammatory drugs, or laxatives, have not been considered among the medications accounting for polypharmacy. Still, since the same operational definition of polypharmacy was used for every year of the study, the conclusion on the increasing burden of medications among older individuals with schizophrenia persist, with the same overestimation of individuals exposed to polypharmacy being homogenous over time. Finally, this study aimed to explore global polypharmacy in older patients with schizophrenia, its prevalence, trends, and patterns over time, and it was thus designed for these purposes only. Therefore, we did not assess the effects of polypharmacy, such as adverse events, hospitalizations or mortality in this population.

Conclusion

We found a noticeable increase in polypharmacy exposure in older adults with schizophrenia, with the proportion of subjects having claimed at least 5, 10, 15, and 20 medications increasing to about 90%, 60%, 35%, and 15% in 2016. This raises concerns about the growing risks of adverse effects and drug-drug interactions that could arise in these patients, especially considering the use of antipsychotic treatments.

The risks and benefits of polypharmacy in older patients with schizophrenia are not well defined yet. There is a need to better understand which combinations of medications provide the greatest benefits and lowest risks and consider the presence of non-psychiatric comorbidities and the concomitant use of psychiatric and non-psychiatric drugs.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: We do not have permission to share the data from the Quebec Integrated Chronic Diseases Surveillance System (QICDSS). Requests to access these datasets should be directed to the Quebec Information access commissioner—Commission d'accès à l'information du Québec.

Ethics statement

For this study, medico-administrative data were analyzed retrospectively. The study protocol was reviewed and approved by the Ethics Committee for sectoral research in population and first-line health of the CIUSSS de la Capitale-Nationale (#2021–2049, 2021–2049_SPPL) and the Ethics committee of the Université du Québec à Rimouski (CÉR-112-849). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

CL and CS conceived the research protocol and the analyses. LR carried out the statistical analyses. AO, CL, CS, and VM interpreted the results and prepared the tables and figures. CL and IT took the lead in writing the manuscript. All authors

provided critical feedback and contributed to the first draft discussion. All authors approved the submitted version of the manuscript.

Funding

This work was supported by the Réseau québécois de recherche sur les médicaments (RQRM) though the RQRM-Pharmacoépidémiologie 2020 grant (CL and CS as principal investigators). CS was the recipient of a Junior 2 salary award from the Fonds the recheche du Québec–Santé.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1080073/full#supplementary-material

SUPPLEMENTAL FIGURE S1
Graphical representation of the combined deprivation index. The combined deprivation index combines social and material deprivation into a grouped deprivation index. Green: most deprived; Yellow: deprived; Blue: mostly socially deprived Orange: mostly materially deprived; Purple: least deprived.

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frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 08 February 2023
DOI 10.3389/fphar.2023.1030849

OPEN ACCESS

EDITED BY
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SPECIALTY SECTION
This article was submitted to Drugs Outcomes Research and Policies, a section of the journal Frontiers in Pharmacology

RECEIVED 29 August 2022
ACCEPTED 27 January 2023
PUBLISHED 08 February 2023

CITATION
Wastesson JW, Fritzell J, Burström B, Johnell K and Fastbom J (2023), Regional variations in excessive polypharmacy and potentially inappropriate drug use among older adults in Sweden: Trends from 2006 to 2020.
Front. Pharmacol. 14:1030849.
doi: 10.3389/fphar.2023.1030849

Regional variations in excessive polypharmacy and potentially inappropriate drug use among older adults in Sweden: Trends from 2006 to 2020

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Introduction: Potentially inappropriate drug use (PID) is common among older adults. Cross-sectional data suggest that there are marked regional variations in PID in Sweden. There is, however, a lack of knowledge about how the regional variations have changed over time.

Objectives: This study aimed to investigate the regional differences in the prevalence of PID in Sweden, 2006–2020.

Methods: In this repeated cross-sectional study, we included all older adults (≥75 years) registered in Sweden, yearly from 2006 to 2020. We used nationwide data from the Swedish Prescribed Drug Register linked at the individual level to the Swedish Total Population Register. We selected three indicators of PID according to the Swedish national "Quality indicators for good drug therapy in the elderly": 1) Excessive polypharmacy (use of ≥10 drugs); 2) Concurrent use of three or more psychotropic drugs; 3) Use of "drugs that should be avoided in older adults unless specific reasons exist." The prevalence of these indicators was calculated for each of Sweden's 21 regions, yearly from 2006 to 2020. The annual coefficient of variation (CV) was calculated for each indicator by dividing the standard deviation of the regions by the national average, to measure relative variability.

Results: In the population of about 800,000 older adults per year, the national prevalence of "drugs that should be avoided in older adults," was reduced by 59% from 2006 to 2020. There was a slight decline in the use of three or more psychotropics, while the prevalence of excessive polypharmacy increased. The CV for excessive polypharmacy was 14% in 2006 and 9% in 2020 compared to 18% and 14% for "use of three or more psychotropics", and stable at around 10% for 'drugs that should be avoided in older adults.'

Conclusions: The regional variation in potentially inappropriate drug use decreased or were stable from 2006 to 2020. The regional differences were largest for the use of three or more psychotropics. We found a general tendency that regions with a good performance at the start of the period performed well across the entire period. Future studies should investigate the reasons for regional variation and explore strategies to reduce unwarranted differences.

KEYWORDS

aged, ageing population, scoping, polypharmacy source: MeSH, inappropriate drug use, trends (source: MeSH NLM), regional variability

1 Introduction

Potentially inappropriate drug use (PID) is common among older adults (Guaraldo et al., 2011; Opondo et al., 2012; Hill-Taylor et al., 2013; Tommelein et al., 2015). PID is associated with adverse drug events, hospitalisations and mortality (Muhlack et al., 2017; Xing et al., 2019). In Sweden, many indicators of PID and hazardous drug use have decreased over time (e.g., "Drugs that should be avoided in older adults unless specific reasons exist", use of antipsychotic drugs, and potential drug-drug interactions) whereas some have been stable or even increased (e.g., excessive polypharmacy) (Hovstadius et al., 2013; Thorell et al., 2020). Large regional variations in the prevalence of PID have been reported for specific years for Sweden (Johnell et al., 2007; Socialstyrelsen, 2017a). However, the long-term trends in these regional differences have not been investigated.

PID among older adults is frequently assessed using consensus-based explicit criteria. Internationally, there exist a number of lists of inappropriate drugs for older adults, for example Beers criteria (Fick et al., 2012; Samuel, 2015; Fick et al., 2019) and STOPP/START criteria (Gallagher et al., 2008; O'mahony et al., 2015). In Sweden, the most frequently used are the "Indicators for good drug therapy in the elderly", introduced by the Swedish National Board of Health and Welfare in 2004 (Socialstyrelsen, 2004) and continuously updated in 2010 (National Board of Health and Welfare, 2010) and 2017 (Socialstyrelsen, 2017b). The different sets of criteria typically share many features and include similar drugs, although some variations exists, partly due to differences in the national drug formularies (Morin et al., 2015). For a comparison between the previous versions of the Swedish criteria and other lists, see Morin et al, (2015) and Fastbom and Johnell, (2015). We selected three of the most general indicators from the Swedish criteria to examine regional variations over time.

Regional variations in drug use can occur for several reasons, often divided into contextual and individual/compositional factors (Morgan et al., 2010). Contextual factors are generally factors distal to the individual, describing the context in which medications are prescribed and consumed. In Sweden, the overall responsibility for medication policy belong to the 21 regions (Wettermark et al., 2008). Each region has its own medication committee making recommendations and governing the drug prescribing in their region. Thus, possible contextual factors may be related to the recommendations issued by the medication committee in each region. This is for example done by producing formulary of essential medicines, most notably the "Wise List" issued by Stockholm healthcare region (Eriksen et al., 2017). Another contextual factor may be "therapeutic traditions" (Ohlsson et al., 2009). This implies that prescribers sharing a common workplace or geographical proximity have similar prescribing patterns. Individual/compositional factors are instead about differences in population characteristics across regions, i.e., inhabitants of a certain region might be different in relation to age, sex, socioeconomics, and health status (Morgan et al., 2010).

Regional variations in general drug use and for specific classes are frequently reported in the literature (Wangia and Shireman, 2013). Fewer studies have investigated trends in regional differences in drug use for older adults (Hogan et al., 2003; Naughton et al., 2006; Jirón et al., 2016; Hyttinen et al., 2019; Nothelle et al., 2019). A notable exception is a Canadian study, finding persistent and unexplained regional variation in commonly used drugs by older adults (Hogan et al., 2003). The differences included both variation in the number of used drugs and type of drugs across the regions. The significant differences identified in that study did not match the regional differences in medical conditions or drug benefit plan. Hence, the authors concluded that the reasons for the regional variation were largely unexplained.

Understanding regional variations in trends of PID is important to describe prescribing patterns and identify regions where performance could be improved. Furthermore, describing regional trends can also serve to generate hypotheses about the causes of these differences. Therefore, this study aimed to i) investigate the overall trend of PID in Sweden 2006–2020, ii) to explore regional variations in this trend.

To this end, we have used data from the nationwide Swedish Prescribed Drug Register (SPDR) to analyse drug use in persons 75 years and older during the years 2006–2020, focusing on three indicators of PID from the Swedish criteria: excessive polypharmacy, use of three or more psychotropic drugs and use of "drugs that should be avoided in older adults unless specific reasons exist."

2 Materials and methods

2.1 Data source

The current study was based on routinely collected data in Sweden, a country with a universal healthcare system. The data were extracted from two Swedish nationwide population-based registers, linked by the unique personal identity number, pseudonymised to the researchers: 1) The Total Population Register at Statistics Sweden provided information about who were residents in Sweden, as well as dates of deaths and moving in/out of the country during the study period (Ludvigsson et al., 2016). 2) The Swedish Prescribed Drug Register (SPDR) at the Swedish National Board of Health and Welfare provided information on all prescribed drugs purchased at pharmacies in Sweden (Wettermark et al., 2007).

2.2 Study design and population

This is a repeated cross-sectional study including all individuals aged 75 years and older and registered as living in Sweden, each year from 2006 to 2020.

2.3 Assessment of outcomes

Data on drug use were extracted from the SPDR. Current drug use on 31 December each year was calculated for each individual, based on the date of drug dispensing, the total amount of drug dispensed and the prescribed daily dose, as previously described (Wallerstedt et al., 2013). The number of different drugs used on the index date is presented as the number of distinct brand names according to the

TABLE 1 Description of the study populations 2006–2020.

	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
All, n	811,377	811,423	809,481	809,149	811,409	815,855	820,905	830,758	845,429	857,888	875,067	900,499	933,409	976,022	1,014,596
Age, mean	82.0	82.0	82.1	82.2	82.2	82.2	82.2	82.1	82.1	82.1	82.0	81.9	81.7	81.6	81.5
Females, %	60.8	60.6	60.4	60.2	59.9	59.6	59.3	58.9	58.5	58.1	57.7	57.2	56.8	56.3	56.0
Number of drugs, mean	4.4	4.4	4.5	4.4	4.7	4.8	4.6	4.6	4.7	4.8	4.8	4.7	4.6	4.6	4.7
Excessive polypharmacy															
Prevalence, %	9.5	9.3	10.1	9.6	10.9	11.0	9.9	10.1	10.7	11.2	11.4	11.0	10.5	11.0	11.6
Regional variation coefficient[a], %	14.0	11.9	11.9	10.7	10.6	10.3	9.7	9.5	9.0	10.5	9.5	9.0	8.7	9.3	9.0
Use of 3 or more psychotropics															
Prevalence, %	3.9	3.7	3.8	3.3	3.9	4.0	3.6	3.5	3.8	4.0	3.8	3.4	3.1	3.3	3.4
Regional variation coefficient[a], %	17.8	15.8	16.3	18.2	17.0	16.0	18.6	17.2	17.2	18.1	16.1	16.9	17.1	14.1	14.1
Drugs that should be avoided in older adults unless specific reasons exist															
Prevalence, %	13.1	12.2	11.9	10.7	11.0	10.6	9.0	8.2	7.6	7.2	6.7	6.3	5.8	5.5	5.4
Regional variation coefficient[a], %	9.6	10.0	9.4	9.3	9.2	8.1	8.6	7.8	8.4	8.1	8.5	8.8	8.7	9.9	10.8

[a]Standard deviation expressed as percent of the mean.

10.3389/fphar.2023.1030849

5th level of Anatomical Therapeutic Chemical (ATC) classification system.

To assess the extent and quality of drug use in older persons, we operationalised three indicators from the Swedish national "Indicators for good drug therapy in the elderly" (Fastbom and Johnell, 2015):

Use of 10 or more drugs (definition of excessive polypharmacy), the number of distinct brand names according to the 5th level of the ATC classification system.

Use of three or more psychotropic drugs (i.e., belonging to ATC-groups N05A, N05B, N05C or N06A; Supplementary Table S1).

Drugs that "should be avoided in older adults unless specific reasons exist" (inappropriate drugs) (list of ATC codes available in Supplementary Table S2).

