



Potentially Inappropriate Psychotropic Drugs in Nursing Homes: An Italian Observational Study

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Abstract

Background and objectives Physicians often face difficulties in selecting appropriate medications for older adults with multiple comorbidities. As people age, they are more likely to be living with a number of chronic conditions (multimorbidity) and be prescribed a high number of medications (polypharmacy). Multimorbidity is frequent in nursing home (NH) residents and the use of potentially inappropriate medications, especially psychotropic drugs, is widespread. This retrospective cross-sectional cohort study examined the frequency of potentially inappropriate psychotropic drugs using the Beers, Screening Tool of Older Persons' Prescriptions/Screening Tool to Alert doctors to Right Treatment (STOPP/START) and Fit FOR The Aged (FORTA) criteria, and their association with mortality.

Methods This retrospective cross-sectional cohort study was conducted on a sample of long-term care NHs across Italy. Of the 34 NHs with an electronic medical records system, 27 met the inclusion criteria, with complete web-based case report forms (CRFs). Residents under the age of 65 years were excluded. We calculated the prevalence of potentially inappropriate psychotropics drugs (antipsychotics, antidepressants and anxiolytics/hypnotics) according to three criteria for prescriptive appropriateness. Univariate and multivariate correlations were examined, taking into account age, sex, comorbidities, and the number of psychotropic drugs, to analyse the relationship between inappropriate psychotropic use and mortality rates. The rate of inappropriate psychotropic prescriptions was calculated with the prevalence of residents receiving potentially inappropriate psychotropic drugs according to the three criteria. We used a logistic model to check for a possible predictive relationship between inappropriate use of psychotropics and mortality. The study evaluated differences in prescriptive appropriateness among NHs by analysing the proportions of potentially inappropriately treated residents at the last visit. Differences were compared with the overall sample mean using confidence intervals (CIs) calculated using Wald's method.

Results This study involved 2555 residents, of whom 1908 (74.7% of the total) were treated with psychotropic drugs; 186 (7.3% of the total) were exposed to at least one psychotropic drug considered potentially inappropriate according to the FORTA criteria. Analysis using the Beers criteria showed that 1616 residents (63.2% of the total) received at least one psychotropic drug considered potentially inappropriate. In line with the Beers recommendation, patients receiving at least three psychotropic drugs were also included and 440 were identified (17.2% of the total sample). According to the STOPP criteria, 1451 residents (56.8% of the total sample) were prescribed potentially inappropriate psychotropic drugs. No correlation was found between potentially inappropriate use of psychotropic drugs and mortality, in either univariate analysis or in a multivariate model adjusted for age, sex and comorbidity index.

Conclusions Different criteria for appropriate drug prescription identify very different percentages of patients in NHs exposed to psychotropics considered potentially inappropriate. The Beers and STOPP/START criteria identified a larger percentage of patients exposed in NHs than FORTA.

1 Introduction

The significant growth of the older population worldwide presents challenges for national and subnational systems to adapt their social and economic structures effectively and to promptly accommodate the increasing number of

older individuals, including those aged 80 years and above, often referred to as the 'oldest old'. Italy, like other European countries, is affected by this trend, and the data from the Statistical Office of the European Union (EUROSTAT) regarding 2020 reveals a scenario in which individuals aged 65 years or over account for 20.6% of the total population [1]. The progressive increase in the age range of the population consequently implies a rise in the number of older people who may be more susceptible to health challenges

Extended author information available on the last page of the article

Key Points

Psychotropic drugs are widely used in nursing homes and different criteria have been developed for correct prescribing.

The Fit FOR The Aged (FORTA) classification has been proposed as a new system to improve drug prescription in older adults.

The percentages of residents exposed to potentially inappropriate psychotropic drugs differed widely between FORTA and Beers criteria or the Screening Tool of Older Persons' Prescriptions/Screening Tool to Alert doctors to Right Treatment (STOPP/START) criteria, reflecting the pathological conditions to which the FORTA recommendations refer and the limited number of drugs considered in the FORTA classification.

No relationship was found between the potentially inappropriate use of psychotropic drugs and mortality.

(the most 'fragile'), as they are most likely to need hospitalisation [2, 3]. Then too, older people frequently have multiple chronic conditions and many symptoms [4]. The aging of the population and the increasing number of older people with multimorbidity are closely reflected in the increased use of polypharmacy [5].

Older patients with several co-existing acute and chronic diseases that require complex medication regimens often live in nursing homes (NHs), where many are given psychotropic drugs to treat psychiatric and behavioural symptoms associated with dementia [6]. Although their effects are reportedly modest, the risk of adverse effects, including delirium and other psychomotor impairments (daytime fatigue, ataxia and falls), is high [7]. For example, antipsychotics may increase mortality and can be associated with serious adverse events, including, but not limited to, pneumonia, cerebrovascular events, parkinsonian symptoms, or a higher incidence of venous thromboembolism [8–11].

