



Drug prescriptions in nursing home residents: an Italian multicenter observational study

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Abstract

Purpose Pharmacoepidemiological studies aimed to distinguish drug use in nursing home (NH) residents with and without dementia could be useful to target specific interventions to improve prescribing. This multicenter retrospective study aimed (i) to describe drug therapy in a large sample of NH residents according to the diagnosis of dementia, and (ii) to record the most frequent potentially severe drug-drug interactions.

Methods This study was conducted in a sample of Italian long-term care NHs. Drug prescription information, diseases, and socio-demographic characteristics of NH residents were collected at three different times during 2018.

Results The mean number of drugs was significantly higher in NH residents without dementia than in those with ($p = 0.05$). Antipsychotics, laxatives, benzodiazepines, antiplatelets, and proton pump inhibitors (PPIs) were most commonly prescribed in patients with dementia, and PPIs, benzodiazepines, and laxatives in those without. The prevalence of patients with potentially severe drug-drug interactions was higher among those without dementia, 1216 (64.7%) and 518 (74.2%, $p < 0.0001$). There were significant differences between the mean numbers of drugs prescribed in individual NH after adjusting the analysis for age, sex, and mean Charlson index, the estimated mean number of drugs prescribed (\pm standard error) ranging from 5.1 (± 0.3) to 9.3 (± 0.3) in patients with dementia ($p < 0.0001$) and from 6.0 (± 0.7) to 10.9 (± 0.50) in those without dementia ($p < 0.0001$). Chronic use of psychotropic drugs was common in NH residents with and without dementia.

Conclusions The wide variability between NHs in drug prescriptions and potentially inappropriate prescribing suggests the need to recommend a standardized approach to medication review of psychotropic drugs, antiulcer, laxatives, and antiplatelets in this complex and vulnerable population.

Keywords Nursing homes · Dementia · Psychotropic drugs

Introduction

Older nursing home (NH) residents often have a number of diseases and frequently require multiple medications [1, 2], which expose them to an increased risk of inappropriate prescribing, adverse drug events, and potentially severe drug-drug interactions (DDIs) [3–5]. NH residents are complex and vulnerable [1] with a higher burden of cognitive deficits than non-institutionalized elderly. The few studies of the

medicines most commonly used in NH residents found that drugs for cardiovascular diseases, psychotropic drugs, laxatives, and analgesics were the most frequently and chronically used [6–8]. Most NH residents do suffer from dementia, with psychiatric and behavioral symptoms [9], so higher prescription of psychotropic drugs is likely [10–12]. However, long-term use of psychotropic drugs in older people raise important safety concerns [13–16] and prescription for only short periods is recommended [17, 18]. Beers criteria [19] recommend limiting the use of psychotropic drugs, avoiding prescription of three or more. Despite these recommendations, long-term use is still common [20], even if successful discontinuation may result in improvements in cognitive and psychomotor function and also working memory, reaction times, balance, and fewer falls [21, 22].

Many older people with Alzheimer's dementia and neuro-psychiatric symptoms can in fact be withdrawn from chronic

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antipsychotic medication with no detrimental effects on their behavior [23].

The contradiction of such wide prescribing of psychotropic drugs despite their side effects and limited evidence for (long-term) effectiveness suggests that these drugs may be widely prescribed inappropriately [24]. Differences in drug prescription between NH residents with and without dementia are expected [8]. Neuropsychiatric symptoms, which commonly lead to nursing home placement [25], are in fact observed in 60 to 98% of patients with dementia, especially in later stages. These symptoms generally require drug treatment, but there is no clear standard of care and pharmacological therapies are often based on local pharmacotherapy customs [26]. Pharmacoepidemiological studies aimed to distinguish drug use in NH residents with and without dementia could be useful to target specific interventions to improve prescribing. Few studies examined the prevalence of polypharmacy and potentially inappropriate medications (PIM) in older people with and without dementia. A large Danish population study found that the likelihood of polypharmacy and PIM was higher for community-dwelling people with dementia, and that dementia slightly decreased the odds of polypharmacy and PIM in NH residents [27]. This multicenter retrospective study is aimed (i) to describe the most commonly used medicines in a large sample of NH residents according to the diagnosis of dementia, and (ii) to assess the most frequent potentially severe DDIs.

