Polypharmacy and Drug-Drug Interactions in Long-Term Care Facilities residents: findings from the Italian Prescription Day Project

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Abstract

Background: Medication prescribing in Long-Term Care Facilities (LTCFs) is characterised by widespread polypharmacy and frequent exposure to potentially clinically relevant drug–drug interactions (DDIs). Methods: Data from the Italian Prescription Day in LTCFs 2024, a national multicentre point-prevalence study conducted in 82 LTCFs, were analysed. Prescriptions were classified using the Anatomical Therapeutic Chemical system, and DDIs were identified using an international consensus list. Resident-level variables were assessed using validated tools, and associations with DDI burden were examined using univariate mixed-effects Poisson regression models. Facility-level organisational characteristics were described by centre-level DDI burden. Results: The analysis included 3,174 residents (mean age 84.8 years; 74.1% women), with a mean of 7.7 prescribed drugs. Drugs acting on the nervous system, alimentary tract and metabolism, and cardiovascular system were most frequently prescribed; furosemide, paracetamol, pantoprazole, quetiapine, and macrogol were the most commonly used active substances. Overall, 42.2% of residents were exposed to at least one potentially clinically relevant DDI, most commonly involving centrally acting drugs, cumulative anticholinergic burden, serotonergic combinations, and potassium-related interactions. Higher DDI burden was associated with greater pharmacological complexity, depression, sleep disorders, cardiopulmonary disease, and behavioural and psychological symptoms of dementia, whereas older age, severe cognitive impairment, malnutrition, and dysphagia were associated with fewer DDIs. Facility-level and staffing characteristics showed limited differentiation, with assisted living facilities under-represented at higher DDI burden. Conclusions: Potentially clinically relevant DDIs are common in Italian LTCFs and are primarily associated with resident-level clinical complexity, highlighting targets for medication review and deprescribing to improve medication safety.

Key words: medication prescribing; medication-related risk; real-world data; anticholinergic burden; multimorbidity.

Introduction

The ageing population and rising rates of institutionalization among older adults have brought increasing attention to medication safety in long-term care facilities (LTCFs). Within this setting, managing pharmacotherapy presents a critical challenge due to multimorbidity, frailty, cognitive impairment, and dysphagia, all of which contribute to a high complexity of care. Polypharmacy (often defined as the regular use of five or more medications) is widespread in LTCFs and is associated with adverse drug events (ADEs) mainly related to drug-drug interactions (DDIs) and potentially inappropriate medications (PIMs), which can lead to accidental falls, functional decline, and a higher need for healthcare utilization (1). The risks associated with polypharmacy in LTCFs are substantial: studies indicate that up to 81% of residents may experience DDIs, and nearly all may be prescribed at least one potentially inappropriate medication (PIM). Prolonged exposure to interacting medications may further increase the risk of adverse drug events (2), reflecting the multifactorial nature of potentially inappropriate prescribing in older adults, which is driven by unclear indications, unfavorable risk–benefit balance, therapeutic duplication, and continuation of existing therapies (3). This widespread burden of drug-related problems highlights the need for structured medication review strategies, as many clinically relevant prescribing issues require dedicated assessment processes and contribute to increased organizational and professional workload in long-term care settings (4). Despite growing interest in deprescribing strategies, inappropriate polypharmacy remains pervasive, and there is considerable heterogeneity across LTCFs—reflecting differences in healthcare organization and local policies (5). The Prescription Day in Long-Term Care Facilities (P-Day LTCFs) Italian Project was designed to provide a comprehensive overview of medication use in long-term care facilities (LTCFs), with the aim of analysing prescription patterns among residents, assessing the prevalence of DDIs, and evaluating the appropriateness of medication administration practices and associated factors.

The primary objective of this paper is to describe the most common prescribed drugs and potentially clinically relevant DDIs among LTCFs residents. The secondary aim is to investigate the association between facility- and resident-level characteristics and the number of DDIs.