Considering the comorbidities, polypharmacy, and changes in pharmacokinetics and pharmacodynamics in older patients [12–14], some medications are potentially inappropriate (potentially inappropriate medications [PIMs], i.e. a drug whose risk of adverse reactions outweighs its benefits) [15, 16]. Criteria for proper prescribing in older adults have been developed in various settings (hospitals, NHs, outpatient clinics, etc.), and have made it possible to investigate the prevalence of potentially inappropriate psychotropic medications. The most widely used criteria in clinical practice are the Beers criteria and the Screening

Tool of Older Persons' Prescriptions/Screening Tool to Alert doctors to Right Treatment (STOPP/START) criteria [17]. Recently, the Fit FOR The Aged (FORTA) classification has been proposed as a new system to improve drug prescription in older adults, as a tool to aid clinicians in screening for unnecessary, inappropriate/harmful and/or omitted drugs in older adults [18]. Thus far, no studies have been conducted in NHs using the FORTA criteria.

With this background, the aims of this study are to describe (1) the prevalence of potentially inappropriate psychoactive drugs in patients in NHs using the Beers criteria, the STOPP/START criteria, and the FORTA classification; and (2) the relation with mortality.

2 Methods

2.1 Data Collection

This retrospective cross-sectional cohort study was conducted on a sample of older adults residing in long-term care NHs in the Korian group across Italy. These facilities provide residential care for people with severe disabilities and older people who need assistance in daily activities. The inclusion criteria were the presence of full data on sociodemographic characteristics, diagnosis (coded based on the International Classification of Diseases, Ninth Revision [ICD-9]), drug treatment, and age 65 years or older [19]. No other exclusion criteria were applied. From the initial pool of 34 NHs, our analysis was conducted on 27 facilities that were able to supply full information on their residents, amounting to a total of 2604 residents. We then excluded 49 residents under the age of 65 years. The dementia was diagnosed by trained neuropsychologists or geriatricians, based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), and classified according to the ICD-9 issued by the World Health Organization [20].

For convenience, we selected and automatically extracted data from case report forms (CRFs) six times during 2018, 2019 and 2020, i.e. T1 (1 April 2018), T2 (1 December 2018), T3 (1 April 2019), T4 (1 December 2019), T5 (1 April 2020) and T6 (1 December 2020), in order to assess the medications prescribed. All drugs given at each time were analysed but no information was accessible for establishing whether a medication was prescribed on a chronic or as-needed basis. Sociodemographic details (age, sex, and NH affiliation), drug therapy, comorbidities (acute and chronic conditions), and date of death (when recorded) were collected at each timepoint. The prevalence of PIMs according to the three criteria was calculated. Data for acute prescriptions, short-term medications used to address medical

needs, were analysed cross-sectionally considering the last available date for each patient. For chronic prescriptions, long-term medications for ongoing medical conditions, earlier timepoints were also examined. Mortality was recorded until 1 December 2020. Medical health records were not reviewed manually.

Data were stored in full agreement with Italian law on personal data protection and the study was examined and approved by the Ethics Committee of the Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS, Institutes for Scientific Research and Care) Carlo Besta Foundation. The ethics approval number is 60_2019.

2.2 Criteria for Potentially Inappropriate Psychotropic Medications

The prevalence of NH residents exposed to potentially inappropriate psychoactive drugs was evaluated using the Beers criteria, the STOPP recommendations in the STOPP/START criteria, and the FORTA classification. The Beers Criteria were developed in the United States (US), and are commonly used in pharmacoepidemiological studies to assess potentially inappropriate prescribing in older people. The criteria were last updated in 2023. In view of the risk of cognitive impairment, delirium, falls and fractures, the Beers criteria for psychotropic drugs advise against using any type of benzodiazepine, or chronic (> 90 days) use of non-benzodiazepine hypnotics (z-drugs) to treat insomnia, agitation, or delirium; caution when using antidepressants (serotonin-norepinephrine reuptake inhibitors [SNRIs], selective serotonin reuptake inhibitors [SSRIs] and tricyclic antidepressants [TCAs]) or antipsychotics to treat behavioural and psychological symptoms of dementia (BPSD) because of a higher risk of cerebrovascular accident (stroke) and death, and the concomitant use of three or more antipsychotic drugs [21].

The STOPP/START criteria (last updated in 2023) were developed in Europe and, as proposed in their second version updated in 2015, list the following as potentially inappropriate: TCAs (e.g. for patients with dementia, glaucoma, constipation), SSRIs for patients with a history of hyponatraemia, chronic (> 30 days) use of benzodiazepines, neuroleptics in patients with Parkinson's disease or as hypnotics, and the concomitant use of two antidepressants, two benzodiazepines or two antipsychotics [22].