Methods

Study design and data collection

This retrospective cross-sectional study was conducted in a sample of Italian long-term care NHs. Socio-demographic details, diagnosis, and drug treatments of each NH resident during the study were collected on web-based Case Report Forms (CRF). Data collection complied fully with Italian law on personal data protection, and the study was approved by the ethics committee of the IRCCS Carlo Besta Foundation. Drug prescription information, diseases, and socio-demographic characteristics of NH residents were collected at three different times during 2018, i.e., T₁ (April 1), T₂ (September 1), and T₃ (December 31).

The prevalence for each drug was calculated considering the last time point for each patient (T₁, T₂, or T₃). A longitudinal analysis was also conducted considering the cohort of patients that was always present at each time (from T₁ to T₃).

Potentially severe DDIs were evaluated using a database (INTERCheck) developed by the IRCCS-Istituto di Ricerche Farmacologiche Mario Negri [28].

The diagnosis of dementia was based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth

edition (DSM-IV), and comorbidities were classified according to ICD-10 codes.

Statistical analysis

The patients' socio-demographic characteristics were described using standard descriptive statistics. We tabulated the percentages for binomial variables, and differences were evaluated with Pearson's chi-squared test. Differences between drug classes used in NH residents with and without dementia were evaluated with Wald's test in a multivariate model adjusted for age, sex, and Charlson comorbidity index (excluding diagnosis of dementia).

We computed means and standard deviations for numerical variables, and differences in groups were analyzed with an F-test. Distribution of Charlson index was also analyzed with median and quartile.

The statistical comparisons in medication prevalence between patients with and without dementia were conducted at univariable level, i.e., without correcting for different medical conditions and demographics, to highlight the differences in the drug exposure in the two groups.

The change from T₁ to T₃ in the prevalence of patients exposed to potentially severe DDIs or treated with duplicate psychotropic drugs, or receiving at least three psychotropic drugs, was analyzed using McNemar's test for dichotomous and unordered categorical data. Psychotropic drugs were defined as prescribing at least one benzodiazepine, antipsychotic, or antidepressant; therapeutic duplicates as prescribing at least two drugs of the same therapeutic class (e.g., two antipsychotics) simultaneously to the same patients.

Differences between NHs in the mean number of drugs in patients with and without dementia were examined using an F-test with a mixed-model to adjust the within-subjects correlation; the model was also adjusted for age, sex, and comorbidity index (as continuously and on categorical levels referred to median value). The diagnosis of dementia was deleted from the comorbidity index to avoid differences in the mean score between the two groups.

The significance criterion (alpha) was set at 0.05 for all tests. With a sample of approximately 1900 patients with dementia and 700 without, we had a statistical power greater than 80% to show differences in means between groups with a small effect size (0.15) or 7% differences between groups in the prevalence of drug therapy or potentially severe DDIs.

Analyses were done with JMP Pro 14 (SAS Institute Inc.).

Results

Among the 2579 patients recruited from 27 long-term care NHs, 1881 (72.9%) had a diagnosis of any type of dementia. The prevalence of females was higher among both the NH residents

with and without dementia (78.3% and 74.9%, $p = 0.04$). Patients with dementia were older, but those without dementia had more comorbidities and received more drugs (8.6 ± 3.7 and 7.1 ± 3.3 , $p < 0.0001$). The mean number of drugs was significantly higher in males with dementia ($p = 0.01$) and those without dementia ($p = 0.05$), and rose significantly with age in both groups. Table 1 summarizes the socio-demographic and clinical characteristics of patients with or without dementia.

The most commonly prescribed drugs were psychotropic (at least one benzodiazepine, antipsychotic, or antidepressant, 76.1%), benzodiazepines (45.9%), proton pump inhibitors (45.6%), laxatives (45.1%), and antipsychotics (45.1%), with some differences between demented and not demented residents. Antipsychotics, laxatives, benzodiazepines, antiplatelets, and proton pump inhibitors (PPIs) were the most commonly prescribed drugs in patients with dementia, while PPIs, benzodiazepines, and laxatives were most common in those without (all unadjusted p values) (Table 2). These differences were confirmed in the multivariate model adjusted for age, sex, and comorbidity index.