2.4 Statistical analysis

Descriptive statistics were used for illustrating the geographical distribution of the three indicators. In order to have a standardised measure of the regional variability, we calculated the annual coefficient of variation (CV), by dividing the standard deviation of the regions by the national average, for each indicator and year. Further, we calculated how the prevalence of each region diverged from the national average for each year and indicator, in order to display the relative difference between regions. As a supplementary analysis, we provide the ranking of the regions in year 2006 and 2020 for each indicator, to display the regions relative performance across the study period. As a *post hoc* analysis, we report the 10 most frequently used psychotropic drugs and "drugs that should be avoided in older adults unless specific reasons exist" in year 2006 and 2020. This was done in order to display changes in item composition over the period. The Statistical Package for the Social Sciences (SPSS Statistics, version XX, Chicago, IL) was used for the analyses.

2.5 Ethical approval

The study was approved by the Regional Ethical Review Board in Stockholm (2016/1001–31/4, 2020–03525; 2021–02004).

3 Results

More than 800,000 individuals aged 75 years and older were included each year from 2006 to 2020. The mean age was about 82 years each study year, and the proportion of females was 61% in 2006 and 56% in 2020 (Table 1). Nationally, there was a 7% increase in the mean number of drugs, and the prevalence of excessive polypharmacy increased by 22%, from 9.5% to 12% from 2006 to 2020. The use of three or more psychotropic drugs decreased by 13% (from 3.9% in year 2006 to 3.4% in year 2020). The use of "drugs that should be avoided in older adults unless specific reasons exist", decreased by 59%, from 13% to 5.4%.

The coefficient of variation (CV) decreased from 14% in 2006 to 9% in 2020 for excessive polypharmacy and from 18% to 14% for the use of three or more psychotropic drugs. For "drugs that should be avoided in older adults unless specific reasons exist" the CV remained stable at around 10% during the study period.

The prevalence of excessive polypharmacy increased in all 21 regions from 2006 to 2020 (Figure 1A). The numbers supporting these figures is also reported in Supplementary Table S3A–C For the indicator "use of three or more psychotropics", the prevalence decreased or remained stable in all but one region. (Figure 1B). Overall, zopiclone (ATC: N05CF01) was the most frequently used psychotropic drug in 2006 and 2020. The use of most of the specific psychotropic drugs declined during the period, with mirtazapine (ATC: N06AX11) as an exception (Supplementary Table S4). The prevalence of use of "drugs that should be avoided in older adults unless specific reasons exist" declined in all regions from 2006 to 2020 (Figure 1C). Of the drugs that should be avoided, all of the frequently used ones declined from 2006 to 2020, except a slight increase in the use of amitriptyline (ATC: N06AA09) which was the most prescribed inappropriate drug in 2020 (Supplementary Table S5).

In Figure 2 the deviation from the national average is presented, by region, across the study period, for each of the three indicators (Figure 2A–C). In each panel the regions are sorted by the mean deviation across the entire study period (depicted by the diamond). For each region, each year is represented by a dot, and the width of the horizontal dotted area indicates the total variation across time from the national average (the vertical zero-line). The red dot represents the first study year (2006) and the yellow dot the last study year (2020). Thus, the order of the red and yellow dot indicates the direction in which the regions are moving, closer or further away from the national average over time. In general, the pattern shows that some regions stay below or over the national average in all years. Moreover, with some exceptions, regions that deviate positively or negatively from the national average move closer to the mean across the period (i.e., the order of the yellow and red dot). The deviation from the national average is largest for the use of three or more psychotropic drugs (Figure 2B).

In a supplementary analysis, we depict the ranking of the regions across indicators to facilitate comparisons between regions in 2006 and 2020 (Supplementary Figure S1). In general, there is a pattern that regions performing in the top/bottom third on one indicator also are ranked in top/bottom third for the two other indicators.

4 Discussion

In this nationwide study of older adults aged 75 years and older from 2006 to 2020, we found a decline in the use of "drugs that should be avoided in older adults unless specific reasons exist" and the use of three or more psychotropic drugs, whilst the prevalence of excessive polypharmacy increased in all 21 Swedish regions. The regional variation decreased or was stable across the study period for all indicators, but was consistently largest for the "use of three or more psychotropic drugs". We found a general pattern that regions with a good performance at the start of the period performed well across the entire period and *vice versa*. Moreover, regions performing well in one indicator was also more likely to perform well on other indicators. We regard the trends towards declining regional differences as positive since this increase the regional equality. Whether the remaining regional variations can be explained by contextual or individual/compositional factors needs to be investigated further.

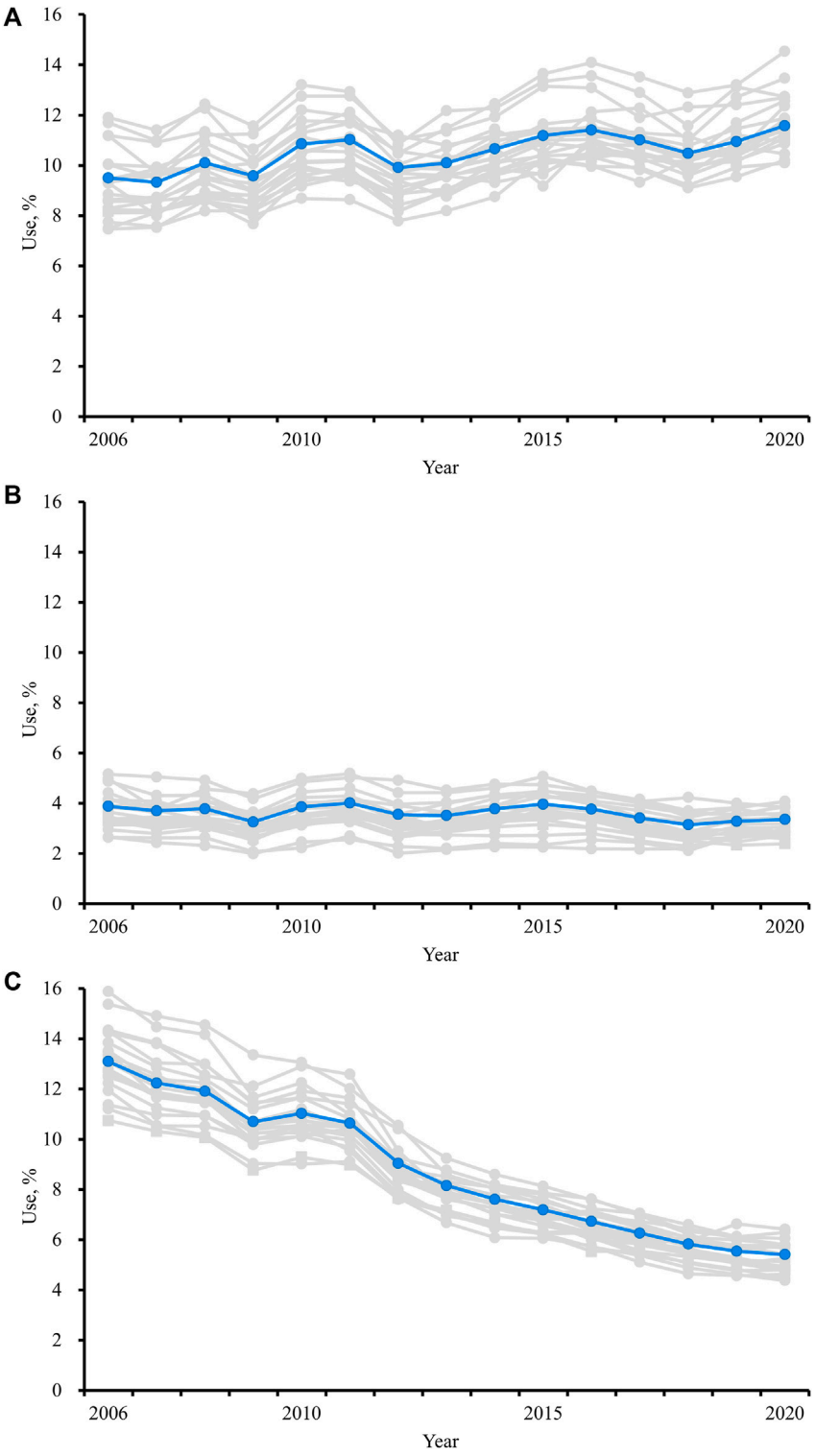

FIGURE 1
Prevalence of **(A)** use of 10 or more drugs, **(B)** use of three or more psychotropic drugs, **(C)** use of 'drugs that should be avoided in older adults unless specific reasons exist', in persons 75 years and older 2006–2020 in Sweden. Blue line: trend for the whole of Sweden. Grey lines: trends for the 21 different regions of Sweden.

We found that the prevalence of "drugs that should be avoided in older adults unless specific reasons exist" and the use of three or more psychotropic drugs declined from 2006 to 2020 in Sweden. The decline was especially evident for "drugs that should be avoided in older adults unless specific reasons exist" and was shared by all 21 Swedish regions. This decline is in line with previous research on trends in regional variation in drug use in older adults (Hogan et al., 2003), previous studies and reports from Sweden (Hovstadius et al., 2013; Thorell

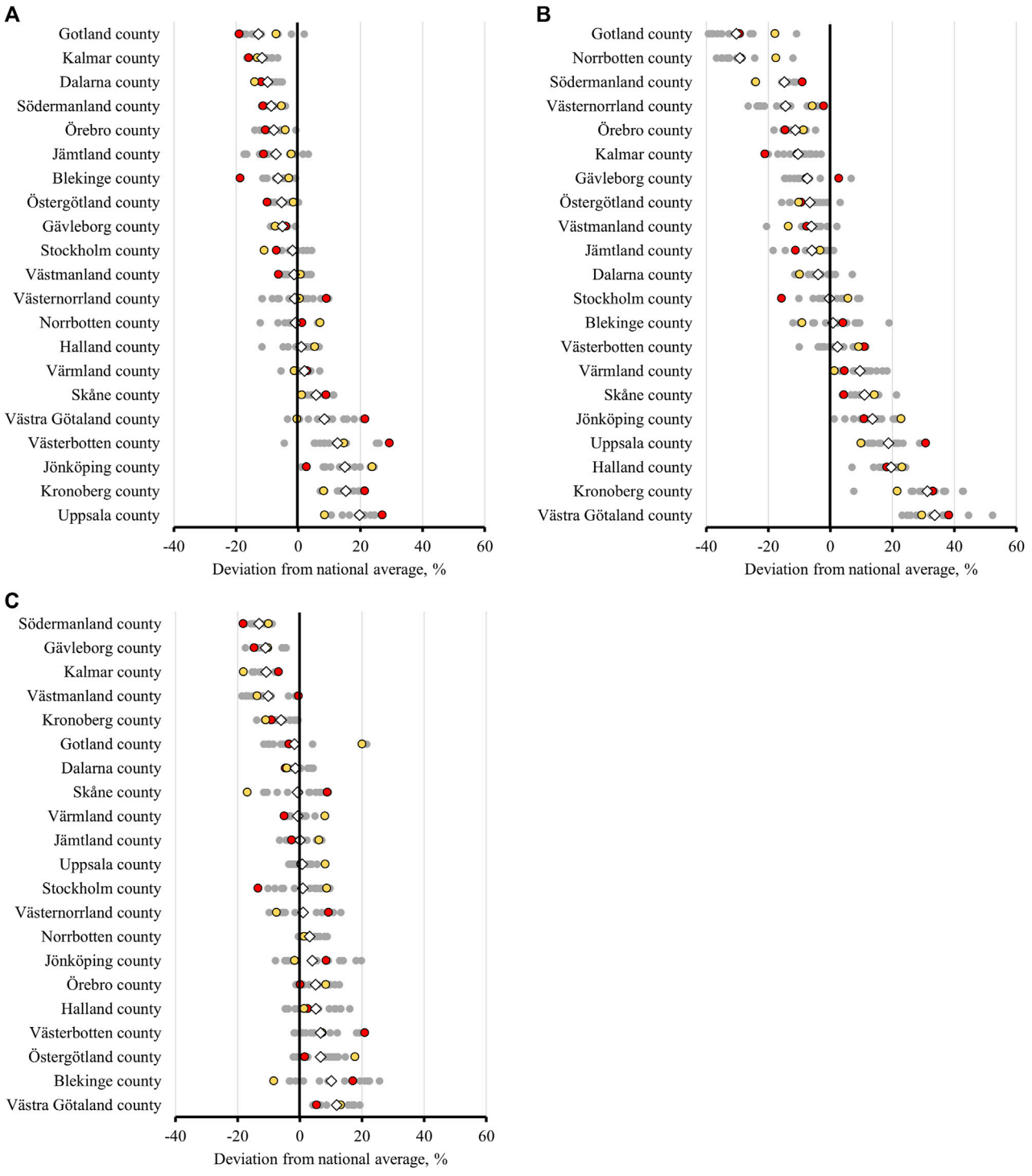

FIGURE 2
Prevalence of **(A)** use of 10 or more drugs, **(B)** use of three or more psychotropic drugs, **(C)** use of 'drugs that should be avoided in older adults unless specific reasons exist', in persons 75 years and older in the 21 regions of Sweden, 2006–2020. (◇) average value for the years 2006–2020; (○) value for each year, red representing 2006 and yellow 2020.

et al., 2020) and international studies of the trends in inappropriate medications (Stuart et al., 2003; Bongue et al., 2009; Lapi et al., 2009). This is likely explained by an overall increase in the awareness of which drugs to avoid in older adults. For the use of three or more psychotropic drugs the decline was, however, less pronounced, although only one region experienced an increase in this prevalence from 2006 to 2020. The moderate decrease for this indicator has also been reported previously in Sweden (Socialstyrelsen, 2016). In contrast, the prevalence of excessive polypharmacy increased in all 21 regions over the study period. The increasing prevalence of polypharmacy is also in line with previous results from Sweden and international studies (Wastesson

et al., 2018). This can probably be inferred to the larger number of available drugs, an increased focus on diagnosing and treating chronic diseases and the increasing use of preventive medications. Overall, our results suggests that the Swedish regions tend to share a similar overall development for the studied indicators but regional differences in magnitudes exist.