The Beers and STOPP/START criteria lack a classification grade for potential inappropriateness (whereas the FORTA criteria specify four levels of prescription appropriateness) and provide recommendations regarding the concurrent use of more than three psychotropic drugs and the use of therapeutic duplicates, respectively.

The FORTA classification (last updated in 2021) is a newer system, developed in Germany, which, for the first time, combined both negative and positive labelling in terms

of individual drugs or drug class. The FORTA criteria classifies medications, with regard to their safety, efficacy and overall age-appropriateness, into four categories from A to D. FORTA A (A-bsolutely) drugs have proved to be particularly beneficial; there is clear-cut benefit in terms of the efficacy/safety ratio in older patients for a given indication; no psychotropic drugs fall into this category. FORTA B (B-eneficial) are beneficial but have some limitations with regard to safety and efficacy. An example is quetiapine prescribed for bipolar disorder (BPD). FORTA C (C-areful) drugs have a questionable safety/efficacy profile, require close monitoring and should be avoided in patients needing three or more prescribed drugs. An example is amitriptyline prescribed for depression, which is particularly contraindicated because of anticholinergic adverse effects in older people. FORTA D (D-on't) drugs should generally be avoided; omit first and review/find alternatives. Every long-acting benzodiazepine falls into this category [18].

The appropriateness of each psychotropic drug was assessed by analysing pathologies and conditions in the patient's medical records. For our study, started in 2021, we employed the 2019 version of the Beers criteria, the second version of the STOPP/START criteria, and the 2021 version of the FORTA criteria.

2.3 Statistical Analysis

Sociodemographic characteristics of the sample were summarised through standard descriptive statistics. The absolute frequency, prevalence of numbers of prescriptions according to the Beers criteria, START/STOPP criteria and FORTA criteria, and any prescriptions not classified by the guidelines were listed. The analysis focused on antipsychotics, antidepressants, benzodiazepines and sedative-hypnotics. For drugs prescribed for the same conditions (depression, BPD, BPSD and insomnia/sleep disorders), we considered the degrees of inappropriateness according to the least appropriate prescription.

The prevalence of residents treated with psychotropic drugs considered potentially inappropriate according to the Beers, STOPP/START and FORTA criteria (drugs belonging to FORTA class C or D) was investigated considering all the clinical conditions in the criteria, which, for the FORTA, included the use of antipsychotics, antidepressants or anxiolytics/hypnotic sedatives. In the analysis for the FORTA criteria, when multiple potentially inappropriate prescriptions were present, the most potentially inappropriate prescription was considered, e.g. FORTA class D, if prescribed simultaneously with drugs in the FORTA class C. Duplicate treatment (prescription of two drugs of the same therapeutic class) was evaluated in line with the STOPP/START criteria, and of three or more psychotropic drugs according to the Beers criteria. Therapeutic duplicates were defined as

prescribing at least two drugs of the same therapeutic class simultaneously to the same patients. To identify duplicates, we considered the third level of the Anatomical Therapeutic Chemical (ATC) code [23].

To assess a possible predictive relationship between inappropriate use of psychotropics and mortality, a logistic model was developed on the whole sample analysed. Inappropriately treated patients were defined as those who were prescribed at least one of the above drugs according to the FORTA, Beers or STOPP/START criteria. We used a univariate and multivariate model adjusted for sex, age, and Charlson Comorbidity Index (CCI) and the number of potentially inappropriate psychotropic drugs prescribed (one, two, or three or more).

The differences in the degrees of prescriptive inappropriateness among NHs was assessed on the basis of the proportion of residents potentially inappropriately treated at the last visit. The differences in each NH were then compared with the overall sample mean using CIs calculated using Wald's method. The significance criterion (α) was 0.05 for all tests. Analyses were performed using SAS 9.4 statistical software (SAS Institute Inc., Cary, NC, USA), and Euler and Venn diagrams were drawn using RStudio (RStudio Inc., Boston, MA, USA).

3 Results

The study was conducted on 2555 residents (77.4% women) with a mean age of 86.9 ± 7.3 (\pm standard deviation) years. Data were collected from 27 Italian NHs. Figure 1 illustrates the resulting number of residents included in the analysis

and the residents prescribed a psychotropic drug considered potentially inappropriate according to the three criteria considered. Sociodemographic details and the main diagnostic-therapeutic characteristics of the residents are reported in Table 1. The mean number of drugs per patient was 7.3 ± 3.6 . Approximately 74.5% of residents had dementia, and the other most frequent diagnoses were cardiovascular, including hypertension (69.0%), and cerebrovascular diseases (44.3%). Table 2 shows the 10 most prescribed drugs by pharmacological classes within the sample.