The prevalence of potentially severe DDIs was higher among those without dementia (1216 (64.7%) and 518 (74.2%), $p < 0.0001$). The most frequent potentially severe DDIs involved drugs with additive effects on QTc prolongation, mainly psychotropic drugs; associations of ACEi or ARBs with potassium supplements that increase the risk of hyperkalemia; and combinations of SSRI or SNRI with antiplatelets, increasing the risk of hemorrhage (Table 3).

A significant difference between the mean numbers of drugs prescribed in individual NH was found after adjusting the analysis for age, sex, and mean Charlson index, with an estimated mean number (\pm standard error) ranging from 5.1 (± 0.3) to 9.3 (± 0.3) in patients with dementia ($p < 0.0001$) and from 6.0 (± 0.7) to 10.9 (± 0.50) in those without dementia ($p < 0.0001$). These results were confirmed adjusting the analysis using Charlson index as categorical; the estimated mean number (\pm standard error) ranged from 5.4 (± 0.3) to 9.6 (± 0.3) in patients with dementia ($p < 0.0001$) and from 6.0 (± 0.7) to 11.0 (± 0.50) in those without dementia ($p < 0.0001$). Differences between individual NHs ($p < 0.0001$) persisted also when considering patients included in the longitudinal phase of the study (Fig. 1). This shows a higher variability among NH residents with dementia, even if the mean number of drugs was significantly lesser. Residents with dementia were not equally distributed among NHs, but no relation between percentage of NH residents with dementia and number of drugs prescribed was found ($p = 0.12$).

These results were confirmed in the longitudinal phase of the study, which included 1312 NH residents with dementia and 466 without dementia. The mean number of drugs was 7.2 ± 3.3 for NH residents with dementia and 8.7 ± 3.6 for those without dementia. The percentage of NH residents exposed to potentially severe DDIs was 63.0% for residents with

dementia and 73.6% for those without dementia. The longitudinal phase of the study found that chronic use of psychotropic drugs was common. NH residents receiving antipsychotics or duplicates (at least two antipsychotics) at each time point (from T₁ to T₃) were 554 (87.1% of those receiving antipsychotics in at least one visit) and 125 (74.6% of those receiving duplicates in at least one visit) among those with dementia, and 137 (91.3%) and 25 (80.6%) among those without dementia. Similarly, 535 (86.7%) and 98 (72.1%) received benzodiazepines or duplicates among residents with dementia, and 220 (90.2%) and 49 (73.1%) among those without dementia. Chronic use of PPI was also found in 495 (87.5%) patients with dementia and 230 (92.0%) of those without dementia.

Discussion

This study found that psychotropic drugs, antiulcer agents, and laxatives were the most commonly used drugs in Italian NHs, with differences between residents with and without dementia. This may allow targeting of specific interventions in the NH setting. Our findings pose for example some important questions for those who work in institutions. Why are psychotropic drugs so commonly used in patients with dementia or antiulcer agents in residents without dementia?

Antipsychotics were the most commonly prescribed in patients with dementia (50% vs 32% of residents without dementia, $p < 0.0001$), but the frequent use of these drugs in the older adults is of concern because they can cause or exacerbate confusion, and those with dementia are more susceptible to these effects [29]. Antipsychotics increase also the risk of cerebrovascular events (ischemic stroke and transient ischemic attack) and mortality in older adults with dementia [30, 31].

Again, we found a high percentage of residents at each time point receiving three or more psychotropic drugs, putting them at increased risk of falls and fractures [19]. In all, the use of any psychotropic drug in NH residents was higher than that reported in Australian and Dutch nursing homes (69.9% and 71.1%), and similar results were found for antipsychotics and benzodiazepines [32]. Different policies in these countries or medical attitude toward drug prescription could explain these differences. Many reasons have been proposed why psychotropic drugs are so commonly used in this setting, and behavioral symptoms are those most commonly cited [33]. However, psychotropic treatment of behavioral disturbances is often not effective in patients with dementia, and in fact there has been some success in reducing these drugs by training staff to use behavioral interventions instead of drugs [32, 34]. The longitudinal phase of the study suggests that chronic use of psychotropic drugs was common, highlighting the need to reduce them. Appropriate regulations sustained by educational interventions could be useful for this purpose.