We found that the differences between regions for the indicators decreased across the study period. The finding that the regional variation was smallest for 'drugs that should be avoided in older adults unless specific reasons exist' can possibly be explained by the fact that the strategies needed to avoid or substitute certain medications and medication classes, are relatively straightforward and therefore easier to implement. Thus, reducing the use of such drugs seems to represent a low hanging fruit compared to remedy other types of PID in older adults. The indicator "use of three or more psychotropic drugs" displayed the largest variation during the entire period. A high degree of variation between regions with regard to psychiatric polypharmacy have also been found in previous work (Okui and Park, 2022). Among potential explanation are regional prescribing patterns (e.g., opioid-belt in United States and benzo-belt in Sweden) or differences in access to specialist prescribers (Wastesson et al., 2014). Yet more detailed analyses of the drugs composing the indicator "use of three or more psychotropic drugs" in Sweden is needed.

Further, we found that the performance rankings between regions were relatively stable across time, similar to previous findings (Jirón et al., 2016). This stability, or path dependency, suggests that either contextual factors [e.g., therapeutic traditions (Ohlsson et al., 2009)] or individual/compositional factors (such as age structure) have been stable over the period (Morgan et al., 2010). The results of this study do not provide insights into the influence of these factors. Future studies in Sweden should attempt to study this in more detail. For example, the large cohorts born after 1945 will gradually join the age group of "persons 75 years and older". This will result in a change in the age structure within this age group, resulting in a lowering of the mean age. This will potentially also result in a lowered prevalence of inappropriate drug use (in the situation that medication use is more appropriate in more recent cohort) if the age composition is not considered in analyses of "persons 75 years and older". The importance of considering demographic changes in the composition of the old older adults will increase in the years to come as we are nearing a pivotal change in the age composition of this age group. In addition, regions who consistently performed well, or improved their rankings drastically during the period, could be more thoroughly examined, to identify successful strategies to reduce inappropriate drug use in older adults. This could potentially be done by mapping the Swedish regions' strategies related to drug policy and incentives to promote rationale drug use over time (Eriksen et al., 2017).

The possibility to make a direct comparison between our results and other countries are somewhat limited. First, different criteria for PIDs are used in different countries and regions. This especially relates to "drugs that should be avoided in older adults unless specific reasons exist", drugs considered inappropriate by one criterium can be considered appropriate according to other criteria. In order to partially circumvent this, we report the specific drugs most frequently contributing to the prevalence of "drugs that should be avoided in older adults unless specific reasons exist" in Sweden. We found that the most commonly used drug of that type in 2020 was amitriptyline which was used by about 1% of the study population. Amitriptyline is commonly reported as one of the most frequently used potentially inappropriate drug also in other countries and according to different criteria (Opondo et al., 2012). Second, international comparisons of psychotropic indicators are complicated due to differences in national drug formula across countries, for example no psycholeptics/psychoanaleptics combinations (ATC: N05C) are approved in Sweden. Last, we report a lower prevalence of excessive polypharmacy than most previous studies (Drusch et al., 2021). This is mainly explained by the use of a 1-day point prevalence in our study, that can be compared with the 3 and 12-month periods used in most other studies (Masnoon et al., 2017). Albeit, PID remains a problem in the old populations in most high-income countries, with 10%–20% affected (Tommelein et al., 2015). This likely results in adverse drug events, unnecessary hospitalisations and increased healthcare costs (Muhlack et al., 2017; Xing et al., 2019). Thus, it is of great importance to monitor trends and regional differences in potentially inappropriate drug use in different contexts. This can potentially help to identify successful strategies to reduce the level of PID.

4.1 Strengths and limitations

The main strength of this study is that the indicators were calculated using nationwide data with high validity from the Swedish Prescribed Drug Register (Wettermark et al., 2007). The study also has a number of limitations. Firstly, it only describes regional ecological trends in medication use in Sweden. We do not attempt to explain which factors contribute to the trends. Secondly, we decided to focus on three general and commonly used indicators of PID rather than all potential indicators of inappropriate drug use. Thirdly, drugs supplied in hospitals or nursing home storerooms are not recorded in the register, which could lead to an underestimation of inappropriate drug use. Fourthly, from the register data we know that the drug was dispensed but not whether it was consumed. In some cases, patients might have been informed to avoid drugs after it was dispensed, which would lead to an overestimation of PID use. Lastly, it should be noted that the National Board of Health and Welfare updated their set of indicators in 2017. In the present study, we use the 2010 version of the criteria to facilitate consistently measured indicators during the period.

5 Conclusion

This nationwide study shows that all Swedish regions shared a decline in the prevalence of "drugs that should be avoided in older adults unless specific reasons exist" and the use of three or more psychotropic drugs, whilst the prevalence of excessive polypharmacy increased, from 2006 to 2020. The regional differences decreased or were stable across the study period for all indicators. The differences were largest for the "use of three or more psychotropic drugs". We found a pattern that regions with a good performance at the start of the period tended to perform well across the entire period and *vice versa*, with a few exceptions. In general, regional variations tended to be consistent across a 15-year period. More work is needed to identify the reasons for the regional variations. This could ultimately provide insights about strategies to improve quality of drug use in older adults.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: Individual data from the Swedish Prescribed Drug Register cannot be made publicly available. Requests to access these datasets should be directed to Registerservice@socialstyrelsen.se.

Ethics statement

The studies involving human participants were reviewed and approved by Ethical Review Board in Stockholm. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

JW and JFa conceived and designed the study, performed the statistical analysis, interpreted the data, drafted, and critically revised the manuscript. JFr, BB and KJ interpreted the data and critically revised the manuscript. All authors gave approval for the final version of the manuscript.

Funding

This work was supported by grants from Swedish Research Council for Health, Working Life and Welfare (Dnr: 2016-07206), the Swedish Research Council and Erik Rönnberg's Donations. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1030849/full#supplementary-material

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frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 08 February 2023
DOI 10.3389/fphar.2023.1098465

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Drugs Outcomes Research and Policies, a section of the journal Frontiers in Pharmacology

RECEIVED 15 November 2022
ACCEPTED 26 January 2023
PUBLISHED 08 February 2023

CITATION
Wang Y, Zhu J, Shan L, Wu L, Wang C and Yang W (2023), Potentially inappropriate medication among older patients with diabetic kidney disease.
Front. Pharmacol. 14:1098465.
doi: 10.3389/fphar.2023.1098465

Potentially inappropriate medication among older patients with diabetic kidney disease

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Objective: Potentially inappropriate medications (PIM) contribute to poor outcomes in older patients, making it a widespread health problem. The study explored the occurrence and risk factors of PIM in older diabetic kidney disease (DKD) patients during hospitalization and investigated whether polypharmacy was associated with it.

Methods: Retrospective analysis of the patients ≥ 65 years old diagnosed with DKD from July to December 2020; the PIM was evaluated according to the American Beers Criteria (2019). Factors with statistical significance in univariate analysis were included in Logistic multivariate analysis to explore the potential risk factors related to PIM.

Results: Included 186 patients, 65.6% of patients had PIM, and 300 items were confirmed. The highest incidence of PIM was 41.7% for drugs that should be carefully used by the older, followed by 35.3% that should be avoided during hospitalization. The incidence of PIM related to diseases or symptoms, drug interactions to avoid, and drugs to avoid or reduce dose for renal insufficiency patients were 6.3%, 4.0% and 12.7%, respectively. The medications with a high incidence of PIM were diuretics (35.0%), benzodiazepines (10.7%) and peripheral α1 blockers (8.7%). Compared with hospitalization, there were 26% of patients had increased PIM at discharge. Multivariate Logistic regression analysis showed that polypharmacy during hospitalization was an independent risk factor for PIM, OR = 4.471 (95% CI: 2.378, 8.406).

Conclusion: The incidence of PIM in hospitalized older DKD patients is high; we should pay more attention to the problem of polypharmacy in these patients. Pharmacists identifying the subtypes and risk factors for PIM may facilitate risk reduction for older DKD patients.

KEYWORDS

potentially inappropriate medication, polypharmacy, diabetic kidney disease, hospitalised and dicharge patient, older patients

1 Introduction

More than 400 million people are suffering from diabetes mellitus (DM) around the world, and nearly half of them are older people (≥65 years old) (Bellary et al., 2021). About 20%–40% of patients with diabetes would develop into diabetic kidney disease (DKD) (Afkarian et al., 2016); it is associated with an increased risk of adverse health outcomes, impaired quality of life, and premature mortality (Alicic et al., 2017).

Older diabetes is a complex and heterogeneous group; in addition to diabetes and associated complications, these patients are still at an increased risk of geriatric syndromes, including falls, chronic pain, depression, and functional and cognitive decline (Clemens et al., 2019). Because of various diseases, older people with DKD have an increased risk of taking multiple medications. A study from Germany showed that 70.4% of patients with an eGFR<60 mL/min took at least five medications, and 17.7% of them took ≥10 medications for a long time (Dorks et al., 2016). But polypharmacy therapy (Typically defined as using five or more pharmaceuticals simultaneously) is related to adverse drug reactions (ADR), common and possibly preventable causes of accidental hospitalization, increased morbidity, mortality and medical care costs. The risk for ADR in patients taking two medications at the same time was 13%, while the risk for patients taking four, seven or more were 38% and 82%, respectively (Zazzara et al., 2021). Therefore, it is necessary to identify and avoid PIM for older patients with DKD.

Many tools can be used to identify the PIM in multiple medications prescription. The American Geriatrics Society Beers Criteria (AGS Beers Criteria) has been proven to be more sensitive than other tools in reducing drug-related adverse events, emergency visits and hospitalization, improving the overall health of patients (Brown et al., 2016). It can find the prevalence of PIM among older patients with different diseases and figure out the types of medications involved in it.

The common PIM in old American drivers were taking medications known to damage driving ability and increase collision risks. The most common PIM treatment for them was benzodiazepines (accounting for 16.6% of total PIM), followed by non-benzodiazepines hypnotics (15.2%) and antidepressants (11.5%) (Li et al., 2019). A French study using this criterion showed that 64.8% of older patients with chronic diseases and multiple medications have PIM at least once (Guillot et al., 2020). In comparison, the prevalence of PIM among these patients of hospitalized in China was higher (about 72.5%) (Tian et al., 2021a). The common medications induced PIM in patients with the chronic coronary syndrome in Beijing were diuretics (37.1%), benzodiazepines (15.2%) and glimepiride (13.1%) after discharge (Zhao et al., 2021).

Polypharmacy is common in older DKD patients as they are more prone to problems such as synchronously controlling glucose, common comorbidities, elevated blood pressure and so on. Studies have reported that pharmacists may play a critical role in managing concurrent DKD, because of their unique perspectives on medications prescribed across conditions and providing actionable medication-related recommendations (Fazel et al., 2017; Zullig et al., 2020). A few studies have shown that the incidence of potentially inappropriate medication (PIM) is high in older patients with chronic kidney disease (CKD) (Roux-Marson et al., 2020; Luthke et al., 2022; Pehlivanli et al., 2022; Sharma et al., 2022); one has reported that proton pump inhibitors (PPI) were the most common medications induced PIM (Pehlivanli et al., 2022), while others revelled that polypharmacy and reduced estimated glomerular filtration rate (eGFR) were predictors for PIM in this population (Luthke et al., 2022; Sharma et al., 2022). There are studies on PIM in older diabetic patients (Oktora et al., 2021), but few studies have explored PIM in older diabetic nephropathy patients in China. The purpose of this study is: 1) To evaluate the PIM of these patients during hospitalization and discharge; 2) To Identify the risk factors of PIM as to provide a better reference for clinicians.

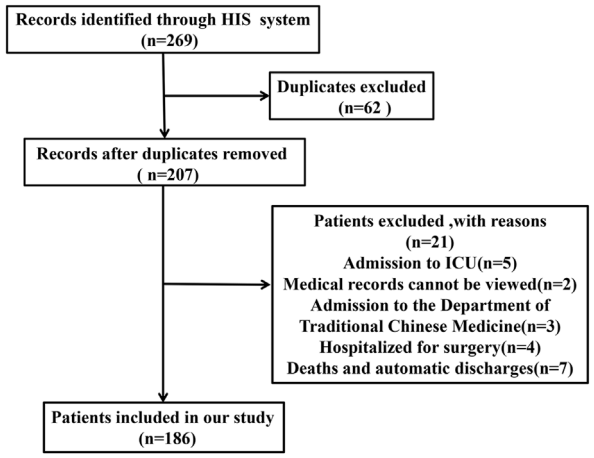

FIGURE 1
The flowchart of this study.