Methods

Study design and population

This study uses data from the P-Day LTCFs 2024 project, a national multicenter point-prevalence study promoted by the Italian Society of Gerontology and Geriatrics (SIGG) and the National Association of Territorial Residences (ANASTE) Humanitas Foundation. The study protocol, including participant eligibility, recruitment procedures, and data collection instruments, has been fully detailed in a previous publication (6). The study protocol was approved by the National Ethics Committee, Istituto Superiore di Sanità, Rome, Italy PRE BIO CE n. 0027032 (20/06/2024). From the 3.400 residents initially on October 1, 2024, enrolled in 82 Italian LTCFs, 3.174 were included in the final analytical sample after exclusion of residents with acute conditions (n=211) and those from facilities with fewer than five enrolled participants (n=15). For each participant, trained physicians and nurses working in the involved LTCFs collected data on sociodemographics, functional and cognitive performance, medical history, and ongoing pharmacological treatments. Moreover, the LTCF contact person provided information about the organizational characteristics through a structured questionnaire created ad hoc for the study. Details on the variables considered for the present analysis are reported below.

Pharmacological therapy assessment and Drug-drug interactions

Drug prescriptions were classified using the Anatomical Therapeutic Chemical (ATC) classification system, a hierarchical system developed by the World Health Organization that classifies drugs according to the anatomical site of action (first level), therapeutic subgroup (second level), pharmacological subgroup (third level), chemical/therapeutic/pharmacological subgroup (fourth level), and chemical substance (fifth level) (7). Potentially clinically relevant DDIs were identified

according to the list proposed by Anrys et al., which includes 66 predefined drug–drug interactions classified using a numeric coding system (DDI-1 to DDI-66). Each code corresponds to a specific interaction pair with a defined mechanism and clinical relevance (8). For each DDI, the prescribed drugs were mapped using ATC classification codes. To minimize misclassification due to alternative ATC coding of the same compound (e.g., acetylsalicylic acid reported as N02BA01 [analgesic] instead of B01AC06 [antiplatelet]), all recorded drugs were cross-validated and back-transformed to their unique DrugBank identifier (9). This was achieved through a customised cleaning pipeline developed explicitly for the present dataset. Most DDIs were identified through ATC code mapping. However, DDI-57 (concomitant prescription of ≥2 anticholinergic drugs) was operationalised differently, as it is not defined by a fixed drug pair. Specifically, DDI-57 was identified by the presence of at least two medications with an Anticholinergic Cognitive Burden (ACB) score of 2 or 3, according to the ACB scale (10).

Residents Characteristics: Resident-level characteristics evaluated as potential correlates of DDI burden included demographic, clinical, functional, cognitive, behavioural, and pharmacological variables. These comprised age, sex, comorbidities, nutritional status, functional dependency, frailty measures, cognitive impairment, behavioural and psychological symptoms of dementia, and measures of medication exposure. All variables were assessed using validated instruments and predefined operational definitions, as described in the methodological reference study (6).

Facilities organizational characteristics

At the facility level, organisational characteristics were collected to describe structural, staffing, and professional features of the care settings. Facilities were geographically classified at the regional level and categorised according to type using the "Codice Mattone 12" framework, as previously described (6), distinguishing medicalised nursing homes (R1), nursing homes (R2), and assisted living facilities (R3); rehabilitation centres were recorded as a separate category.

Structural variables included total bed capacity, number of available beds, and number of residents enrolled at the time of data collection. Staffing characteristics comprised the number of nurses per

20 residents during morning, afternoon, and night shifts, used as indicators of nursing staff availability. The presence of key healthcare professionals, including a geriatrician, psychologist, general practitioner, and an educational or professional coordinator, was also recorded.

The average time (in minutes) required for drug administration was recorded for each working shift (morning, mid-morning, lunch, mid-afternoon, evening, night), based on the reported average time per nurse per 20-bed unit. This information enabled the characterization of organizational heterogeneity across facilities and the exploration of the relationship between available resources, nursing workload, and the complexity of pharmacological therapy.

Statistical analysis

The analysis was designed to pursue the following objectives:

- Characterize drug prescribing in Italian LTCFs, including the prevalence of polypharmacy (5+drugs) and specific classes of drugs.
- Estimate the prevalence and typology of DDIs, with particular attention to high-risk pharmacological combinations.
- Identify resident-level clinical and demographic factors (age, sex, frailty, disability, multimorbidity, and selected chronic conditions) associated with the burden of DDIs.
- Examine the association between facility-level organizational characteristics and DDIs across recruitment centers

Participants' characteristics were described using mixed-effects models to account for the multicentric design of the study. Recruitment centres were modelled as random effects, with the unadjusted intercept as estimate: the mean for continuous variables (linear mixed models) or the proportion for categorical variables (binomial generalized linear mixed models with logit link). For categorical variables with more than two levels, each level was transformed into a separate binary indicator. Ninety-five percent confidence intervals (95% CI) were obtained using the Wald method.