Table 1 Main details of the 2579 NH residents in the analysis[§]

	Dementia, no. (%) (1881)	No dementia, no. (%) (698)	<i>p</i>
Age, years (mean ± SD)	87.3 (7.0)	85.4 (7.9)	< 0.0001
Age group, no. (%)			< 0.0001
65–79	258 (13.7)	161 (23.1)	
80–84	332 (17.7)	119 (17.1)	
85–90	617 (32.8)	216 (30.9)	
90+	674 (35.8)	202 (28.9)	
Women, no. (%)	1472 (78.3)	523 (74.9)	0.04
Drugs, no. (mean ± SD)	7.1 (3.3)	8.6 (3.7)	< 0.0001
Sex			
Male	7.5 (3.4)	9.0 (3.8)	< 0.0001
Female	7.1 (3.3)	8.4 (3.7)	< 0.0001
Age group			
65–79	7.0 (3.4)	8.6 (4.0)	< 0.0001
80–84	7.5 (3.4)	8.8 (3.7)	0.0002
85–90	7.2 (3.3)	9.0 (3.9)	< 0.0001
90+	7.0 (3.3)	8.0 (3.2)	< 0.0001
Main comorbidities, no. (%)			
Diabetes	308 (16.4)	145 (20.8)	0.009
Anxiety	233 (12.4)	202 (28.9)	< 0.0001
Psychosis	38 (2.2)	49 (7.0)	< 0.0001
Depression	63 (3.3)	94 (13.5)	< 0.0001
Parkinson's disease	168 (8.9)	47 (6.7)	0.07
Essential hypertension	1283 (68.2)	502 (71.9)	0.07
Cerebral atherosclerosis	720 (38.3)	178 (25.6)	< 0.0001
Cardiac dysrhythmias	370 (19.7)	174 (24.9)	0.004
Chronic bronchitis	259 (13.7)	113 (16.2)	0.12
Constipation	467 (24.8)	177 (25.4)	0.78
Gastritis and duodenitis	168 (8.9)	69 (9.9)	0.46
Renal failure	194 (10.3)	85 (12.2)	0.18
Osteoarthritis	756 (40.2)	240 (34.4)	0.007
Osteoporosis	397 (21.1)	123 (17.6)	0.05
History of fractures	57 (3.0)	18 (2.6)	0.54
Urinary incontinence	1710 (90.9)	533 (76.4)	< 0.0001
Fecal incontinence	1204 (64.0)	272 (39.0)	< 0.0001
History of myocardial infarction	77 (4.1)	45 (6.4)	0.01
Heart failure	117 (6.2)	59 (8.5)	0.04
Transient cerebral ischemia	28 (1.5)	16 (2.3)	0.16
Charlson index, (mean ± SD)*	2.3 (1.8)	2.7 (2.0)	< 0.0001
Charlson index, median (25–75 percentile)*	2.0 (1–3)	2.0 (1–4)	0.0002

*Excluding diagnosis of dementia

[§] Univariable analysis

We found very high use of PPIs (about 46%), which were the most common drugs in patients without dementia. The prevalence was similar to that observed in Australia and The Netherlands, but higher than in Finland, France, and the USA, where NH residents taking PPIs were between 22 and

38% [35–37]. This suggests an urgent need to optimize PPI prescriptions in NHs. Although their overuse is widespread, PPIs can cause serious adverse reactions with heavy implications for drug costs [38], and their regular use in NHs has been associated with diarrhea and other adverse events [39].