2 Materials and methods

2.1 Study design, setting, and patients

This retrospective study was carried out at the First Affiliated Hospital of Jinan University in China, a tertiary public general teaching hospital with 1900 beds. The study included patients aged 65 or older with DKD as the primary diagnosis, which was searched by the International Statistical Classification of Diseases and Related Health Problems (ICD-10) coding system for code N08 (DKD) (WHO International, 2020); those patients were admitted into hospital between July 2020 and December 2020. The anonymity and confidentiality of patients and their data were always protected.

Total 269 medical records were extracted from patients aged 65 or older with DKD as the primary diagnosis through the hospital information system (HIS). The inclusion criteria were: 1) Patients aged 65 years or older and hospitalized for more than 24 h; 2) Patients who were not in the final stage of their disease undergoing palliative care; 3) Non-automatic discharge or death within 3 months; 4) Patients admitted to non-ICU or Chinese medicine department; 5) Admitted for non-surgical treatment. Exclusion criteria were: Patients hospitalized in the same department for two times or more within 3 months. The flow chart for selecting medical records is shown in (Figure 1).

2.2 Data collection

Two independent clinical pharmacists gathered data from the HIS; the following information was recorded: Age, sex, hospitalization ID,

TABLE 1 Characteristics of the population and univariate analysis for PIM.

Variable	Patients with at least 1 PIM (*n* = 122)	Patients without PIM (*n* = 64)		P
Gender			X^2 = 2.066	0.151
Male	65 (53.3%)	27 (42.2%)		
Female	57 (46.7%)	37 (57.8%)		
Age (year)			H = 0.622	0.430
65–74	64 (52.5%)	38 (59.4%)		
75–84	42 (34.4%)	18 (28.1%)		
≥ 85	16 (13.1%)	8 (12.5%)		
BMI	23.97 ± 3.52	23.64 ± 3.42	t = −0.626	0.532
Complicatoins				
Hypertension	109 (89.3%)	56 (87.5%)	X^2 = 0.143	0.706
CHD	53 (43.3%)	28 (43.8%)	X^2 = 0.002	0.968
Gout	34 (27.9%)	14 (21.9%)	X^2 = 0.788	0.375
COPD	2 (1.6%)	1 (1.6%)	X^2 = 0.002	0.968
SI	12 (9.8%)	5 (7.8%)	X^2 = 0.207	0.649
HLP	20 (16.4%)	6 (9.4%)	X^2 = 1,720	0.190
Reason for admission			X^2 = 0.189	0.664
Infection	18 (14.8%)	11 (17.2%)		
Non-infection	104 (66.2%)	53 (82.8%)		
Department			H = 0.022	0.882
Nephrology	50 (41.0%)	27 (42.2%)		
Endocrinology	32 (26.2%)	18 (28.1%)		
Cardiology	12 (9.8%)	3 (4.7%)		
Others	28 (23.0%)	16 (25.0%)		
LOS			H = 4.164	0.041*
≤7 days	18 (14.8%)	17 (26.6%)		
8–14 days	70 (57.4%)	35 (54.7%)		
>14 days	34 (27.9%)	12 (18.8%)		
CKD stage			H = 1.278	0.258
Stage 1	5 (4.1%)	1 (1.6%)		
Stage 2	13 (10.7%)	8 (12.5%)		
Stage 3	37 (30.3%)	24 (37.5%)		
Stage 4	21 (17.2%)	13 (20.3%)		
Stage 5	46 (37.7%)	18 (28.1%)		
Dialysis			X^2 = 1.576	0.209
Yes	33 (27.1%)	12 (18.8%)		
No	89 (72.9%)	52 (81.2%)		
CCI			H = 0.557	0.456
<5	47 (38.5%)	28 (43.8%)		
5–10	74 (60.7%)	36 (56.3%)		
>10	-	1 (0.8%)		
NOC			H = 4.827	0.028*
<7	32 (26.2%)	27 (45.2%)		
7–14	84 (68.9%)	35 (54.7%)		
>14	6 (4.9%)	2 (3.1%)		
NOD			H = 26.111	0.000*
1–5	1 (0.8%)	2 (3.1%)		
6–10	17 (13.9%)	30 (46.9%)		
11–20	96 (78.7%)	31 (48.4%)		
21–35	8 (6.6%)	1 (1.6%)		
TrMe	1.29 ± 1.09	1.14 ± 0.96	t = −0.907	0.365

PIM, potentially inappropriate medication; BMI, body mass index; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; SI, systemic infections; HLP, hyperlipidemia; LOS, length of stay; CCI, charlson comorbidity index; NOC, numbers of complications; NOD, number of drugs; TrMe, Traditional medication; * With $p < 0.05$.

TABLE 2 Number of medications and PIM at admission and discharge.

	Admission n (%)	Discharge n (%)
Polypharmacy (>5)	183 (98.4)	146 (78.5)
Number of patients prescribed with PIM	122 (65.6)	92 (49.5)
1 PIM	48 (39.3)	47 (51.1)
2–3 PIM	57 (46.7)	38 (41.3)
4–6 PIM	17 (13.9)	7 (7.6)
Total number of PIM	300	188
Medications that should be avoided	106 (35.3)	62 (33.0)
Medications that should be used with caution	125 (41.7)	89 (47.3)
Potentially clinical important drug-drug interactions to be avoided	12 (4.0)	8 (4.3)
Medications with drug-disease/syndrome interactions	19 (6.3)	12 (6.4)
Medications that should be adjusted along with kidney function	38 (12.7)	17 (9.0)

PIM, potentially inappropriate medication; IQR, interquartile range.

departments, the reasons for admission, length of stay, diagnosis, the number of complications and medications, the quantity of Chinese patent medicine, calculated Charlson Comorbidity Index (CCI) (to quantify the presence of co-existing diseases) and Creatinine Clearance (Ccr) [Cockcroft-Gault equation is used to estimate Cr clearance (Cockcroft and Gault, 1976)], both of them were used an online calculator.

2.3 Outcome measurements

According to the Beers Criteria (2019) (By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel, 2019), drugs during hospitalization and discharge medication were evaluated (injection solvents and external preparations were excluded). The occurrence of PIM and drug types were analyzed: 1) Medications that should be avoided; 2) Medications that should be used with caution; 3) Medications with drug-disease/syndrome interactions; 4) Potentially clinically important drug-drug interactions to be avoided, with the severity of interactions was searched through Lexi-Interact (https://www.uptodate.com/drug-interactions); 5) Medications that should be adjusted along with kidney function. We referred to the designations of quality of evidence and strength of recommendations in Table 1 of the Beers Criteria (2019).

Two pharmacists manually identified PIM at the patient level; the senior pharmacist verified all PIM. All authors discussed any discrepancies until consensus was achieved. This study evaluated all medications listed in the patient records during hospitalization and discharge for PIM. The same medication was considered a different kind of PIM if found in the different tables of the 2019 Beers list of medications that should be separately counted.

2.4 Statistical analyses

Statistical analysis was performed using SPSS 26 (*SPSS Inc., Chicago, IL, USA*). Descriptive analysis was performed on the types of PIM and the involved drugs. The measurement data were expressed as Mean ± SD; the counting data were expressed as numbers and constituent ratios. Independent sample *t*-test was used for measurement data, chi-square test or Kruskal-Wallis test was used for classified variables, factors with statistical significance in univariate analysis were included in Logistic multivariate analysis to explore the potential risk factors related to PIM, with $p < 0.05$ was considered statistically significant.

3 Results

3.1 Baseline characteristics

A total of 186 patients were included in the study, including 92 males and 94 females, with an average age of 74.87 ± 7.44 years (65–93 years) and an average BMI of 23.87 ± 3.48 kg/m^2. In addition to the diagnosis of DKD, the most common complications were hypertension, accounting for 88.7% (165/186), followed by coronary heart disease (43.5%) and gout or hyperuricemia (25.8%). Stage IV and V of CKD were 18.3% and 34.4%. Patients undergoing dialysis accounted for 24.2%, and 75.8% had no dialysis. The average length of stay was 11.8 ± 5.42 days. Patients using five more medications during hospitalization were 98.4%. And 65.6% of patients had at least one PIM during hospitalization, while 49.5% were at discharge. The demographic statistics are shown in Table 1. Patients using five more medications during hospitalization were 98.4%. The average number of medications were 13 (Interquartile range were 10–15) in hospitalization, while at discharge were 9 (Interquartile range were 6–12). And 65.6% patients had at least one PIM during hospitalization, while 49.5% at discharge (Table 2).

3.2 Prescriptions with PIM for DKD patients

A total of 186 patients with DKD were included in the analysis, of which 122 patients (65.6%) had PIM. According to

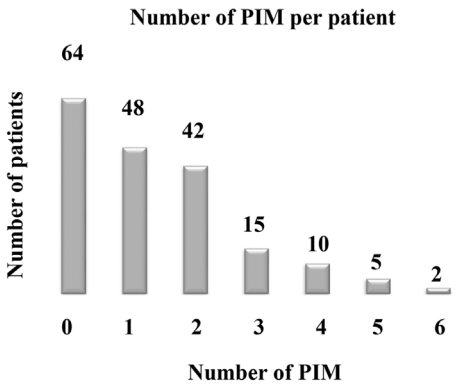

FIGURE 2
Number of potentially inappropriate medications per patient.

the criteria, patients having at least 1 item of PIM were 39.3%, while patients with 2-3items of PIM and 4-6 items were 46.7% and 13.9%, respectively (Figure 2; Table 2). Among the items included in the analysis, PIM occurred in 300 medication regiments during hospitalization, 106 (35.3%) items of drugs should be avoided, 125 (41.7%) should be used with caution, 38 (12.7%) were a dosage that should be adjusted according to renal function or to is avoided. In comparison, there were 62 (33.0%), 89 (47.3%), and 17 (9.0%) items, respectively, for discharge medications (Table 2). The medications with high incidence PIM were diuretics (35.0%), benzodiazepines (10.7%), peripheral α1 blockers (8.7%) and spironolactone (6.7%) during hospitalization. In comparison, the medications at discharge were diuretics (35.6%), benzodiazepines (11.7%), peripheral α1 blockers (10.6%) and novel oral anticoagulants (6.4%) (Table 3).

According to the analysis of the changes in PIM between hospitalization and discharge medications, it was found that about 19% of patients had no PIM during hospitalization nor at discharge, 44% of patients had less PIM at discharge than hospitalization. But here a surprising thing was that 26% of patients still had more PIM than hospitalization at discharge, and 11% had the same PIM at release, which indicated that 37% of patients may still have drug-related adverse events due to PIM (Figure 3).

In this study, 12 cases of drug interactions that should be avoided, accounting for 4.0% of total PIM, including four issues of opioids and pregabalin (which may increase the risk of severe sedation-related adverse events including respiratory depression or death) and 1 case of opioids and benzodiazepines (may increase the risk of overdose). The above interactions were classified as level D in the *Up-to-date database*, which means the scheme needs to be modified. There were 3 cases of simultaneous use of potassium-preserving diuretics and RAS blockers. The drug interaction grade was C, and the risk of hyperkalemia should be monitored during simultaneous use. There were 4 cases of combination using α1 blocker and a loop diuretic. The Beers Criteria suggested an increased risk of urinary incontinence in older women in this combination. Still, here was no specific interaction between the medications in the *Up-to-date database* (Table 4).

3.3 Factors associated with PIM

Univariate analysis found that patients with longer hospitalization, more comorbidities and polypharmacy in hospitalization, were more likely to develop PIM ($p < 0.05$) (Table 1). Logistic multivariate analysis found that polypharmacy was an independent risk factor for PIM in older DKD patients, with an OR = 4.471 (95% CI:2.378, 8.406) (Figure 4).

4 Discussion

4.1 The incidence of PIM

For the first time, this study paid attention to PIM in older Chinese patients with DKD. It was found that 65.6% (122/186) patients had at least one PIM during hospitalization, while 49.5% were at discharge. Here a surprising thing was that 26% of patients still had more PIM than hospitalization at discharge.

The study has proved that there was little difference between the 2017 Chinese and 2019 AGS/Beers criteria (Tian et al., 2022), so the Beers criteria was also capable for Chinese. Our results are comparable to the PIM rate of (Beezer et al., 2022), who reported that the incidence of PIM was 61.1% during hospitalization in older patients with heart failure. Still, the PIM after discharge was higher, which was 64.0%. Our results are higher than those of Roux-Marson et al. (Roux-Marson et al., 2020), who found that 57.6% of older patients with advanced renal disease had PIM at least once. Although they included a cohort of older patients with age 75 years old or older, the drug categories 9 (7–11) are lower than this study 13 (4–35). The result was also higher than a single-center study in Japan, where patients with PIM at admission and discharge were 47.2% and 32.2%, respectively (Komagamine et al., 2019). However, people with lower eGFR often tend to have more PIM with more medications and are associated with a higher risk of readmission and death (Kang and Hong, 2019). Disparities in these results may be due to the different basis of the population included in studies, doctors' distinctive prescription habits, and the accessibility of medications in different countries (Sarwar et al., 2017).