3.1 Fit FOR The Aged (FORTA) Potentially Inappropriate Psychotropic Medications

Of the 2555 residents in the analysis, 1908 (74.7%) were treated with psychotropic drugs and the prevalence of residents receiving appropriate and inappropriate psychotropic drugs is shown in Table 3, which includes all possible prescription combinations. The combined total of all rows corresponds to the overall number of patients who received potentially inappropriate psychotropic drugs. Despite their high prescription rates, many of these drugs, including promazine, levosulpiride, paroxetine, clotiapine, fluvoxamine, clobazam and etizolam, are not included in the FORTA criteria.

A total of 186 residents, 7.3% of the total sample and 9.7% of those treated with psychotropic drugs, were exposed to at least one psychotropic drug considered potentially inappropriate; 20 residents (0.8% of the sample; 1.0% of residents prescribed psychotropic drugs) were treated with psychotropic drugs considered potentially useful (FORTA class A/B) and 1702 (66.6% of the total sample; 89.2% of



Fig. 1 Exclusion criteria and the residents treated potentially inappropriately according to the three criteria. *CRFs* case report form, *FORTA* Fit FOR The Aged, *NHs* nursing homes, *STOPP* Screening Tool for Older Peoples' Prescriptions

Table 1 Sociodemographic characteristics of nursing home residents in the study

Sample	
No. of patients	2555
No. of NHs involved	27
Age, years (mean \pm SD)	86.9 \pm 7.3
No. of women (%)	1971 (77.4)
No. of daily drugs (mean \pm SD)	7.3 \pm 3.6
Diseases [<i>n</i> (%)]	
Hypertension	1762 (69.0)
Heart failure	276 (10.8)
Acute myocardial infarction	118 (4.6)
Cerebrovascular diseases	1131 (44.3)
Peripheral vascular diseases	350 (13.7)
Dementia	1903 (74.5)
Depression	120 (4.7)
Rheumatic diseases	50 (2.0)
Chronic obstructive pulmonary disease	409 (16.0)
Mild liver disease	131 (5.1)
Mild to severe liver disease	4 (0.2)
Kidney diseases	374 (14.6)
Diabetes	465 (18.2)
Malignancy (including lymphoma and leukaemia, no skin cancer)	168 (6.6)
Metastatic solid tumours	11 (0.4)
Peptic ulcer	22 (0.9)
Skin ulcers	95 (3.7)
Hemiplegia or paraplegia	92 (3.6)
CCI (mean \pm SD)	3.3 \pm 1.9
Outcome [<i>n</i> (%)]	
Mortality	1584 (62.0)

CCI Charlson Comorbidity Index, NH nursing home, SD standard deviation

residents prescribed psychotropic drugs) could not be classified by the FORTA criteria.

The prevalence of residents treated with psychotropic drugs was then assessed in relation to the diagnoses considered in the FORTA criteria: 108 residents with depression received at least one psychotropic drug, corresponding to 4.2% of the total sample and 5.7% of those were treated with psychotropic drugs. Among these, 17 residents received a psychotropic drug alone or in combinations belonging to the FORTA B class; 78 received psychotropic drugs, at least one belonging to the FORTA C or D class; 17 patients received combinations of at least three inappropriate categories of psychotropic drugs and 13 (11.8% of patients with depression) were not classified according to the FORTA criteria, such as those receiving paroxetine.

Table 2 Most prescribed drugs by pharmacological classes

Drug	Residents [<i>n</i> (%)]
Antidepressants	
Trazodone	173 (7.0)
Sertraline	167 (6.5)
Citalopram	164 (6.4)
Mirtazapine	115 (4.5)
Paroxetine	54 (2.1)
Duloxetine	41 (1.6)
Venlafaxine	30 (1.2)
Amitriptyline	27 (1.1)
Escitalopram	27 (1.1)
Fluvoxamine	2 (0.1)
Total	800 (31.3)
Antipsychotics	
Quetiapine	518 (20.7)
Haloperidol	306 (12.0)
Promazine	190 (7.4)
Levosulpiride	119 (4.7)
Olanzapine	114 (4.6)
Risperidone	74 (2.9)
Clotiapine	46 (1.8)
Pericizine	25 (1.0)
Clozapine	11 (0.4)
Amisulpride	8 (0.3)
Total	1411 (55.2)
Benzodiazepines and z-drugs	
Lorazepam	319 (12.5)
Zolpidem	219 (8.6)
Bromazepam	193 (7.6)
Triazolam	172 (6.6)
Alprazolam	151 (5.9)
Diazepam	114 (4.5)
Delorazepam	69 (2.7)
Lormetazepam	25 (1.0)
Flurazepam	10 (0.4)
Brotizolam	9 (0.4)
Total	1281 (50.1)

Thirty-two residents with dementia-related sleep disorders received at least one psychotropic drug (1.3% of the total sample and 1.6% of those treated with psychotropic drugs). Of these, 6 (18.7%) received at least one FORTA class C or D drug, while the remaining 26 (81.3%) took antidepressants or anxiolytics/hypnotic-sedatives not covered by FORTA criteria for these disorders, e.g. residents receiving zolpidem or lorazepam.