Table 2 Medications most commonly prescribed

Drugs	Dementia, no. (%)	No dementia, no. (%)	Model 1 (<i>p</i>)	Model 2 (<i>p</i>)
Antipsychotics	939 (49.9)	223 (32.0)	< 0.0001	< 0.0001
Laxatives	845 (44.9)	319 (45.7)	0.72	0.54
Benzodiazepines	835 (44.4)	348 (49.9)	0.01	0.009
Antiplatelets	820 (43.6)	272 (39.0)	0.03	0.02
Proton pump inhibitors	798 (42.4)	379 (54.3)	< 0.0001	< 0.0001
Beta blockers	248 (35.5)	529 (28.1)	0.0003	0.002
High-ceiling diuretics	592 (31.5)	310 (44.4)	< 0.0001	< 0.0001
Antidepressants	584 (31.1)	251 (36.0)	0.0185	0.05
ACEi ^a /ARBs ^b	541 (28.8)	245 (35.1)	0.02	0.004
Acetaminophen	515 (27.4)	212 (30.4)	0.13	0.06
Cholecalciferol	342 (18.2)	163 (23.4)	0.003	0.003
Antiepileptic drugs	264 (14.0)	127 (18.2)	0.009	0.23
Calcium-channel blockers	252 (13.4)	133 (19.1)	0.0003	0.002
Levothyroxine	241 (12.8)	94 (13.5)	0.66	0.90
Folic acid	224 (11.9)	75 (10.7)	0.41	0.29
Opioids	216 (11.5)	136 (19.5)	< 0.0001	< 0.0001
Oral anticoagulant	201 (10.7)	112 (16.0)	0.002	0.003
Heparins	181 (9.6)	74 (10.6)	0.46	0.97
Nitrates	171 (9.1)	91 (13.0)	0.003	0.002
Antiparkinson drugs	160 (8.5)	51 (8.2)	0.32	0.11
Statins	154 (8.2)	96 (13.8)	< 0.0001	0.007
Iron	151 (8.0)	66 (9.5)	0.25	0.46
Insulin	126 (6.7)	58 (8.3)	0.16	0.73
Potassium supplements	109 (5.8)	44 (6.3)	0.63	0.88
Alfa-blocker for BPH ^c	107 (5.7)	69 (9.9)	0.0002	0.002
Metformin	98 (5.2)	49 (7.0)	0.08	0.54
Potassium-sparing diuretics	90 (4.8)	56 (8.2)	0.002	0.006
Corticosteroids	78 (4.5)	42 (6.0)	0.04	0.05
Xanthine-oxidase inhibitors	83 (4.4)	61 (8.7)	< 0.0001	0.0005
5-alfa-testosterone-reductase	64 (3.4)	29 (4.2)	0.36	0.64
Bisphosphonate	60 (3.2)	43 (6.7)	0.0006	0.0004
Antidementia	55 (2.9)	2 (0.3)	< 0.0001	0.0006
NSAIDs ^d	25 (1.3)	31 (4.4)	< 0.0001	< 0.0001
At least one psychotropic drug, no. (%)	1458 (77.5)	524 (75.1)	0.19	0.11
At least three psychotropic drugs, no. (%)	397 (21.1)	133 (19.1)	0.25	0.11
Duplicates				
Antipsychotic, no. (%)	261 (13.9)	55 (7.9)	< 0.0001	< 0.0001
Benzodiazepines, no. (%)	150 (8.0)	88 (12.6)	0.0003	0.0004
Antidepressant, no. (%)	75 (4.0)	21 (3.0)	0.24	0.1483

^a Angiotensin-converting enzyme inhibitors

^b Angiotensin II receptor blockers

^c Benign prostatic hyperplasia

^d Non-steroid anti-inflammatory drugs

Model 1 is unadjusted; model 2 is adjusted for age, sex, and Charlson index (excluding diagnosis of dementia)

Potentially severe DDIs were more frequent in NH residents without dementia, and the greater use of antidepressants resulted in a higher prevalence of patients exposed to the risk

of serotonergic syndrome, hyponatremia, and gastrointestinal hemorrhage.