Compared with other studies (Al-Azayzih et al., 2019; Tian et al., 2021b), we also paid attention to the PIM of DKD patients' discharged medications. Through our study, we suggested that pharmacists should pay more attention to the medication problem of patients with chronic diseases in the community, which is obviously a blank in China. We also found that pharmacists can identify the potential risks of DKD patients; they play a positive role in medication management and disease control for patients with chronic diseases. Generally speaking, for our study group, the incidence of PIM in older patients with DKD is higher, so it is more necessary for clinical pharmacists to participate in identifying PIM and medication monitoring. They can play a crucial role in medication reconciliation by minimizing the risk of PIM.

4.2 Related medications with PIM

The results showed that medications with high incidence of PIM in hospitalization were diuretics, benzodiazepines and peripheral α1 blockers, taking a percentage of 35.0%, 10.7%, and 8.7%, respectively. Diuretics were the most common medications with PIM, accounting for 35.0%, which was consistent with the incidence of PIM in patients with cardiovascular disease (Zahwe

TABLE 3 Prescribed PIM according to the Beers criteria at admission and discharge.

The 2019 beers criteria	Quality of evidence[a]	Strength of recommendation[a]	PIM use frequency		
			Admission *n* = 300 (%)	Discharge *n* = 188 (%)	Change (%)
Medications that should be avoided			106 (35.3)	62 (33.0)	−2.3
Gastrointestinal medications	Moderate	Strong	2 (0.7)	0	−0.7
Antihistamines, first-generation	Moderate	Strong	2 (0.7)	0	−0.7
Digoxin>0.125 mg/d in heart failure	Moderate	Strong	1 (0.3)	1 (0.5)	0.2
Nifedipine, immediate release	High	Strong	10 (3.3)	1 (0.5)	−2.8
Sulfonylureas, long-acting	High	Strong	1 (0.3)	1 (0.5)	0.2
NSAIDs, non-selective	Moderate	Strong	10 (3.3)	3 (1.6)	−1.7
Benzodiazepines	*Moderate*	*Strong*	*32 (10.7)*	*22(11.7)*	*1.0*
Non-benzodiazepine	Moderate	Strong	10 (3.3)	5 (2.7)	−0.6
Barbiturates	High	Strong	1 (0.3)	1 (0.5)	0.2
Antipsychotic medications	Moderate	Strong	4 (1.3)	3 (1.6)	0.3
Peripheral α1 blockers	*Moderate*	*Strong*	*26 (8.7)*	*20(10.6)*	*1.9*
Antidepressant medications	High	Strong	1 (0.3)	1 (0.5)	0.2
Endocrine agents	Moderate	Weak	5 (1.7)	3 (1.6)	−0.1
Antithrombotics	Moderate	Strong	1 (0.3)	1 (0.5)	0.2
Medications to be used with caution			125 (41.7)	89 (47.3)	5.6
SSRIs	Moderate	Strong	5 (1.7)	4 (2.1)	0.4
NOAC-rivaroxaban and dabigatran	*Moderate*	*Strong*	*7 (2.3)*	*12(6.4)*	*4.1*
Diuretics	*Moderate*	*Strong*	*105 (35.0)*	*67(35.6)*	*0.6*
Tramadol	Moderate	Strong	7 (2.3)	5 (2.7)	0.4
Aspirin for primary prevention	Moderate	Strong	1 (0.3)	1 (0.5)	0.2
Medications with drug-disease/syndrome interactions			19 (6.3)	12 (6.4)	0.1
Cardiovascular heart failure	High	Strong	7 (2.3)	4 (2.1)	−0.2
Parkinson disease	Moderate	Strong	3 (1.0)	2 (1.1)	0.1
History of fails or fractures	High	Strong	3 (1.0)	3 (1.6)	0.6
Kidney/urinary tract Chronic kidney disease stage 4 or higher	Moderate	Strong	5 (1.7)	3 (1.6)	−0.1
Gastrointestinal History of gastric	Moderate	Strong	1 (0.3)	0	−0.3
Medications that should be adjusted along with kidney function			38 (12.7)	17 (9.0)	−3.7
Spironolactone	Moderate	Strong	20 (6.7)	10 (5.3)	−1.4
Rivaroxaban	Moderate	Strong	4 (1.3)	2 (1.1)	−0.2
Enoxaparin	Moderate	Strong	4 (1.3)	0	−1.3
Famotidine	Moderate	Strong	2 (0.7)	1 (0.5)	−0.2
Pregabalin	Moderate	Strong	6 (2.0)	2 (1.1)	−0.9
Trimethoprim-sulfamethoxazole	Moderate	Strong	1 (0.3)	1 (0.5)	0.2

(Continued on following page)

TABLE 3 (*Continued*) Prescribed PIM according to the Beers criteria at admission and discharge.

The 2019 beers criteria	Quality of evidence[a]	Strength of recommendation[a]	PIM use frequency		
			Admission *n* = 300 (%)	Discharge *n* = 188 (%)	Change (%)
Colchicine	Moderate	Strong	1 (0.3)	1 (0.5)	0.2

Italic indicated the medications with high incidence of PIM.
PIM, potentially inappropriate medication; NSAIDs, Non-steroidal anti-inflammatory drugs; SSRIs, Selective serotonin re-uptake inhibitors; NOAC, novel oral anticoagulants.
[a]Adapted from: By the American Geriatrics Society Beers Criteria Update Expert P, American Geriatrics Society 2019 Updated AGS, Beers Criteria (R) for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc 67, 674–694 (2019).

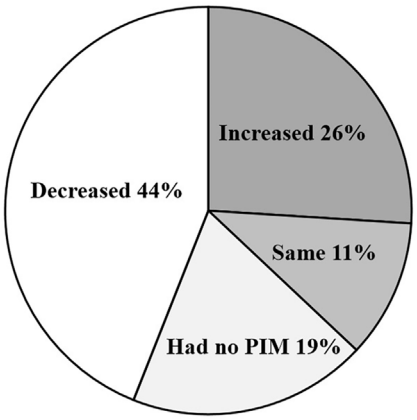

FIGURE 3
Change in the number of PIM between hospitalization and discharge. There were 44% patients had less potentially inappropriate medication (PIM) at discharge than hospitalization, 26% patients had more PIM than hospitalization at discharge; 19% patients had no PIM during hospitalization nor at discharge; 11% had the same PIM at release as in hospitalization.

et al., 2019). In this study, 88.7% of patients were complicated with hypertension and 52.7% with stage IV-V renal insufficiency. Diuretics are often used to treat edema and hypertension, but excessive using will increase the risk of hypotension, renal impairment, and electrolyte abnormality. Based on the results, it is suggested that clinicians should closely monitor the electrolyte level and renal function during diuretics use in those populations.

Benzodiazepines (10.7%) are another common medication for PIM in hospitalization. Recent studies have found that 6%–9% of non-psychiatric department inpatients use antipsychotics, while 9%–12% of patients aged 65 or more use (Loh et al., 2014). A growing number of studies indicated that antipsychotics were widely used in hospitals for non-mental disease purposes, such as managing delirium or possible delirium (Herzig et al., 2016). High sensitivity to benzodiazepines in older people may lead to falls, cognitive impairment, delirium and dementia, increasing the risk of hip fractures in women (Diaz-Gutierrez et al., 2017). Therefore, psychological and behavioral therapy should be the first choice in treating insomnia in older people. If benzodiazepines cannot be avoided, short-acting and low-dose medications should be preferred. Meanwhile, medication education should be done, and monitoring of adverse reactions should be strengthened.

α-blockers are usually used to control intractable or refractory hypertension in patients with CKD. Using α-blockers in CKD patients is associated with a higher risk of kidney disease progression but a lower risk of cardiac events and mortality than alternative medications (Hundemer et al., 2021). Although it has a higher risk of postural hypotension, based on our study population (Patients with hypertension were 88.7%, but the proportion of refractory hypertension is unknown), whether to continue using should be weighed according to the patient's situation.

The top three medications with high PIM at discharge were still diuretics (35.6%), benzodiazepines (11.7%) and peripheral α1 blockers (10.6%). But what we should pay more attention to were novel oral anticoagulants (NOACs), accounting for 6.4%. In advanced CKD patients (i.e., Stage 4 and particularly stage 5), NOACs were not recommended due to the paucity of RCT data (Giugliano et al., 2013; Stamellou and Floege, 2018). Meanwhile, a major challenge of using anticoagulants among older patients was their higher risk of bleeding (Hasan et al., 2018). Importantly, patients receiving NOACs need regular checks of renal function to avoid overdosing. Therefore, patients at discharge should not only self-monitor the risk prescription of diuretics, benzodiazepines and peripheral α1 blockers, but also pay attention to the bleeding or coagulation risk brought by the NOACs. Clinical pharmacists should strengthen relevant prescription education, which may be neglected.

In this study, the incidence of PIM in drug interactions that should be avoided was the lowest (4%). Although the proportion increased to 4.3% at discharge, the incidence was still lower than that reported by (Bories et al., 2021). However, our study mainly classified the drug interactions as C-D, indicating that about 4% of patients still need to monitor or adjust treatment regimens closely. Doctors prescribing medications for older patients need to understand the drug's catabolic pathway, the protein binding rate, and the induction and inhibition of cytochrome P450 to avoid drug interactions caused by multiple medications. Drug-drug interaction prevention for ageing should be included in the drug monitoring plan.

An important finding in this study was that 26% of the included patients still had increased PIM at discharge. This indicates that about one-third of patients who did not experience PIM-related adverse events during hospitalization still face the potential risk of home medication due to the increased PIM after discharge. At the same time, PIM was significantly correlated with ADR in older patients with chronic diseases in China community (Li et al., 2015). Meanwhile, each patient used an average of 1.24 ± 1.04 kinds of Chinese patent medicine injections or oral preparations during hospitalization, among which oral practices will continue after discharge. Still, no relevant standards or guidelines regarding whether these medicines existed PIM. Wang et al. (2020) comprehensively analyzed the data in the Annual Report on Adverse Drug Reaction Monitoring from 2009 to 2018 released by the China National Medical Products Administration; they found that the proportion of ADR related to proprietary Chinese

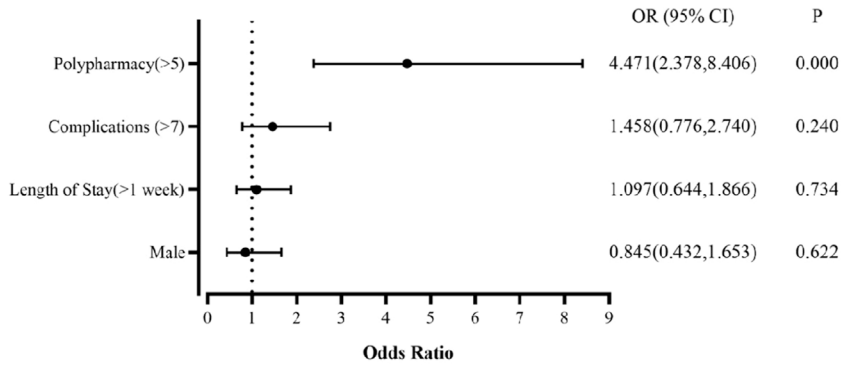

FIGURE 4
Binary logistics regression analysis of factors related to PIM.

TABLE 4 Potentially clinical important drug-drug interactions to be avoided using the 2019 Beers Criteria.

Object drug/ Class	Interacting drug/Class	Quality of evidence[a]	Strength of recommendation[a]	n (%)	Risk rationale	Severity
Potassium-sparing diuretics	RAS inhibitors	Moderate	Strong	3 (1.0)	Hyperkalemia or kidney injury	**C[a]**
Opioids	Pregabalin	Moderate	Strong	4 (1.3)	Increased risk of severe sedation-related adverse events, including respiratory depression and death	**D[b]**
Doxazosin	Furosemide	Moderate	Strong	4 (1.3)	Urinary incontinence	**NA[c]**
Opioids	Benzodiazepines	Moderate	Strong	1 (0.3)	Increased risk of overdose	**D[b]**

C[a]: monitor therapy; D[b]: consider therapy modification; NA[c]: no interaction.
RAS, Renin-angiotensin system.
[a]Adapted from: By the American Geriatrics Society Beers Criteria Update Expert P, American Geriatrics Society 2019 Updated AGS, Beers Criteria(R) for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc 67, 674–694 (2019).

medicines was 10%–20%. The older people in China lack reliable knowledge of multiple medications (Lai et al., 2018). In China, pharmacists and family physicians rarely intervene in rational medication use at home for the older. How to guarantee and monitor the safety of home medication in the older is a problem worthy of further consideration by medical staff.