These analyses were repeated by stratifying participants according to the presence of at least one DDI.

To investigate the association between residents' characteristics and the number of DDIs, we fitted univariable (unadjusted) generalized linear mixed-effects models with a Poisson distribution and log link. Each model included a random intercept for recruitment center to account for the multicenter design. Continuous variables were standardized (centered on the mean and divided by the standard deviation). Wald 95% confidence intervals (CIs) were computed. Beta coefficients on log-scales are reported. Given moderate overdispersion in the DDI count distribution (variance exceeding the mean), we also conducted sensitivity analyses using negative binomial mixed-effects models; because results were similar in both magnitude and direction, only Poisson model estimates are reported.

Facility-level associations were explored descriptively by first calculating, for each center, the proportion of residents with ≥2 DDIs. Centers were then classified into three categories based on this proportion—low (<10%), moderate (10%–20%), and high (≥20%)—and facility-level characteristics were summarized within these categories using means (standard deviations) for continuous variables and counts (percentages) for categorical variables. This analysis was restricted to the 75 centers with complete facility-level information. All analyses were conducted in R version 4.5.0 (R Core Team, Vienna).

Results

Sample Characteristic: The characteristics of the study population have been comprehensively described in our previous work (6); for completeness, the corresponding data are reported in Table 1. The study population had a mean age of 84.8 years (95% CI 84.1–85.4), with a predominance of women (74.1% - 95% CI: 71.8%-76.3%). Most residents had lived in the facility for at least 12 months (72.0% - 95% CI: 67.8%-75.9%). Multimorbidity and functional impairment were highly prevalent, with a mean of 4.4 (95% CI: 4.1-4.7) chronic conditions and 96.0% (95% CI: 94.3%-

97.2%) of residents presenting at least one Activity of Daily Living (ADL) limitation. Almost half of the residents met criteria for severe frailty (48.5% - 95% CI: 43.1%-54.0%), and dementia was diagnosed in 47.9% (95% CI: 39.1%-56.8%) of residents. Behavioral and psychological symptoms of dementia (BPSD) were common, with a mean burden score of 14.8 (95% CI: 11.6-18.0) and a mean of 4.1 symptoms (95% CI: 3.2-5.0), measured by the Neuropsychiatric Inventory (NPI). Polypharmacy was common, with a mean of 7.7 (95% CI: 7.3-8.1) unique active principles prescribed per resident. Dysphagia was observed in 14.7% (95% CI: 11.9%-18.0%) of the study population, and 0.9% (95% CI: 0.5%-1.8%) were fed through nasogastric tube or Percutaneous Endoscopic Gastrostomy (PEG). The prevalence of specific chronic conditions is detailed in e-Table 1 in the Supplement.

Pharmacological therapy assessment: A total of 24,701 drug prescriptions were initially identified. After data cleaning, 913 prescriptions were excluded due to invalid ATC codes, and 8 duplicate entries were removed, resulting in 23,780 prescriptions included in the analysis. When considering individual active principles, the total number of prescriptions was 23,780, whereas 23,321 prescriptions were identified when prescriptions were aggregated by ATC codes, reflecting some prescriptions sharing the same ATC classification. The proportion of drugs prescribed within each hierarchical level of ATC is visualised with an interactive sunburst plot presented as e-Figure 1 in the Supplement.

At the ATC first level, drugs acting on the nervous system were the most frequently prescribed (7,095 prescriptions, 30.4%), involving 87.0% of residents, followed by medications targeting the alimentary tract and metabolism (5,776 prescriptions, 24.8%; 85.6% of residents) and the cardiovascular system (4,948 prescriptions, 21.2%; 74.7% of residents). Drugs related to blood and blood-forming organs accounted for 10.1% of prescriptions and were prescribed to 57.4% of participants. The full distribution of prescriptions according to ATC first level is reported in Table 2, section A. At the ATC fifth level, the ten most frequently prescribed active substances were furosemide, paracetamol, pantoprazole, bisoprolol, quetiapine, macrogol, colecalciferol, trazodone,

acetylsalicylic acid, and lansoprazole, each prescribed to more than 16% of the participants. These drugs mainly belonged to therapeutic classes targeting cardiovascular conditions, gastrointestinal disorders, pain management, constipation, and neuropsychiatric symptoms. The top ten ATC fifth-level drugs are reported in Table 2, section B.