Table 3 Most frequent potentially severe DDIs

Drug combination	Potential adverse events	Patients, no. (%)		
		Dementia, no. (%)	No dementia, no. (%)	<i>p</i>
Drugs with additive effects on QTc prolongation	Increased risk of QTc prolongation and torsades de pointe	812 (43.3)	289 (41.4)	0.42
Potassium + ACEi ^a or ARBs ^b	Increased risk of hyperkalemia	203 (10.8)	92 (13.2)	0.09
ASA ^c + SSRIs ^d or SNRI ^e	Increased risk of hemorrhage	119 (6.3)	62 (8.9)	0.02
Diuretics + SSRI	Hyponatremia	111 (5.9)	97 (13.9)	<0.0001
Benzodiazepines + opioids	Respiratory depression and excessive sedation	99 (5.3)	73 (10.5)	<0.0001
Enalapril + furosemide	Renal failure and hypotension	56 (3.0)	21 (3.0)	0.97
Digoxin + high-ceiling diuretics	Digoxin toxicity	54 (2.9)	22 (3.2)	0.71
SSRIs + opioids	Serotonergic syndrome	44 (2.3)	37 (5.3)	<0.0001

^a Angiotensin-converting enzyme inhibitors

^b Angiotensin II receptor blockers

^c Acetylsalicylic acid

^d Selective serotonin re-uptake inhibitors

^e Serotonin-norepinephrine re-uptake inhibitors

However, the frequent prescribing of these medications does not necessarily indicate poor quality of care because the use of numerous medications in the care of complex, elderly NH residents can be appropriate and may be necessary to optimize medical and functional status. However, we found

a wide variability between NH drug prescriptions in a model adjusted for age, sex, and comorbidity. The mean numbers of drugs prescribed to the residents of each NH varied widely (5–9 in patients with dementia and 6–11 in those without), thus reflecting different medical approaches toward drug