4.3 Factors associated with PIM

Although older DKD patients with longer hospitalization and more comorbidities were prone to have PIM in univariate analysis, there was no statistical significance in multivariate analysis. Multivariate analysis found that polypharmacy was an independent risk factor for PIM in these patients. Previous studies have shown that polypharmacy was significantly associated with PIM (Oliveira et al., 2012; Mazhar et al., 2018). Older patients often have multiple comorbidities; they are more susceptible to adverse effects of medications (Lees and Chan, 2011). Prescribing cascades occur when medications are treated for adverse effects of other existing medications, and as a result, older tend to accrue polypharmacy burden over time. Studies have been published that pharmacist-led deprescribing interventions were feasible and might lead to improved outcomes and cost savings for older with cancer and polypharmacy (Whitman et al., 2018) and that person-centered care provided by a multidisciplinary primary care team, including a pharmacist, can improve therapeutic adequacy in older patients (Rovira et al., 2022). Therefore, in our study the multidisciplinary team, including the pharmacist, was necessary to avoid or reduce PIM caused by polypharmacy in older DKD patients.

4.4 Strengths and limitations

This study has some limitations: 1) As a retrospective study, we only conducted a single-center study with a limited sample size on older patients with DKD, which might not represent the prevalence of PIM in all older with DKD due to different medication habits of doctors. 2) We only made PIM evaluations for hospitalization orders and discharge medications, excluding over-the-counter medications. However, Chinese patent medications, and dietary supplements may need to pay more attention to the actual PIM prevalence in this population. 3) We only analyzed PIM according to medical orders and could not assess potential prescription omission. Meanwhile, as the discharge medicine in China is limited to 7 days of course treatment, we could not evaluate medications with long-term use described in the Beers Criteria. Despite this, based on the consistency of current risk

factors with previous reports, suggestions and references could be provided to implement corresponding medication intervention measures in the future.

5 Conclusion

The incidence of PIM in hospitalized older DKD patients is high; we should pay more attention to the problem of polypharmacy in these patients. Identifying the subtypes and risk factors for PIM may facilitate risk reduction for older DKD patients.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

This study was approved by the IRB of the First Affiliated Hospital of Jinan University (No. KY-2022-057). This was a retrospective study, all subjects were anonymous, written consent was not applicable.

Author contributions

YW and WY designed the study. LS, LW, and JZ collected and analyzed the data. YW, JZ, and CW organized the manuscript. WY and CW reviewed the papers and revised the manuscript. All the authors (YW, WY, JZ, CW, LS, and LW) have readied and approved the final manuscript. All authors contributed toward data analysis, drafting and revising the paper and agreed to be accountable for all aspects of the work.

Funding

The study was supported by research grants from the Guangdong Provincial Bureau of Traditional Chinese Medicine (No. 20222041) and Guangdong Provincial Hospital Pharmaceutical Research Fund (No. 2022A11).

Acknowledgments

The author would like to thank all pharmacists and doctors who have participated in this project.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 17 May 2023
DOI 10.3389/fphar.2023.1128605

OPEN ACCESS

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RECEIVED 20 December 2022
ACCEPTED 21 April 2023
PUBLISHED 17 May 2023

CITATION
Zito S, Poluzzi E, Pierantozzi A, Onder G, Da Cas R, Ippoliti I, Lunghi C, Cangini A and Trotta F (2023), Medication use in Italian nursing homes: preliminary results from the national monitoring system. *Front. Pharmacol.* 14:1128605. doi: 10.3389/fphar.2023.1128605

Medication use in Italian nursing homes: preliminary results from the national monitoring system

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Background: The aging population has increased concerns about the affordability, quality, and nature of long-term care for older people, emphasizing the role of nursing homes. Unlike acute hospital and primary care, there is a lack of drug consumption data in long-term care to understand regional or national healthcare policies.

Objectives: This study aimed to describe medication consumption by older adults and expenditure in Italian nursing homes (NHs).

Methods: Data on drug consumption and costs from the administrative medicine informational flows that detect medicines packages supplied to patients in health facilities and NHs were used. Data on the characteristics of the healthcare residence were from the Italian Health Ministry. Records for the year 2019, selecting the nursing homes exclusively providing elderly or mixed (elderly and disabled) were used.

Results: In 2019, the total expenditure on medicines in NHs amounted to 25.38 million euros, the average cost to 1.30 and the expenditure per bed to 436.18 euros. Cardiovascular drugs were the highest-consuming therapeutic class (177.0 defined daily doses—DDDs/100 days of NH stay; 22.2% of total) followed by drugs acting on the alimentary tract and metabolism (167.6% and 21.0%) and blood drugs (160.4% and 20.1%). The treatment of hypertension and heart failure was widely the most frequently used, with the consumption being driven mainly by furosemide and ramipril. Antiulcer drugs were used on average in more than half of the days of NH stay (58.5 DDDs/100 days of NH stay), representing a therapeutic category for which deprescribing initiatives are recommended. On average, almost all patients received a dose of benzodiazepines, antipsychotics and antidepressants (37.6, 35.9, and 17.7 DDDs/100 days of NH stay, respectively), confirming the high prevalence of use for these medicines. Antibiotics reached 6.8 DDDs/100 days of NH stay.

Conclusion: The availability of data in this specific setting allows the identification of the main interventions toward improving appropriateness and represents a challenge for drug utilization research. Data from this study suggest that proton pump inhibitors (PPIs), benzodiazepines and antibacterials can be areas of improving prescribing appropriateness.

KEYWORDS
elderly, prescribing appropriateness, quality of healthcare, medication use, nursing homes

Introduction

The aging population has increased concerns about the affordability, quality, and nature of long-term care for older people, emphasizing the role of nursing homes, their clinical practice, and their economic sustainability (Avorn and Gurwitz, 1995; Tolson et al., 2013). Indeed, by 2050, the population in the European Union could reach 218 million people aged 60 or over, of which 1.3 million people with severe dependency in Italy alone (Pickard et al., 2007). The demand for long-term care is therefore increased by the number of older adults (aged 65 and over) suffering from multiple chronic diseases and different degrees of disability (Ouslander and Osterweil, 1994; Tolson et al., 2013). The response to this health need differs significantly from country to country and sometimes within the same state (Tolson et al., 2013) also because there is not a universally accepted definition for long-term care service or nursing home (Ribbe et al., 1997).

Assessment of older people's pharmacological regimens in terms of appropriateness, adherence, and risk of drug interactions have too often neglected in any care setting. Residents in nursing homes are more likely to be chronically ill, with cognitive and functional impairments (Avorn and Gurwitz, 1995). These patients show age-related physiological changes that influence the pharmacokinetics and pharmacodynamics of drugs (Ruggiero et al., 2010). Since the presence of concomitant diseases and the use of multiple drugs simultaneously, the risk for potentially inappropriate drug prescription is high among these patients, with clinical consequences in terms of both adverse events and reduced benefits (Avorn and Gurwitz, 1995; Halvorsen, Selbaek, and Ruths, 2017; Tolson et al., 2013). However, nursing homes represent an ideal setting for periodic medication reviews by taking advantage of continuous professional support in monitoring healthcare status and helping medication adherence.

The Italian long-term care system for older adults is mainly based on home and residential care services provided by municipalities (for the social care part) and regions (for the healthcare/nursing-related part). According to the Italian Institut of Statistics (ISTAT), about 12,800 residential facilities existed in 2019 throughout Italy, with regional variability in the number of facilities for every 100,000 inhabitants (from 12.4% per thousand residents in Southern Italy to 31.9% in Eastern Northern Italy) (Italian Institute of Statistics - ISTAT. n.d.) Residential care in Italy is mainly delivered through nursing homes (Jessoula et al., 2018). Admission is based on healthcare needs but also income levels. The criteria for access to nursing homes and home care are quite different within the Country, depending on the region and the municipality of residence, as well as on the criteria for co-payment. Around 2.2% of the elderly subjects can access nursing homes, and about 5%–6% can access home care (Jessoula et al., 2018). In 2019 in Italy, about 300,000 beds in public nursing homes were occupied by older individuals (65 years and above) (Italian Institute of Statistics - ISTAT. n.d.).

Unlike acute care hospitals and primary care, there is no comparable data in long-term care to understand regional or national healthcare policies. While some studies on older adults in home care have been carried out in Europe, similar comparative investigations on institutional care (i.e., nursing homes - NHs) are missing (the SHELTER project et al., 2012). There are significant regional differences in the availability and organization of nursing homes in Italy according to differences in regional healthcare systems. Data on medications used in Italian nursing homes are scarce. Nursing home residents generally have more than two chronic conditions (multimorbidity (Johnston et al., 2019)). They are therefore treated with many medications (namely, polypharmacy (Sirois et al., 2019)) since there is little guidance for treating these complex patients. As reported by Onder et al. in their recent guidelines for managing older adults with multimorbidity and polypharmacy, a multidisciplinary and individualized approach is necessary, as well as the identification of those at higher risk for adverse outcomes of polypharmacy (Onder et al., 2022).

An Italian drug utilization study performed on a network of nursing homes in Northern Italy found that psychotropic medications (benzodiazepines, antipsychotics, or antidepressants), followed by proton pump inhibitors, laxatives, and antihypertensive drugs, were the most used. Mainly, psychotropics were the most commonly prescribed drugs in patients with dementia leading to a possible exacerbation of cognitive pathology, risk of serious adverse events, and drug interactions. Instead, antiulcer agents were the most widely used drugs in the cohort without cognitive disorders (L. Pasina et al., 2020a).

Objective

This study aims to describe medication consumption by older adults and expenditures in Italian nursing homes. Describing and discussing medication consumption ad costs in nursing homes will help identify potential inappropriateness areas and define relevant monitoring and intervention approaches.

Methods

Data sources

We used data on drug consumption from the "Direct and *per conto* distribution" flow. Direct distribution refers to the delivery of medications by public facilities such as Local Health Authorities or hospitals to out-of-hospital patients; these medicines belong to a defined list and are purchased by those facilities, usually at lower price. The *per conto* distribution, which means "on behalf of", refers to the distribution of the same medicines by affiliated pharmacies; this channel is particularly used in rural areas. The information collected in the database includes the pharmaceutical service that supplied the medicine, the prescribed medicines, the supply model (direct or *per conto* distribution), costs of services (in case of *per conto* distribution), the dispensing date, the number of packages, the Anatomical Therapeutic Chemical [ATC] and the defined daily dose [DDD]. For the present analysis, data for the year 2019 were extracted, and nursing homes were selected as pharmaceutical service that supplied the medicine. Data for

2018 were also collected in order to assess stability of data flow. Among NHs providing data, only those providing elderly or mixed care (to elderly and disabled patients) were considered for the present study. Data on the characteristics of the healthcare residences were from the Italian Health Ministry. In particular, the relevant dataset contains the description, for each structure, of the number of beds, the healthcare type, and the region they belong to.

To ensure the data quality, only regions where at least 80% of the facilities regularly sent data through this flow were selected (Autonomous Provinces of Bolzano, Veneto, Friuli Venezia Giulia, Emilia Romagna, and Umbria). Instead, residences with less than five beds or with an extreme amount of Defined Daily Doses (DDDs) per bed (less than the third or more than the ninety-seventh percentile of the distribution) were excluded.

Data analysis

Pharmaceutical data were collected according to the Anatomical Therapeutic Chemical (ATC) classification established by the World Health Organization Collaborating Centre (WHO-CC) for Drug Statistics Methodology, and results were presented both by first and fifth ATC level. Moreover, data were analyzed according to therapeutic categories based on the ATC classification (e.g., antihypertensive, antidiabetic drugs) to perform further insights (Supplementary Table S1) (Italian Medicines Agency, 2021). Drug consumption was measured as the number of Defined Daily Doses (DDDs) (WHO Collaborating Centre for Drug Statistics Methodology, 2022).

Indicators as cost of nursing home (NH) stay per day, DDDs per 100 days of NH stay, and DDD average cost were calculated. The cost of NH stay per day is referred only to drugs expenditure. In order to assess the efficient use of resources in this setting, we also present the percentage of generics used in each therapeutic category.

The indicator DDDs/100 days of NH stay represents the number of DDDs used in a hospital nursing home divided by bed days and multiplied by 100. Analogously, the cost of NH stay per day was calculated by dividing the total expenditure by the number of days in NH provided in the reference time period. The "DDD average cost" indicator was estimated by dividing the total spending by the number of DDDs provided in the reference time period.

Analysis of antibacterial consumption (reported as total DDDs and percentage of total antibacterial consumption for each active substance) was also performed on the basis of the AWaRe classification (World Health Organization, 2019), released by the WHO to support countries' antibiotic stewardship. The Access group includes antibiotics with lower resistance potential, and the Watch group is for antibiotics at relatively high risk of selection of bacterial resistance. In contrast, antibiotics in the Reserve group should be treated as "last resort" options.

Results

Characteristics of the sample and overall consumption and expenditure for medications

We analysed data on drug utilisation in a sample of 802 nursing homes in five Italian Regions in 2019, accounting for a total number of 58,191 beds. They represent approximately 28.5% of the total number of beds in the Italian nursing homes (Supplementary Table S2).