Nineteen residents (0.7% of the total sample and 1% of those treated with psychotropic drugs) diagnosed with

Table 3 Prevalence of residents receiving appropriate and inappropriate psychotropic drugs according to the FORTA criteria

	Appropriate (FORTA A or B) [n (%)]	Inappropriate (FORTA C or D) [n (%)]
Psychotropics ^a	20 (0.8)	186 (7.3)
Antipsychotics	4 (0.2)	17 (0.7)
Antidepressants	16 (0.6)	7 (0.3)
Anxiolytics/hypnotics	0	30 (1.2)
Antipsychotic + antidepressant	0	15 (0.6)
Antipsychotic + benzodiazepine	0	45 (1.8)
Antidepressant + anxiolytic/hypnotic	0	40 (1.6)
Antipsychotic + antidepressant + anxiolytic/hypnotic	0	32 (1.3)

FORTA Fit fOr The Aged

^aAt least one antipsychotic, antidepressant or anxiolytic/hypnotic

epilepsy were prescribed at least one anxiolytic-hypnotic sedative drug; 16 received a psychotropic drug belonging to FORTA class C or D, 3 took psychotropic drugs belonging to FORTA class B and all received at least one unclassified psychotropic drug for this disorder, e.g., triazolam or delorazepam.

Four residents (0.2% of the total sample and 0.2% of those treated with psychotropic drugs) diagnosed with BPD had been prescribed at least one psychotropic drug. Two received drugs belonging to FORTA class B and two received psychotropic drugs not classified by FORTA for this disorder, e.g., haloperidol.

Only 68 residents (2.6% of the total, 3.6% of those treated with psychotropic drugs) with insomnia had been prescribed at least one psychotropic drug; none were appropriate (alone or in combination) [FORTA class A or B], while 46 (67.6%) took psychotropic drugs (alone or in combination), at least one of which belonged to FORTA class C or D. Eight patients received combinations of at least three categories of inappropriate psychotropic drugs and 23 received at least two. The most prescribed drug for insomnia is quetiapine (517 prescriptions), which is not classified by FORTA criteria for this disorder.

Fifty-four (2.1%, 2.8%) residents with dementia-related behavioural and cognitive disorders were receiving at least one psychotropic drug; 47 (87%) received psychotropic drugs belonging to FORTA class C or D, and none were receiving appropriate psychotropic drugs (alone or in combination) [FORTA class A or B]. Furthermore, 11 patients received inappropriate combinations of psychotropic drugs such as quetiapine and haloperidol. Five were prescribed psychotropic drugs not classified by the FORTA criteria for this disorder, e.g. promazine.

3.2 Beers and Screening Tool of Older Persons' Prescriptions/Screening Tool to Alert doctors to Right Treatment (STOPP/START) Potentially Inappropriate Psychotropic Medications

Analysis using the Beers criteria showed that 1616 residents (63.2% of the total sample and 84.7% of the residents treated with psychotropic drugs) received at least one psychotropic drug considered potentially inappropriate. Table 4 describes the prevalence of potentially inappropriate psychotropic medications according to the Beers and STOPP/START criteria. A total of 1086 patients were prescribed anxiolytics/hypnotic-sedatives and formed the biggest subgroup (42.5% of the total sample and 56.9% of those treated with psychotropic drugs), followed by 894 residents treated with antipsychotics (35.0% of the total sample and 46.9% given psychotropic drugs) and 29 given TCAs (1.1% of the sample and 1.5% of the patients treated with psychotropic drugs).

According to the STOPP criteria, 1395 residents were treated with a potentially inappropriate psychotropic drug. The prevalence of residents receiving duplicate therapy was also examined: 280 patients (11.0% of the sample) were prescribed at least two antipsychotic drugs; 214 residents (8.4%) were receiving duplicate therapy with anxiolytics/hypnotic-sedatives; and 71 residents (2.8% of the total) were prescribed at least two antidepressants. In accordance with the Beers recommendation, we also examined the percentage of patients receiving at least three psychotropic drugs: 440 residents (17.2% of the total) were being given at least three drugs active on the central nervous system.