Prevalence and distribution of DDI: Overall, DDIs were frequently observed among LTCF residents. 42.2% of residents were exposed to at least one potential clinically-meaningful drug-drug interaction. Specifically, 27.2% of residents presented one DDI, 11.0% had two DDIs, and 4.0% were exposed to three or more DDIs. A small but clinically relevant proportion of residents presented with a high burden of interactions, with up to seven concomitant DDIs observed in individual cases (Figure 1).

Types of DDIs: Only DDIs with a prevalence of at least 1% of participants were included in the descriptive analysis, highlighting a consistent pattern of inappropriate prescribing across centres, despite the heterogeneity in the number of residents recruited. As reported in Table 3, among all identified DDIs, the most frequent was the concomitant use of three or more centrally acting drugs, including opioids, antipsychotics, benzodiazepines or Z-drugs, barbiturates, antiepileptics, or antidepressants. This interaction accounted for more than half of all detected DDIs (51.7%) and involved approximately one-third of the residents (33.2%). The second most frequent inappropriate prescription was the concomitant use of two or more anticholinergic drugs, representing 11.0% of all DDIs and affecting 7.1% of residents. Other commonly observed interactions included the combination of selective serotonin reuptake inhibitors (SSRIs) with other serotonergic drugs, including tramadol (6.3% of DDIs; 4.1% of participants), and the concomitant use of two or more potassium-sparing drugs (5.5% of DDIs; 3.5% of participants).

Potentially clinically relevant cardiovascular and renal risk–related interactions were also frequently detected. These included the combination of ACE inhibitors or angiotensin receptor blockers (ARBs) or potassium-sparing diuretics with potassium supplements (2.8% of DDIs), diuretics combined with oral non-steroidal anti-inflammatory drugs (NSAIDs) (2.8%), antiplatelet drugs,

including aspirin, combined with NSAIDs (2.3%), and ACE inhibitors or ARBs combined with NSAIDs (1.7%). Additionally, potentially harmful combinations such as acetylcholinesterase inhibitors with heart rate–lowering drugs and digoxin combined with thiazide or loop diuretics were observed in over 1% of residents.

Factors associated with DDI burden: Table 4 reports the variables showing the strongest and most clinically relevant associations with DDI burden, while the results for all resident-level characteristics are provided in e-Table 2 in the Supplement. A higher number of DDIs was strongly associated with greater pharmacological complexity, the presence of several clinical conditions (including depression, sleep disorders, obesity, structural heart disease, heart failure, and chronic obstructive pulmonary disease), and of behavioural and psychological symptoms, both in terms of number and overall burden. Conversely, older age, severe cognitive impairment, dysphagia, and malnutrition were associated with a lower number of DDIs. Functional dependency and frailty measures showed no relevant association with DDI burden.

Centre-level variability in DDI: Results are presented in e-Table 3 in the Supplement, divided into two sections: geographic and facility-related characteristics, and organisational standards.

In the first section, the geographic and facility-related characteristics were generally equally distributed across centers with increasing proportions of residences with at least two DDIs. A notable trend was observed for R3 facilities, which were progressively less represented across increasing DDI burden categories and were absent among centres with ≥20% of residents presenting with multiple DDIs.

The second section describes organisational standards. Median bed capacity and availability, and the number of enrolled residents showed overlapping distributions across DDI burden categories. Similarly, staffing indicators, including nurse-to-resident ratios across shifts, psychologists, and the presence of general practitioners, geriatricians, facility-based physicians, and a medical director (24%, 39.2%, 69.6%, and 70.9% of facilities, respectively, in the overall sample) were broadly comparable across groups, although a trend was detected for the presence of a geriatrician and

educational coordinator. Overall, no single structural or organisational characteristic appeared to discriminate centres with a higher versus lower DDI burden.