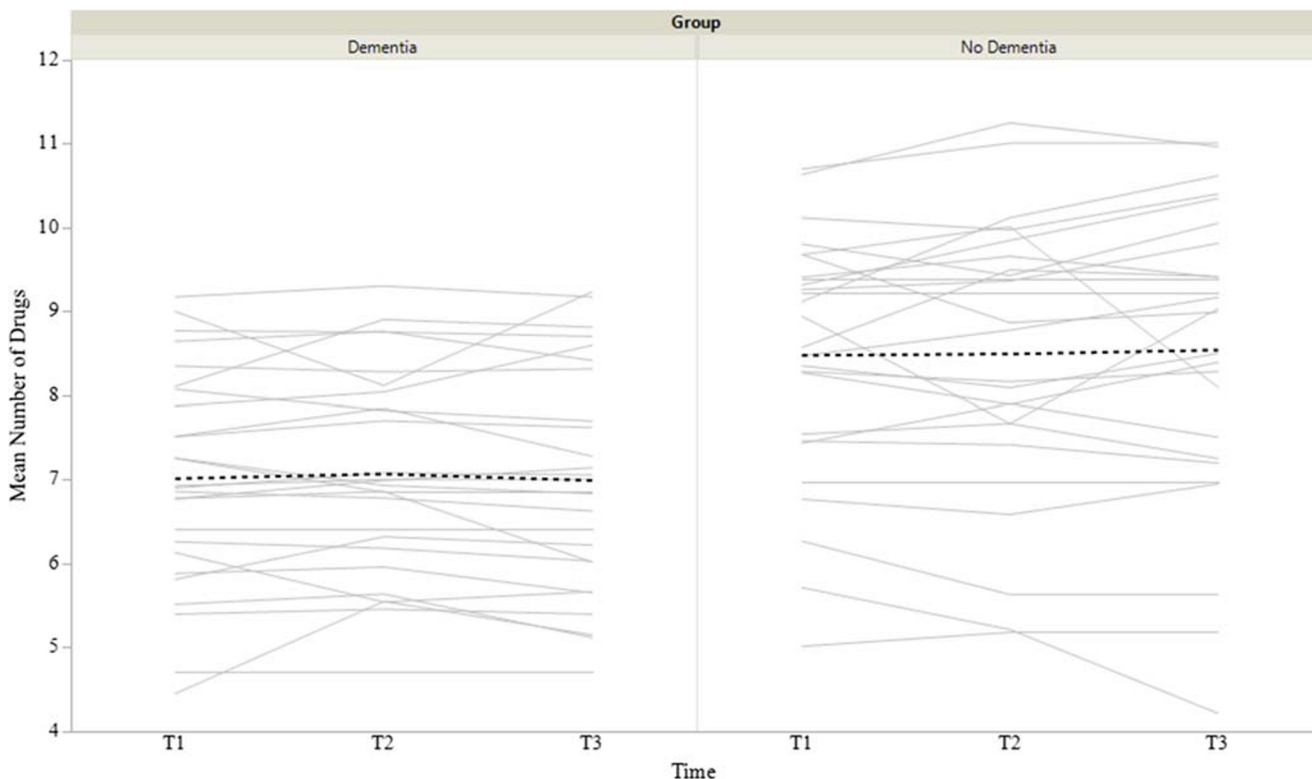


Fig. 1 Difference between the mean numbers of drugs prescribed in single NH after adjusting the analysis for age, sex, and mean Charlson index

prescriptions. There was no relationship between the prevalence of dementia and the mean number of medications prescribed in individual NH. This was confirmed in the longitudinal phase of the study, showing no changes in the use of psychotropic drugs and suggesting the lack of an appropriate medication review in this fragile and vulnerable population.

The quality of drug prescribing to NH patients has worsened during the last two decades, and this should be of concern for clinicians and policy makers, especially considering the high and chronic use of multiple psychotropic medications [5]. Benefits of drug treatments are generally overestimated and harms underestimated [40]. So prescribers need to pay more attention to the benefit-risk ratio for each drug used, because drugs with a very small expectation of benefit raise the risk of adverse reactions and costs.

Our results support the concern about the high levels of psychotropic use among NH residents. NHs are an ideal setting for comprehensive drug regimen review and de-prescribing, which is all too often neglected in elderly patients in all clinical settings. Our findings suggest that psychotropic drugs, antiulcer agents, laxatives, and antiplatelets need an appropriate medication review in NHs.

De-prescribing is often difficult involving identifying a problem (use of an inappropriate drug) and a therapeutic decision (withdrawing it with close follow-up) [41], but discontinuation of potentially inappropriate medication is feasible in NHs with multicomponent interventions [42, 43]. For example, the combination of educational interventions (“ex cathedra” presentations) and the use of computerized prescription support system (INTERCheck [28]) was found to significantly reduce the prescription of potentially inappropriate psychotropic drugs, psychotropic duplicates, and of drugs associated to potentially severe DDIs [42].

In Italy, regular medication reconciliation is encouraged at each transition of care (including admission in nursing homes) by a Ministry of Health recommendation [44], but this does not ensure that a periodic medication review is performed. Patients can also be visited and prescribed drugs by different specialists and, thus, monitoring of pharmacotherapy is often inadequate.

A strength of this study is that this is the first to examine the difference between individual NHs in relation to different indicators of appropriateness of drug therapy (mean number of drugs, potentially severe DDIs, duplicates of psychotropic drugs, or residents receiving at least three psychotropic drugs), independently by age, sex, and comorbidity of residents.

Limits of the study include the lack of scales to evaluate behavioral symptoms, the lack of data on adverse clinical outcomes, and causes of death limited the possibility of checking the relations between drugs and adverse reactions. Another limit is that the reproducibility and generalizability of the results outside Italy is uncertain.

Conclusion

Both the numbers and types of drugs used differed in older adults with and without dementia. NH residents with any type of dementia used a large number of antipsychotic drugs, while in those without dementia, PPIs and benzodiazepines were the most commonly used. The wide variability between NHs in drug prescriptions and potentially inappropriate prescribing suggests the need to recommend a standardized approach to medication review in this complex and vulnerable population.

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Authors' individual contributions All Authors participated in drafting of the manuscript or critical revision of the manuscript for important intellectual content and provided approval of the final submitted version. Individual contributions are as follows: LP designed the study, interpreted data, and wrote the manuscript; AN, MT, and LC did and interpreted statistical analyses; AN and AI made the final critical revision for important intellectual contents. All authors approved the final version of the paper.

Compliance with ethical standards

Data collection complied fully with Italian law on personal data protection, and the study was approved by the ethics committee of the IRCCS Carlo Besta Foundation.

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent All data were anonymous and informed consent was not required for the purpose of this study.

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