The Venn diagram shown in Fig. 2 sets out the percentages of residents who received potentially inappropriate

Table 4 Prevalence of residents receiving potentially inappropriate psychotropic drugs according to the Beers and STOPP/START criteria

	Beers [n (%)]	STOPP/START [n (%)]
Psychotropic drugs prescribed		
Psychotropics ^a	1616 (63.2)	1451 (56.8)
Antipsychotics	894 (35.0)	906 (35.5)
SSRI	–	0
TCA ^s	29 (1.1)	14 (0.5)
Paroxetine	54 (2.1)	–
Anxiolytics/hypnotics	1086 (42.5)	750 (29.4)
Therapeutic duplication		
Antipsychotics	–	280 (11.0)
Antidepressants	–	71 (2.8)
Anxiolytics/hypnotics	–	214 (8.4)
At least three psychotropics	440 (17.2)	–

SSRI selective serotonin reuptake inhibitor, STOPP/START Screening Tool for Older Peoples' Prescriptions/Screening Tool to Alert doctors to Right Treatment, TCAs tricyclic antidepressants, – indicates criterion of inappropriateness not included

^aAt least one antipsychotic, antidepressant or anxiolytic/hypnotic

psychotropic medication based on the three criteria mentioned. The majority of the FORTA recommendations appeared to be covered by the Beers criteria (the overlap includes 94.6% of subjects considered inappropriate according to FORTA) and the STOPP/START criteria (81.2% overlap). The Beers criteria include almost all subjects considered potentially inappropriately treated according to the STOPP/START criteria, leaving out just 31 residents; 1.9% are treated potentially inappropriately according to the STOPP/START.

NHs varied widely in the prevalence of residents with potentially inappropriate psychotropic drugs, ranging from 2.3 to 28.3% according to the FORTA criteria (electronic supplementary material [ESM] Fig. S1), from 45.7 to 76.2% using the Beers criteria (ESM Fig. S2), and from 43.1 to 77.1% using the STOPP/START criteria (ESM Fig. S3); no relationship was found between the differences and the numbers of inpatients. NHs with the lowest prevalence of residents treated potentially inappropriately according to the FORTA criteria did not necessarily match those with the lowest prevalence using the Beers or STOPP/START criteria.

3.3 Relation with Mortality

Among the 2555 patients in the analysis, 1584 died during the observation period. The median time between the first and last visits was 525 days (25–75 IQ: 244–975). Of those who died, 105 were exposed to at least one potentially inappropriate psychotropic drug according to the FORTA criteria, 982 according to the Beers criteria, and 883 according to STOPP/START criteria. No relationship was found between the potentially inappropriate use of psychotropic drugs and mortality, in either univariate analysis (FORTA: odds ratio [OR] 0.78, 95% CI 0.58–1.06, $p = 0.11$; Beers: OR 0.87, 95% CI 0.73–1.02, $p = 0.09$; STOPP/START: OR 0.90, 95% CI 0.76–1.20, $p = 0.17$), or in a model adjusted for age, sex, comorbidity index and number of potentially inappropriate psychotropic drugs (FORTA: OR 0.89, 95% CI 0.65–1.23, $p = 0.49$; Beers: OR 0.90, 95% CI 0.72–1.14, $p = 0.39$; STOPP/START: OR 1.04, 95% CI 0.84–1.31, $p = 0.70$). These results were confirmed in a model adjusted for age, sex, and comorbidity index, layering the number of

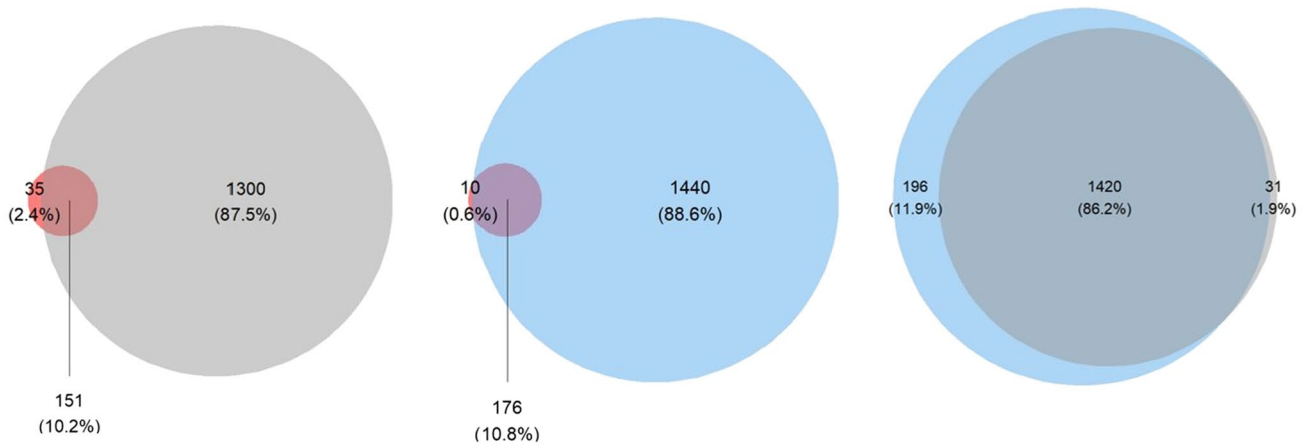


Fig. 2 Venn diagrams of residents who received incorrect psychotropic medication according to FORTA (red), Beers (light blue) and STOPP/START (grey) criteria. FORTA Fit fOr The Aged, STOPP/

START Screening Tool for Older Peoples' Prescriptions/Screening Tool to Alert doctors to Right Treatment

potentially inappropriate psychotropic drugs (one, two, and three or more) (Table 5).