Discussion

In this paper, we described patterns of drug prescription and administration in a highly vulnerable population. The results confirm the high level of complexity of resident older adults, in line with previous research conducted in different geographical areas, but in the same setting of care (2). The mean age of 85 years, the high prevalence of dementia (48%) and frailty (48.5%), and the average of more than seven drugs prescribed per resident illustrate the well-known triad of advanced age, multimorbidity, and polypharmacy that characterizes this population (11,12). Polypharmacy was widespread, with a mean of 7.7 medications per resident, in line with previous reports from LTCFs (13). Given age-related pharmacokinetic/pharmacodynamic changes and multimorbidity (14), this exposure plausibly inflates the risk of DDIs (15,16). In our sample, 42.2% of residents were exposed to at least one inappropriate drug combination. Specifically, more than one out of four residents presented one DDI, 11.0% had two DDIs, and 3.9% were exposed to three or more DDIs, patterns that call for systematic medication review and deprescribing pathways tailored to LTCFs (17).

Drug Prescriptions. The most frequently ongoing medications in our study—furosemide, pantoprazole, paracetamol, quetiapine, and macrogol—provides further insight into prescribing priorities in LTCFs. Furosemide, the most prescribed drug, reflects the high burden of cardiovascular and renal comorbidities in this population. Still, its widespread use raises concerns regarding the appropriateness of such prescription as well as the risk of dehydration, electrolyte imbalance, and falls, especially in frail older adults (18). Paracetamol was also highly prevalent, consistent with guidelines recommending it as the first-line analgesic in older adults due to its favorable safety profile compared with NSAIDs (19). Its use is particularly appropriate for pain management; however, in long-term care settings, prolonged or chronic use warrants regular

reassessment, as evidence of effectiveness for persistent musculoskeletal pain is limited and inappropriate continuation may occur (20-21).

Pantoprazole and lansoprazole were also frequently prescribed, reflecting the widespread use of proton pump inhibitors (PPIs) in older adults. Chronic PPI use has been associated with adverse outcomes, including increased risk of fractures, pneumonia, *Clostridium difficile* infection, vitamin B12 deficiency, kidney disease, and possibly delirium (22). In our study, however, the cross-sectional design and point-prevalence approach did not allow us to capture information on treatment duration, thereby limiting our ability to evaluate appropriateness relative to guideline-recommended time frames.

Quetiapine, on the other hand, was among the most prescribed psychotropics, reflecting the high prevalence of dementia and behavioral and psychological symptoms. Nevertheless, the use of atypical antipsychotics in LTCFs remains controversial due to the well-documented risks of cerebrovascular events and increased mortality (23,24). Macrogol prescription was common, highlighting the burden of chronic constipation, which is highly prevalent among institutionalized older adults due to polypharmacy, reduced mobility, and dietary factors (25).

Drug–drug interactions

The most common DDIs were: concomitant use of ≥3 centrally acting drugs; prescription of ≥2 anticholinergic agents; SSRI plus another serotonergic drug, including tramadol, and concomitant use of ≥2 potassium-sparing drugs.

These findings align with a large US cohort study reporting a higher prevalence than our study (61.6%); however, interaction patterns were similar, mainly involving centrally acting, anticholinergic, serotonergic, and cardiovascular drugs (2).

Each of these DDIs may pose significant risks to frail residents. Multiple centrally acting agents (opioids, antipsychotics, benzodiazepines/Z-drugs, barbiturates, antiepileptics, antidepressants) potentiate sedation, cognitive impairment, and falls (26).

Evidence from a community-dwelling cohort demonstrated more than double the odds of falling when taking two or more CNS-active medications (27). Similarly, longitudinal data from the Health, Aging, and Body Composition study showed an increased risk of recurrent falls associated with both polypharmacy and high-dose CNS regimens (28). Moreover, initiation of CNS-active drugs was associated with nearly a threefold higher hazard of fall-related injury (29). Falls were also more common in hospitalized older adults with potentially causal drug-drug interactions (30). In long-term care settings, some studies have identified both antidepressants and benzodiazepines, but not antipsychotics, as risk factors for falls in UK care homes (31), and benzodiazepine initiation in LTCFs has been shown to trigger a significant acute increase in fall risk (32).