Total consumption of drugs amounted to 797.86 DDDs per 100 days of NH stay. On average, the 2019 expenditure for medicines for each day of NH stay was 1.30 euros, and the total expenditure per bed was 436.18 euros. Drugs acting on the cardiovascular system (ATC: C) showed the highest consumption (177.0 DDDs/100 days of NH stay), accounting for 22.2% of all DDDs (Table 1), followed by drugs acting on the alimentary tract and metabolism (ATC: A; 167.6 DDDs/100 days of NH stay and 21.0% of total DDDs), blood drugs (ATC: B; 160.4 DDDs/100 days of NH stay and 20.1% of total DDDs), and of those acting on the central nervous system (CNS; ATC: N; 133.8 DDDs/100 days of NH stay and 16.8% of total DDDs). Blood drugs were those with the highest cost per day of NH stay (0.33 euro and 25.7% of total expenditure; Table 1; Figure 1), followed by CNS drugs (0.30 euro and 23.1% of total expenditure) and drugs acting on the alimentary tract and metabolism (0.27 euro and 20.5% of total expenditure. Antiparasitic products had the highest cost per DDD (1.11 euro), followed by anti-infective agents (1.06 euro). Nevertheless, these classes accounted only for 0.2% and 6.0% of costs per day of NH stay, respectively.

Medication consumption and expenditure by therapeutic class and active substance

The class with the highest consumption were the antihypertensives with 145.0 DDDs/100 days of NH stay, followed by antianemic preparations (72.9 DDDs/100 days of NH stay), drugs for constipation (71.9 DDDs/100 days of NH stay), dermatologicals (61.3 DDDs/100 days of NH stay), and drugs for peptic ulcer and gastro-esophageal reflux disease (58.5 DDDs/100 days of NH stay; Table 2).

Platelet aggregation inhibitors, drugs for genitourinary disorders, and antipsychotics were those with the highest utilization of generic drugs, with 79.1%, 57.6%, and 55.7%, respectively.

Anticoagulants had the highest cost per day of NH stay (0.21 euro), while antibiotics had the highest cost per DDD (0.97 euro).

Vitamin B12 (cyanocobalamin) was the substance with the highest consumption (58.98 DDDs per 100 days of NH stay; Table 3). Among the other active substances, drugs indicated for hypertension, heart failure, or nephropathies (furosemide and ramipril, 48.73 and 36.66 DDDs per 100 days of NH stay, respectively), acid-related diseases (lansoprazole, 34.56), antiplatelets (acetylsalicylic acid, 29.44) and the treatment of constipation (lactulose, 28.00) were those with the highest number of DDDs/100 days of NH stay.

Enoxaparin was the medication with the greatest expenditure per day of NH stay (0.10 euro), accounting for 20.95 DDDs per day. Oxygen, sodium phosphate, and seine cost 0.07, 0.05, and 0.04 euros, respectively, per day of NH stay (Table 3; Supplementary Table S5).

Table 4 shows the first 20 antibiotics by consumption in 2019 in nursing homes. Among them, the Access group accounted for 53.1% of total DDDs in 2019, while the watch group accounted for 44.6%.

TABLE 1 Consumption, expenditure, and DDD average cost by ATC I level in NH residents (2019).

ATC I level	DDDs per 100 days of NH stay	%	Cost (euros) for a day of NH stay	%	DDD average cost
A	167.6	21.0	0.27	20.5	0.16
B	160.4	20.1	0.33	25.7	0.21
C	177.0	22.2	0.06	4.8	0.04
D	78.6	9.9	0.07	5.0	0.08
G	10.3	1.3	0.01	0.7	0.09
H	16.1	2.0	0.02	1.5	0.12
J	7.3	0.9	0.08	6.0	1.06
L	1.9	0.2	0.01	1.1	0.71
M	15.0	1.9	0.01	1.0	0.09
N	133.8	16.8	0.30	23.1	0.22
P	0.2	0.0	<0.005	0.2	1.11
R	15.3	1.9	0.05	3.5	0.30
S	6.9	0.9	0.01	1.1	0.21
V	7.2	0.9	0.08	5.8	1.04
Total	**797.6**	**100.0**	**1.3**	**100.0**	**0.16**

DDD: defined daily dose.
Anatomical Therapeutic Chemical (ATC) classification: A - alimentary tract and metabolismo; B - blood and blood forming organs; C - cardiovascular system; D - dermatologicals; G - genito urinary system and sex hormones; H - systemic hormonal preparations, excl. sex hormones and insulins; J - antiinfectives for systemic use; L - antineoplastic and immunomodulating agents; M - musculo-skeletal system; N - nervous system; P - antiparasitic products, insecticides and repellents; R - respiratory system; S - sensory organs; V - various.
Bold types are about total values.

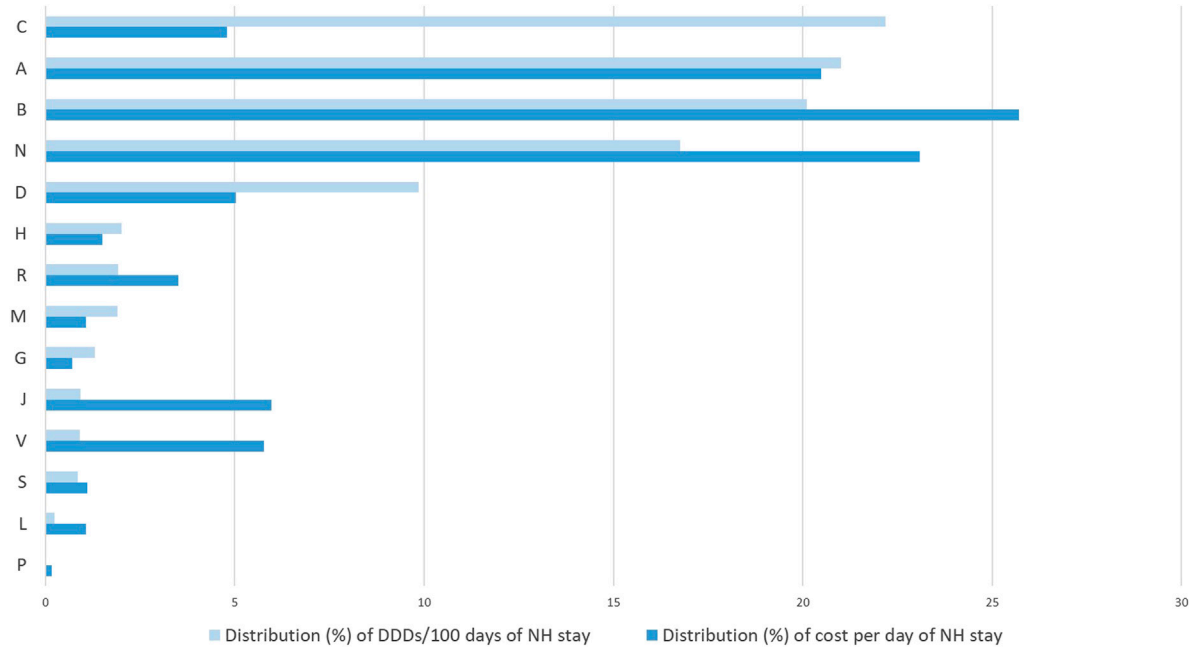

FIGURE 1
Percentage distribution (%) of DDDs/100 days of NH stay and cost (euros) per day of NH stay by ATC I level in nursing home residents (2019). DDD: defined daily dose; Anatomical Therapeutic Chemical (ATC) classification: A - alimentary tract and metabolismo; B - blood and blood forming organs; C - cardiovascular system; D - dermatologicals; G - genitourinary system and sex hormones; H - systemic hormonal preparations, excl. sex hormones and insulins; J - antiinfectives for systemic use; L - antineoplastic and immunomodulating agents; M -musculo-skeletal system; N - nervous system; P - antiparasitic products, insecticides and repellents; R - respiratory system; S - sensory organs; V - various.

TABLE 2 Consumption, expenditure and percentage of generics by therapeutic category in NH residents (2019).

Therapeutic category	DDDs/100 days of NH stay	Cost (euros) per day of NH stay	DDD average cost	% Of generic consumption	% Of generic expenditure
Antihypertensives	144.98	0.04	0.03	26.25	30.91
Antianemic preparations	72.88	0.03	0.05	0.19	0.73
Drugs for constipation	71.86	0.15	0.21	0.00	0.00
Dermatologicals	61.25	0.04	0.07	0.02	0.18
Drugs for peptic ulcer and GERD	58.50	0.02	0.03	23.54	60.52
Platelet aggregation inhibitors	43.47	0.01	0.03	79.09	62.82
Benzodiazepines	37.60	0.01	0.02	0.00	0.00
Antidepressants	35.91	0.05	0.13	34.32	17.96
Anticoagulants	30.22	0.21	0.69	0.00	0.00
Antipsychotics	17.69	0.08	0.47	55.65	21.42
Lipid-lowering agents	17.47	0.00	0.01	2.34	15.83
Antidiabetics	14.01	0.05	0.34	14.64	2.70
Blood substitutes and perfusion solutions	13.70	0.08	0.59	5.53	5.60
Agents acting on cardiovascular system	12.77	0.02	0.14	7.74	5.55
Osteoporosis drugs	11.12	0.01	0.12	19.18	17.38
Antiepileptics	9.96	0.04	0.38	27.84	19.26
Drugs for genitourinary disorders	9.19	0.01	0.07	57.61	47.51
Asthma and COPD drugs	8.69	0.04	0.45	9.07	2.40
Corticosteroids for systemic use	8.39	0.01	0.11	12.36	11.66
Antibiotics for topical use	8.37	0.01	0.16	0.00	0.00
Pain therapy	8.16	0.05	0.61	0.31	0.18
Anti-Parkinson drugs	7.82	0.04	0.49	23.09	23.20
Drugs for thyroid disorders	7.64	0.00	0.03	29.34	30.47
Drugs for gastrointestinal tract and metabolism	7.53	0.02	0.26	0.00	0.00
Antipyretics	7.06	0.01	0.17	0.00	0.00
Antibiotics	6.83	0.07	0.97	14.00	13.68
All other non-therapeutic products	6.72	0.00	0.04	0.00	0.00
Preparations inhibiting uric acid production	6.14	<0.01	0.05	9.12	9.21

DDD: defined daily dose.

Amoxicillin-clavulanic acid combination (access) and ceftriaxone (watch) accounted for half of the DDDs, and among the ten most used antibiotics, seven were in the watch group.

As reported in Supplementary Tables S3–5, a trend in reduction of total consumption and expenditure seemed to be triggered before pandemics (−5.2% in total consumption and −1.4% in total expenditure): it was especially driven by decreasing in drugs for constipation, benzodiazepines and dermatologics. On the contrary, antipyretics and pain therapy increased (by 9.5% and 6.0%, respectively), as well as antianemic preparations, antidepressants, and antipsychotics.

Discussion

This study is the first to analyse medication consumption in nursing homes in Italy using relevant national data flows. The availability of national monitoring on drug utilization in this

TABLE 3 Consumption, expenditure and DDD average cost for the first 20 most used substances in NH residents (2019).

Medication	DDDs/100 days of NH stay	Cost (euros) of NH stay per day	DDD avarage cost
CYANOCOBALAMIN	58.98	0.00	182.67
FUROSEMIDE	48.73	0.01	150.93
RAMIPRIL	36.66	0.00	113.53
LANSOPRAZOLE	34.56	0.00	107.02
ACETYLSALICYLIC ACID	29.44	0.01	91.17
LACTULOSE	28.00	0.02	86.73
CHLOREXIDINE/BENZALCONIUM	22.49	0.00	69.65
ENOXAPARINA	20.95	0.10	64.88
AMLODIPINE	16.30	0.00	50.48
SODIUM HYPOCHLORITE	15.85	0.01	49.08
SODIUM CHLORIDE	14.62	0.03	45.29
SEINE	14.08	0.04	43.61
ATORVASTATIN	11.80	0.00	36.55
OMEPRAZOLE	11.64	0.01	36.05
LORAZEPAM	10.79	0.00	33.41
SODIUM PHOSPHATE	10.75	0.05	33.30
SERTRALINE	9.97	0.00	30.89
PANTOPRAZOLE	7.42	0.00	22.98
TRIAZOLAM	7.26	0.00	22.49
MACROGOL 3350/SODIUM CHLORIDE/SODIUM BICARBONATE/POTASSIUM CHLORIDE	6.92	0.02	21.44

DDD: defined daily dose.

specific care setting has an important adding value for the early identification of room for improvement in the quality of care offered and possible changes in practice.

Overall consumption and expenditure for medications

We found a high pharmacological burden on nursing home residents, with an average consumption of 8 daily doses for each subject each day. Four therapeutic areas (alimentary and metabolism, blood, cardiovascular and nervous system medications) shared almost equally 80% of consumption. At the same time, expenditure was especially ascribable to three of these classes as cardiovascular medicines have a lower economic burden compared to the other classes. On the contrary, when considering drug utilization and expenditure for the general Italian older population, we noticed that adults 65 years and above were reimbursed by the Italian National Health System an average of 3.4 doses of medicines per day, of which about 50% were cardiovascular medicines (Supplementary Table S6). Cardiovascular medicines, however, accounted only for 24% of total expenditure. Moreover, while alimentary and blood medications accounted for 28% of the total consumption and nervous system medications for only 5% (Supplementary Table S6), the first two classes covered slightly less than 40% of the expenditure, followed by nervous system medications with 10%. Even if consumption and expenditure in NH residents and the older general population are not directly comparable (mostly because of different indicators and different sources of data), it seems that NH residents are exposed to a higher degree of polypharmacy than the general population and that this higher consumption might be driven by the alimentary and metabolism, blood and particularly nervous system medications. Nevertheless, as mentioned before, direct comparison is not possible. For example, while benzodiazepines are included in the nervous system medication consumption for the NH setting, this is not the case for the general older population, for which benzodiazepines are not reimbursed by the public drug plan and therefore are not accounted for in the data flow for the general population. As a consequence, nervous system medication doses are underestimated for the general older population. Still, benzodiazepines alone cannot explain the large amount of doses of nervous system medications consumed in NHs. Nursing homes are, by definition, the places where the prevalence of frailty and multimorbid older individuals go when they cannot stay at home (Damiano et al., 2022). Frailty is present in about 50% of nursing home residents, while its prevalence is between 12%–

TABLE 4 Consumption of the first 20 most used antibiotics in nursing home residents in 2019.