This logistic regression showed that age and comorbidity were significantly associated with an increase, albeit small, in the risk of mortality: for age, the OR was 1.07 (95% CI 1.06–1.08, $p < 0.0001$) with the FORTA, Beers and STOPP/START criteria; and for comorbidity, the OR was 1.12 (95% CI 1.07–1.17, $p < 0.0001$) with all the criteria considered.

4 Discussion

This study found definite differences between the prevalence of residents exposed to psychotropic drugs considered potentially inappropriate according to the FORTA, Beers and STOPP/START criteria. Approximately 7.3% were exposed to a psychotropic drug considered potentially inappropriate according to the FORTA criteria, but this rose to more than 60% when applying the Beers or STOPP/START criteria. The rates of inappropriate use of psychotropic drugs with the Beers and STOPP/START criteria are consistent with other studies in NHs, suggesting that the proportion of older adults exposed to potentially inappropriate psychotropic drugs is between 50% and 70% [24–26].

Although the STOPP/START criteria and the FORTA list have been associated with positive patient-related outcomes when used as interventions in recent randomised controlled trials [27–30], only one study compared the prevalence of PIMs using these criteria [31]. That study, conducted in geriatric wards in a primary care setting in Kuwait, found that over half the participants were prescribed at least one PIM according to the Beers and STOPP/START criteria, and about 40% received at least one drug in the FORTA C or D list.

The larger difference between the prevalence we found with the FORTA and Beers or STOPP/START criteria might be related to the different settings (NHs vs. primary care), and, consequently, the differences in medical conditions for which psychotropic drugs are prescribed and the small

number of psychotropic drugs considered in the FORTA classification. About 90% of residents treated with antipsychotics, antidepressants, or benzodiazepines, with substantial clinical conditions, turned out to be unclassifiable because of the incomplete list of drugs included in the criteria, which did not accurately reflect the prescription patterns in the NHs examined, despite the fact that many drugs have similar mechanisms of action to those analysed and could probably be easily included in existing recommendations.

A case in point is paroxetine, an SSRI with a mechanism of action similar to fluoxetine, sertraline and citalopram, but with greater anticholinergic and interaction potential. According to the FORTA criteria, sertraline and citalopram are appropriate (class B) for depression; fluoxetine is not classified for depression but is classified for BPSD, and paroxetine is not classified for any condition. Likewise, amitriptyline is considered inappropriate (class C), while clomipramine is not classified in the FORTA lists.

The FORTA criteria classifies 296 drugs/classes of drugs in 30 categories in relation to precise clinical diagnoses or syndromes [32]. The targets are individual indications (an implicit list that requires a patient's characteristics/diagnosis). This is a novelty among negative listings that focus exclusively on problems with drug prescriptions (omissions or dangerous drugs in frequently used pharmaceutical classes) that should be avoided for geriatric patients because of age-related changes (regardless of the patient's individual characteristics and history). The FORTA classification is especially useful in settings where older adults' medical history can be assessed, ideally similar to NHs, where the residents are frail older people with disability or self-sufficiency problems, comorbidity, and controlled adherence to therapy. However, our results suggest that many drugs are not listed and this may be mainly due to the fact that the classification of drugs in the FORTA criteria, while validated by a panel of European experts, tends to reflect prescribing patterns in Germany, where they were devised and initially validated.

Table 5 Relationship with mortality and the prevalence of potentially inappropriate psychotropic drugs according to the FORTA, Beers and STOPP/START criteria in a model adjusted for age, sex, comorbidity index and number of potentially inappropriate psychotropic drugs

Criteria	OR (95% CI)	<i>p</i> value	One potentially inappropriate psychotropic drug		Two potentially inappropriate psychotropic drugs		Three or more potentially inappropriate psychotropic drugs	
			OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value
FORTA	0.89 (0.65–1.23)	0.49	0.74 (0.50–1.08)	0.12	0.99 (0.53–1.86)	0.98	1.5 (0.57–4.01)	0.41
Beers	0.90 (0.72–1.14)	0.39	0.81 (0.67–0.99)	0.04	0.96 (0.76–1.21)	0.71	0.83 (0.60–1.16)	0.27
STOPP/START	1.04 (0.84–1.31)	0.70	0.87 (0.72–1.05)	0.14	0.92 (0.72–1.16)	0.47	0.96 (0.67–1.37)	0.81

CI confidence interval, FORTA Fit for The Aged, OR odds ratio, STOPP/START Screening Tool for Older Peoples' Prescriptions/Screening Tool to Alert doctors to Right Treatment

This makes FORTA recommendations less easily applicable in other countries.