While benzodiazepines have been consistently associated with an increased fall risk, evidence regarding antidepressants is heterogeneous. Recent studies, using designs that mitigate confounding by indication (e.g., target trial emulation), have reported a lower risk of fall-related injuries among treated vs untreated older adults with depression (33), and LTCF-based analyses suggest that fall risk may vary over time, depending on treatment timing, indication, and clinical context (34). Accumulated anticholinergic burden is associated with delirium, functional decline, and dementia (35), advocating routine use of anticholinergic scales and substitution with lower-burden alternatives. Despite these risks, anticholinergic agents remain commonly prescribed for conditions such as overactive bladder, depression, and Parkinson's disease, underscoring the need for systematic monitoring with anticholinergic burden scales in LTCFs (36,37).

The interaction between SSRIs and other serotonergic agents, including tramadol, highlights the potential for serotonin syndrome—a rare but serious adverse event characterized by autonomic instability, neuromuscular abnormalities, and altered mental status (38).

Finally, the concomitant use of two or more potassium-sparing drugs, including mineralocorticoid receptor antagonists, ACE inhibitors, ARBs, NSAIDs, or trimethoprim-sulfamethoxazole, was less frequent but clinically dangerous. Such combinations markedly increase the risk of hyperkalemia, potentially leading to arrhythmias or sudden cardiac death (39). Given the frequent coexistence of

heart failure, chronic kidney disease, and hypertension in LTCF residents, this interaction warrants special attention.

Inappropriate prescribing is influenced by multiple factors, among which the carry-over of previously initiated therapies often driven by reluctance to deprescribe, time constraints, and poor information sharing (3) may perpetuate treatments beyond their original indication, contributing to both overuse and underuse and highlighting the need for structured medication review processes (40). In our study, a higher number of DDIs was associated with BPSD, whereas severe cognitive impairment was linked to a lower DDI burden. This may reflect reduced treatment intensity and medication load in advanced dementia, where prescribing is often simplified and focused on comfort, with deprescribing of non-essential therapies (41). Conversely, BPSD may increase DDI risk through greater use of psychotropic and CNS-active medications, frequently used in combination (42).

Overall, the prevalence of these DDIs highlights the urgent need for proactive medication review processes, the use of explicit criteria (e.g., STOPP-frail), and clinical decision support tools to minimize avoidable harm in LTCFs, as well as monitoring protocols (electrolytes, electrocardiography, falls surveillance) tied to riskier combinations (43).

In the Italian LTCF setting, prescribing responsibility is distributed across general practitioners, facility-based physicians, and geriatricians, with pharmacists involved where available. In our sample, these professionals were variably represented and could be present within the same facility; notably, no pharmacist was formally integrated into the care team. Given regional variability in organisational requirements, different prescribing models likely coexist. However, no structural or staffing characteristic—including the presence of geriatricians—clearly discriminated centres with higher versus lower DDI burden.

The distribution of participating centres across regions was heterogeneous and varied across DDI impact categories. However, limited regional sample sizes make it difficult to determine whether these patterns reflect centre-level prescribing policies, broader regional practices, or other contextual factors. No clear organisational differences emerged between low-, medium-, and high-

impact centres, which were similar in terms of facility size and staffing levels. The under-representation of R3 facilities in higher DDI burden categories likely reflects differences in resident case-mix and clinical complexity, as these settings typically include residents with lower multimorbidity and medication exposure.

Finally, although conducted in Italian LTCFs, our findings may be generalizable to other countries, as resident characteristics (advanced age, multimorbidity, frailty, and polypharmacy) and the types of DDIs identified are consistent with those reported internationally (2).

Conclusion

Strengths of this study include its large national, multicentre design and the availability of detailed resident-level data on drug prescribing and DDIs. Several limitations should be acknowledged. The point-prevalence design identifies potential DDIs rather than clinically manifest adverse events and does not allow assessment of temporal relationships, causality, or clinical outcomes such as hospitalizations and mortality. Additional limitations include potential reporting bias in medication data and heterogeneity between facilities, possibly reflecting unmeasured organisational or contextual factors.

Based on our findings, improving prescribing appropriateness in LTCFs requires: (1) identifying high-risk residents (polypharmacy, BPSD); (2) prioritizing high-risk DDIs (CNS-active drugs, anticholinergic burden, serotonergic and potassium-related combinations); (3) regularly reassessing treatment appropriateness and deprescribing where needed; and (4) adopting tools and clinical decision support systems to enhance prescribing quality.

Future intervention studies are needed to determine whether integrating these strategies can effectively reduce DDIs and to evaluate their clinical impact among LTCF residents.

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Conflict of Interest

The authors declare that they have no conflicts of interest related to this work.