Antibiotic	ATC V level	DDDs	% Of total DDDs	2019 AWaRe classification
AMOXICILLIN/CLAVULANIC ACID	J01CR02	65,454.61	39.1	A
CEFTRIAXONE	J01DD04	19,143.50	11.4	W
CLARITHROMYCIN	J01FA09	13,631.00	8.1	W
SULFAMETHOXAZOLE/TRIMETHOPRIM	J01EE01	11,002.75	6.6	A
PIPERACILLIN/TAZOBACTAM	J01CR05	10,244.70	6.1	W
CEFIXIME	J01DD08	8,470.00	5.1	W
AZITHROMYCIN	J01FA10	7,827.00	4.7	W
MEROPENEM	J01DH02	6,090.00	3.6	W
CEFOTAXIME	J01DD01	4,630.25	2.8	W
NITROFURANTOIN	J01XE01	4,470.00	2.7	A
AMOXICILLIN	J01CA04	4,204.00	2.5	A
DOXYCYCLINE	J01AA02	2,190.00	1.3	A
FOSFOMYCIN (IV)	J01XX01	1,958.00	1.2	R
CEFTAZIDIME	J01DD02	1,402.50	0.8	W
AMIKACIN	J01GB06	1,217.50	0.7	A
NORFLOXACIN	J01MA06	1,173.00	0.7	W
VANCOMYCIN (IV)	J01XA01	993.00	0.6	W
TEICOPLANIN	J01XA02	633.50	0.4	W
MOXIFLOXACIN	J01MA14	570.00	0.3	W
CEFALEXIN	J01DB01	380.00	0.2	A
Total[a]	—	**167,462.06**	**100%**	—

[a]Total consumption for all the medications in the J01 group.
DDD: defined daily dose. 2019 AwaRe classification: A = access group; R = reserve group; W= watch group. Anatomical Therapeutic Chemical (ATC) classification.
Bold types are about total values.

24% in community-dwelling older individuals (Kojima, 2015; O'Caoimh et al., 2021). Multimorbidity and polypharmacy can indeed increase pharmaceutical expenditures for older individuals in nursing homes, as well as the risk of potentially inappropriate prescriptions, which also cause greater costs (Caucat et al., 2020).

Medication consumption and expenditure by therapeutic class and active substance

Cardiovascular medicines

In our sample, the treatment of hypertension and heart failure was widely the most frequently used, with the consumption being driven mainly by furosemide and ramipril. This finding can be thus considered consistent with the most frequent diagnoses in the older population, with evidence supporting deprescribing for these medications being still scarce (Reeve et al., 2020). The use of cardiovascular medicines in NH residents seems, in fact, similar to those of outpatients 65 and older (1.62 DDDs vs. 1.77 DDDs per subject per day), although in the nursing home population, prevention of cardiovascular events should probably be a medical need with lower priority, since subjects are more strictly monitored and with a general shorter life expectation, thus with lower impact of cardiovascular risk (e.g., for cholesterol level reduction by statins).

Gastrointestinal medicines

Antiulcer drugs (namely, PPIs) were used on average in more than half of the days of NH stay (58.5 DDDs/100 days of NH stay). This finding confirms the high PPIs consumption in Italian nursing homes previously reported (Pasina et al., 2020b), which enormously exceeds the use in other countries. Use of PPIs in the elderly is appropriate only for current main gastric or duodenal disorders or prevention of NSAID gastric effects. However, based on our data, NSAIDs are only rarely used, as well as the prevalence of main gastrointestinal diagnoses should be low. Moreover, differences with other countries suggest that Italian nursing homes should implement deprescribing initiatives on PPIs, taking advantage of relevant evidence from original studies and authoritative guidelines (Visser et al., 2021; Onder et al., 2022).

Laxatives are another drug class with high use and are well known for their risk of misuse or abuse (Gage et al., 2010; Gustafsson

et al., 2019). Constipation and relevant laxative use may reflect physiological changes in older individuals (e.g., slower bowel motility) or be a consequence of medication use, for instance, drugs with a marked anticholinergic effect (e.g., antidepressants or antipsychotics) (Clark et al., 2010). However, chronic use of laxatives should be strongly discourdged since it can lead to adverse effects such as electrolyte imbalances and abdominal symptoms (Mounsey, Raleigh, and Wilson, 2015), with consequent worsening of health status, without adequate relief of symptoms.

Neuropsychiatric medicines

As for other highly consumed medications, a study comparing drug use between community-dwelling older adults and those in nursing homes in Oslo showed that older individuals were more likely to use antipsychotics, paracetamol, anxiolytics, antidepressants, and loop diuretics (Fog et al., 2019). On the other hand, antidepressants, antihypertensives, antithrombotics, calcium supplements, and vaccines could be even underused in this kind of patients (Avorn and Gurwitz, 1995).

In our study, benzodiazepines, antipsychotics, and antidepressants counted for about 90 DDDs/100 days of NH stay: on average, almost all patients receive a dose of these medicines daily. Aggregated data do not allow to distinguish single therapies with a full dose for each patient from polytherapy with low doses or even from polytherapy with higher doses for a lower percentage of patients (which are the most frequent pattern of use (Spinewine, Evrard, and Hughes, 2021)). The main reasons for using these classes could range from generic anxiety disorders and insomnia to behavioral disorders in patients with dementia. Nursing homes represent a specific setting for these diagnoses. However, benzodiazepines are considered inappropriate in older individuals by now (American Geriatrics Society Beers Criteria Update Expert Panel, 2019), which could explain the trend in decreasing use in a recent study among individuals 65 years and older in Canada (Gosselin et al., 2022). Nevertheless, in that study, the prevalence of benzodiazepine use remained high (about 30%) among older adults with at least two chronic conditions (Gosselin et al., 2022).

In nursing homes, managing residents with psychiatric or behavioral disorders with non-pharmacological treatments is, unfortunately, time- and resource-consuming. Thus, drug therapy is generally considered the most straightforward approach, especially when nursing homes suffer staff shortages (French et al., 2022). A recent study conducted in Norwegian nursing homes showed that prescription rates of psychotropic drugs such as antidepressants, antipsychotics, anxiolytics, sedatives, and hypnotics increased by almost 10% 6 months after nursing home admission (Callegari et al., 2021). Tolerance development, adverse effects, and risk of clinically significant interactions shortly challenge the sustainability of these drug therapies and can contribute to worsening older residents' health status. This finding confirms that benzodiazepines should not be used in older adults (especially if long-term use is planned), and antipsychotics require strict monitoring of maintenance of benefits and safety profile. As for antidepressants, they would be recommended only in a minority of patients, namely, those with major depression, whereas adverse effects and interactions remain a frequent risk (National Institute for Health and Care Excellence. (2022)), and older individuals are those with the highest risk for chronic use once the treatment has been started (Lunghi et al., 2020). As a matter of fact, data from 2018 on the same sample of NHs of our study showed that benzodiazepine use was decreased by more that 10%, probably due to already ongoing initiatives on this area also in our Country drived by a positive impact of other published experiences (Supplementary Table S3).

Antinfectives

In our study, antibiotics did not rank in the first place because their cycles are usually short, and their cumulative amount is necessarily lower than drugs chronically used. They reached 6.8 DDDs/100 days of NH stay. The most used antibiotic medication was the combination of amoxicillin and clavulanic acid, accounting for almost 40% of total antibiotic DDDs. Although this combination is a broad-spectrum antibiotic, it is among the Access group in the 2019 AwaRe classification (World Health Organization, 2019), with lower resistance potential than antibiotics in the other groups. Ceftriaxone and clarithromycin were the second and third most used antibiotics in our sample. They are listed in the Watch group of the 2019 AwaRe classification (World Health Organization, 2019); for their potential to induce resistance, they should consider only for a limited number of cases.

The use of antibiotics in nursing homes could be attributable to preventing or treating urinary tract or respiratory infections, often without verifying the real need for treatment or identifying the best treatment option. Therefore, broad-spectrum antibiotics are preferred without a strong awareness of resistance risk. However, authoritative recommendations and real-practice studies agree that admission from a nursing home is not a sufficient condition to initiate empirical broad-spectrum antibiotics. (Goossens et al., 2005; Lopes et al., 2021).

Rooms for improvement

Findings from our study suggest specific areas of interventions toward an improvement of the appropriateness of drug use in Italian nursing homes. These interventions require key steps to be implemented: 1. sharing among the whole care team (clinicians, general practitioners, nurses, pharmacists) criteria to be used in the identification of the inappropriate use of a drug, 2. medication reviewing supported by digital tools, and 3. therapeutic changes, including the definition of patient's follow-up, shared with patient and caregiver. The use of educational interventions and computerized prescription of drugs, which informatic tools may support, could stimulate this type of action and not only be applied at the nursing home level but also exported to other care settings (Lunghi et al., 2022; Crisafulli et al., 2022). A multicenter, prospective pilot study confirms that the combination of educational programs and informatic media can reduce the use of potentially inappropriate drugs in care homes (Pasina et al., 2016).

Strengths and limitations

The main strength of this study is that we reported recent data on medications used in nursing homes in different Italian regions. Drug use data in nursing homes are rarely available since they are not part of surveillance programs, nor are they usually monitored through electronic tools. Our data flow represents a precious resource for the surveillance of medicine consumption among institutionalized older individuals and for monitoring habits

and trends of exposure to medicines in this specific setting. The final aim is to help healthcare professionals maximize safe drug therapy for the elderly while maintaining evidence-based effective treatments. Moreover, we could access consumption data on not-reimbursed medications, such as benzodiazepines, thus overcoming the inherent limitation of many healthcare databases, which detect only reimbursed services. A further limitation is the lack of diagnosis in the national data flow. This does not allow us to specifically assess the treatment appropriateness for single patients and therefore provide percentages of inappropriateness.

The DDDs/100 days of NH stay indicator is best suited to assess drug consumption in settings with institutionalized patients (including nursing homes). It allows comparisons among different areas and time trends, regardless of occupancy of the number of beds and relevant occupancy differences.

Nevertheless, this study also has some limitations. First, data collection from nursing homes has involved only a few regions, especially in northern Italy. The results are thus not representative of the entire nursing home population but only of the Italian regions included in the analysis. However, with the implementation of data collection throughout the Country, this limitation will be overcome soon, at least partially, and will allow better comparisons between different regions. When data on national and regional trends will be also available, they will represent valuable support for assessing the efficacy of local initiatives and comparing them with international experiences. The flow is nevertheless still under development. Therefore, the coverage and representativeness of Italian nursing homes are far from satisfactory. The implementation of data collection in Italian nursing homes would represent valuable input for each region to improve its specific areas of inappropriateness by striving for the best reliable standards. Time trends and comparisons among different geographical areas and types of nursing homes could be available in the following years. Moreover, even if data on drug use can be easily combined with clinical data since the population is well defined, and any health event virtually misses from monitoring initiatives, at present, our data are only aggregated and thus lack population characteristics (e.g., socio-demographic information, indication of use, comorbidity burden, and clinical outcomes). Moreover, a large heterogeneity exists between different nursing homes in the management of medication allocation. As an example, in some nursing homes medications are supplied directly by local health authorities, while in others they are supplied through general practitioner. Consequently, no stratification on age group, gender, or condition can be performed. Finally, the varying regional availability of beds in the nursing home could result in a selection of the population accessing these facilities.

Conclusion

Monitoring drug therapy in nursing homes represents a challenge for drug utilization research. Improving the quality of healthcare for older patients is one of the main goals of high-middle income countries. The availability of data on drug use in this specific setting allows the identification of the main therapeutic areas needing interventions and the assessment of their consequences. In Italy, cardiovascular medicines, followed by antiulcer and laxative agents, and drugs used for psychiatric disorders were the most used. Most of these medications, especially PPIs and benzodiazepines, together with broad-spectrum antibacterials, can be the target of quality improvement initiatives, as suggested by the relevant Italian recommendations.

Data availability statement

The datasets generated during and/or analysed during the current study are not publicly available because of data sharing legal restrictions, the dataset including individual records cannot be made publicly available. However, aggregated data will be shared on reasonable request to the corresponding author.

Author contributions

SZ, EP, and CL wrote manuscript with input from all authors SZ, EP, AC, and CL aided in interpreting the results and worked on the manuscript SZ, EP, AP, GO, AC, RD, II, and FT conceived the idea AP and RD checked data quality and analysed the data FT, GO, AC, RD, SZ, and EP were involved in planning and supervised the work. All authors discussed the results and commented on the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1128605/full#supplementary-material

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