The main strength of this multicentre observational study is the comparative evaluation of the Beers, STOPP/START and FORTA criteria in a large sample of older adults with high rates of psychotropic drug use. In this specific setting, where the use of psychotropic drugs is exceptionally high and therapeutic adherence is certain, this is the only study that compares the relevance of the Beers, STOPP/START and FORTA criteria in NHs. Our results suggest greater relevance of the Beers and STOPP/START criteria in clinical practice to assess the potentially inappropriate use of psychotropic drugs. The wide differences between NHs in the prevalence of potentially inappropriately treated residents confirms the need to improve the prescription of psychotropic medications in this setting.

A review of the literature concludes that only a few studies have addressed the relations between inappropriate drug use and health outcome measures [33]. The FORTA criteria, when applied to specific well-defined care settings, can help clinicians optimise drug treatment in older patients, as seen in a number of studies, including VALFORTA, the only randomised controlled trial using these criteria, conducted in geriatric clinics in Germany. The VALFORTA study demonstrated that appropriate review of therapy using the FORTA classification can improve the quality of pharmacotherapy and the related clinical endpoints, while reducing the number of adverse drug reactions [30]. In a randomised clinical trial, application of the STOPP/START criteria by physicians on unselected hospitalised older adults resulted in significant reductions in the incidence of adverse drug reactions (21.0% in control participants and 11.7% in the intervention group) and lowered medication costs in acutely ill older adults [34].

We found no relation between potentially inappropriate use of psychotropic drugs and mortality after 525 days, probably because antipsychotic-related mortality in patients with dementia is higher in the first months of drug use, while our NH residents were generally chronically treated, and population-based studies found higher short-term mortality (6–12 months) among patients treated with antipsychotic drugs [35, 36]. This was confirmed by the unexpected inverse relation between mortality and the use of one potentially inappropriate psychotropic drug found for the Beers criteria in the univariate model, suggesting low predictive power of these recommendations among long-term users of psychotropic medications.

Although one of the FORTA criteria's strengths is that their application requires deeper knowledge of a patient's clinical history than the STOPP/START and Beers criteria, as the three main elements of therapeutic appropriateness (over-, under- and inappropriate treatment) can only be

ascertained if the patient's characteristics are known; it can therefore become a challenge when these data are missing.

The lack of data on adverse drug reactions, as well as the patients' quality of life, possible falls and behavioural disorders, is one of the study's major limitations as it prevents us from assessing the relationship between the use of potentially inappropriate psychotropic drugs and these negative outcomes.

We could not employ the latest versions of the Beers and STOPP/START criteria as the starting date of the analysis is also a limitation. Another limitation is that we cannot definitely state that our sample of NHs is representative of the Italian NH population, therefore the generalisability of the results specifically pertaining to the prevalence of residents treated with PIMs may be limited.

5 Conclusions

Different criteria for appropriate drug prescription identify very different proportions of patients exposed to psychotropics considered potentially inappropriate. In NHs, the Beers and STOPP/START criteria identify larger percentages of patients exposed than the FORTA criteria. The wide differences among NHs on the potentially inappropriate use of antidepressants, antipsychotics and hypnotics/sedatives suggests the need for periodic medication review in this particular setting, populated by vulnerable older patients with numerous diseases. There was no association between potentially inappropriate psychotropic drug use and mortality using the FORTA, Beers or STOPP/START criteria.

Since this population is steadily growing and will continue to grow, appropriate prescribing for older adults is increasingly important. Regardless of the criteria used, there is ample room for improvement in the appropriate use of psychotropic drugs, suggesting how important it is to ensure continuous education of healthcare personnel on their correct indications and possible adverse events.

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Declarations

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Conflict of interest Marina Azab, Alessio Novella, Aladar Ianes and Luca Pasina have no conflicts of interest that are directly relevant to the contents of this article.

Ethical approval This study was approved by the Ethics Committee of the IRCCS Carlo Besta Foundation (ethics approval number 60_2019).

Consent to participate This was a retrospective study and data collection complied fully with Italian law on personal data protection. All data were anonymous and informed consent was not required for the purpose of this study.

Consent for publication Not applicable.

Data availability statement The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

Code availability The codes that support the findings of this study are available on request from the corresponding author.

Author contributions All authors participated in drafting of the manuscript or critical revision for important intellectual content. Individual contributions were as follows: MA and LP designed the study, interpreted the data, and wrote the manuscript; AN interpreted the statistical analyses, and AI undertook the final critical revision for important intellectual content. All authors read and approved the final version of the paper and agree to be accountable for this work.

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