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Data Availability Statement

The datasets generated and/or analysed during the current study are available from the authors upon reasonable request. Requests for access to anonymised data can be addressed to any of the authors, subject to compliance with applicable ethical and data protection regulations.

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Table 1. Characteristics of the study population (N = 3.174) Values are means (95% CI).

Variable	Total
Age, years, mean (95% CI)	84.8 (84.1–85.4)
Female sex, n (%)	2339 (74.1)
Length of stay ≥12 months, n (%)	2239 (72.0)
Number of chronic diseases, mean ± SD	4.4 ± 2.3
ADL lost, mean ± SD	4.4 ± 1.7
≥1 ADL impairment, n (%)	2440 (96.0)
Frailty (NH criteria), mean ± SD	6.6 ± 3.0
Severe frailty (≥8 criteria), n (%)	1178 (48.5)
Dementia, n (%)	1679 (47.9)
CDR score 4–5, n (%)	646 (14.7)
Dysphagia, n (%)	564 (14.7)
BPSD burden, mean ± SD	14.8 ± 19.0
Number of drugs (active principles), mean ± SD	7.7 ± 3.6

Values are reported as mean ± standard deviation (SD), mean (95% confidence interval), or number (percentage). Note: ADL Activities of Daily Living; BPSD Behavioral and Psychological Symptoms of Dementia; CDR Clinical Dementia Rating; NH Nursing Home; SD standard deviation.

Table 2. Distribution of drug prescriptions according to Anatomical Therapeutic Chemical (ATC) classification system.

Section A.

ATC First Level- Anatomical Main Groups	Prescriptions, N (%)	Participants, N (%)
Nervous system	7095 (30.4)	2760 (87.0)
Alimentary tract and metabolism	5776 (24.8)	2717 (85.6)
Cardiovascular system	4948 (21.2)	2372 (74.7)
Blood and blood forming organs	2355 (10.1)	1823 (57.4)
Systemic hormonal preparations, excl. sex hormones and insulins	567 (2.4)	545 (17.2)
Musculo-skeletal system	535 (2.3)	501 (15.8)
Various	503 (2.2)	493 (15.5)
Respiratory system	388 (1.7)	317 (10.0)
Genito urinary system and sex hormones	371 (1.6)	304 (9.6)
Sensory organs	341 (1.5)	287 (9.0)
Dermatologicals	287 (1.2)	274 (8.6)
Antineoplastic and immunomodulating agents	65 (0.3)	63 (2)
Antiinfectives for systemic use	71 (0.3)	61 (1.9)
Antiparasitic products, insecticides and repellents	19 (0.1)	19 (0.6)

Section B

ATC Fifth Level- Active Substance	Prescriptions, n (%)	Participants, n (%)
Furosemide	1050 (4.5)	1050 (33.1)
Paracetamol	888 (3.8)	888 (28.0)
Pantoprazole	883 (3.8)	883 (27.8)
Bisoprolol	788 (3.4)	788 (24.8)
Quetiapine	740 (3.2)	740 (23.3)
Macrogol	649 (2.8)	649 (20.4)
Colecalciferol	646 (2.8)	646 (20.4)
Trazodone	628 (2.7)	628 (19.8)
Acetylsalicylic acid	582 (2.5)	582 (18.3)
Lansoprazole	525 (2.3)	525 (16.5)

Values are reported as number (% of total prescriptions) and number (% of participants).

Table 3. Prevalence of inappropriate Drug–Drug interactions (DDIs) among LTCF residents

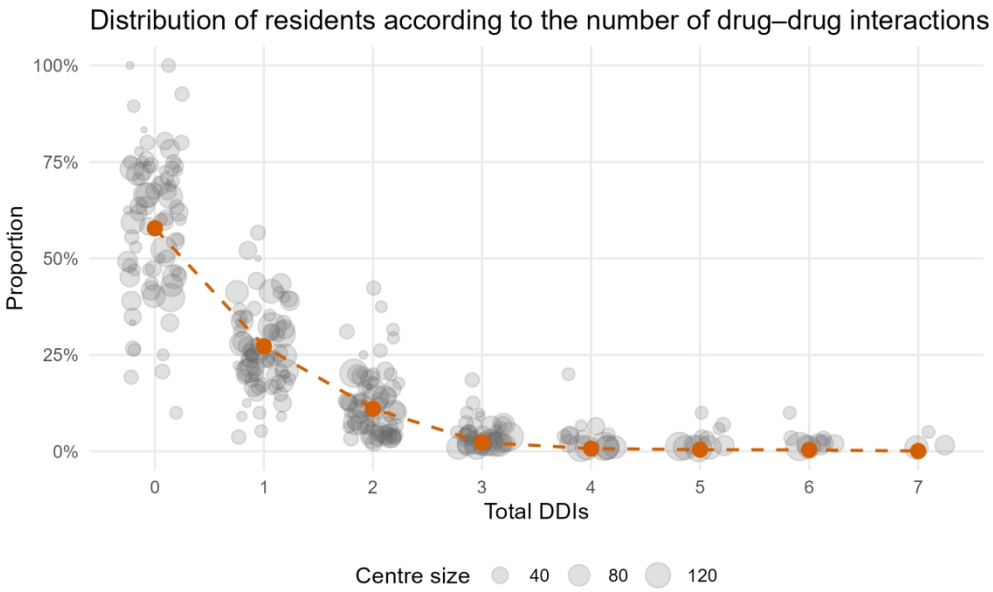
DDI code	Description	n	p_DDI (%)	p_part (%)
DDI_36	Concomitant use of ≥3 centrally acting drugs	1054	51.7	33.2
DDI_57	Concomitant use of ≥2 anticholinergic drugs	225	11.0	7.1
DDI_38	SSRI + another serotonergic drug (± tramadol)	129	6.3	4.1
DDI_21	Concomitant use of ≥2 potassium-sparing drugs	112	5.5	3.5
DDI_22	ACE inhibitor/ARB/potassium-sparing diuretic + potassium supplement	57	2.8	1.8
DDI_24	Diuretic + oral NSAID	57	2.8	1.8
DDI_20	Antiplatelet drug (including aspirin) + oral NSAID	47	2.3	1.5
DDI_50	Acetylcholinesterase inhibitor + heart rate–lowering drug	42	2.1	1.3
DDI_6	Digoxin + thiazide or loop diuretic	41	2.0	1.3
DDI_23	ACE inhibitor or ARB + oral NSAID	35	1.7	1.1
DDI_39	NSAID + SSRI/SNRI	33	1.6	1.0

Values are reported as absolute number of occurrences (n), proportion of total DDIs (p_DDI), and proportion of participants exposed (p_part). Only DDIs affecting at least 1% of the study population are reported.

Table 4. Univariate mixed-effects Poisson regression analysis of factors associated with DDIs.

Variable	β (95% CI)
Unique ATC codes (Z)	0.59 (0.54–0.63)
Unique active substance (Z)	0.58 (0.54–0.62)
Depression	0.41 (0.31–0.51)
Sleep disorders	0.36 (0.19–0.53)
Obesity	0.35 (0.19–0.51)
Structural heart disease	0.29 (0.20–0.39)
Heart failure	0.20 (0.04–0.35)
COPD / other respiratory disease	0.20 (0.08–0.31)
Number of BPSD (Z)	0.18 (0.11–0.25)
Age (Z)	−0.11 (−0.15–−0.07)
Malnutrition	−0.42 (−0.72–−0.13)
Severe cognitive impairment (CDR 4–5)	−0.24 (−0.36–−0.12)
Dysphagia	−0.18 (−0.30–−0.05)

Data are reported as regression coefficients (β) with 95% confidence intervals (CI). Positive coefficients indicate an association with a higher number of DDIs, whereas negative coefficients indicate an association with a lower number of DDIs. Models include a random intercept for centre; continuous variables were standardised (Z-scores).



Distribution of the proportion of residents according to the total number of drug–drug interactions (DDIs) identified. Grey dots represent centre-level proportions, with point size proportional to centre sample size. Orange points and dashed line indicate the overall mean proportion across centres, showing a progressive decrease in the proportion of residents as the number of concomitant DDIs increases.

Distribution of the proportion of residents according to the total number of drug-drug interactions (DDIs) identified.
Grey dots represent centre-level proportions, with point size proportional to centre sample size. Orange points and
dashed line indicate the overall mean proportion across centres, showing a progressive decrease in the proportion of
residents as the number of concomitant DDIs increases.

169x119mm (300 x 300 DPI)