



Potentially inappropriate medications among elderly people with neurocognitive disorders – A nationwide register-based study using 3 different explicit criteria

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ABSTRACT

Background: The use of potentially inappropriate medications (PIMs) is a problem since it might contribute significantly to adverse drug reactions and hospital admissions among elderly with major neurocognitive disorder (NCD). To assess the appropriateness of drug treatment, different explicit criteria have been developed. **Objectives:** To investigate and compare the prevalence of PIM users among elderly with major NCD on a nationwide basis using 3 different explicit criteria. Furthermore, the study aimed to investigate factors associated with the use of PIMs.

Methods: This nationwide register-based study included 35,212 people, 65 years or older, diagnosed with major NCD and registered in the Swedish registry for cognitive/dementia disorders up to June 30, 2017 and alive December 31, 2017. PIMs were identified using 3 different explicit criteria; the Swedish quality indicators, the EU(7)-PIM list and the AGS Beers Criteria. PIM use was defined as having collected a minimum of one PIM at least once between July 01 – December 31, 2017.

Results: The numbers of people using one or more PIMs were 7629 (21.7%) according to the Swedish quality indicators, 11,838 (33.6%) according to the EU(7)-PIM list, and 12,002 (34.1%) according to AGS Beers Criteria. Antipsychotics, antithrombotic agents and anxiolytics were the most frequently used PIM class according to the different assessment tools, respectively. The use of PIMs was positively associated with vascular dementia and Lewy body dementia/Parkinson's disease dementia, regardless of the assessment tool used. However, the association between using at least one PIM and age, sex, MMT-value and frontotemporal dementia, differed depending on the criteria used.

Conclusions: The different results and included PIMs indicate the different perspectives on PIMs between criteria, which make it difficult to compare the results. However, psychotropic drug use requires further highlighting, as well as the association between PIM use and different types of major NCD.

1. Introduction

Hospital admission rates increase with age^{1–3} and, although the prevalence differs between studies,⁴ it has been observed that up to 30% of unplanned hospitalizations among the elderly are caused by drug-related problems (DRPs).^{5,6} The prevalence is even higher among the vulnerable subgroup of the elderly with major neurocognitive disorder (NCD).⁷ Undertreatment of cardiovascular diseases, such as atrial fibrillation and heart failure, as well as too high doses and adverse drug reactions (ADRs) caused by potentially inappropriate medications (PIMs), are examples of DRPs that might contribute significantly to

hospital admissions among elderly with NCD.⁷

One definition of PIMs is “drugs which should not be prescribed for this population because the risk of adverse events outweighs the clinical benefit, particularly when there is evidence in favor of a safer or more effective alternative therapy for the same condition”.⁸ Examples of PIMs are anticholinergics used for, e.g., urinary incontinence, overactive bladder and extrapyramidal symptoms associated with conditions such as Parkinson's disease. These medications increase the risk for ADRs such as falling, confusion, cognitive impairment, and constipation - side effects that become particularly harmful among people with major NCD.^{9–11} Another example of PIMs is antipsychotics, which are

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commonly prescribed for behavioral and psychological symptoms (BPS) among people with major NCD. These types of medication are associated with side effects, e.g., sedation, higher risk of falling, increased risk of blood clotting, stroke, and infection. Moreover, an increased risk of worsening of other NCD symptoms can be considered, and even increases the risk of death.^{12–14} A third example of drugs that can be considered PIMs are non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs is one of the most commonly prescribed classes of drug, accounting for 5–10% of all prescribed medications each year. In the elderly, these medications are associated with ADRs, such as increased risk of gastrointestinal bleeding, cardiovascular side effects and nephrotoxicity. Additionally, they are commonly involved in drug-drug interactions.¹⁵

To assess whether medications are to be regarded as PIMs, different criteria have been developed. Implicit criteria are patient-specific, and the prescribing physician undertakes an individual assessment of the appropriateness of the drug treatment. Explicit criteria are non-patient specific, and can be applied with little clinical judgment, and the identified drug is regarded as inappropriate, regardless of intraindividual differences.¹⁶

The Swedish quality indicators for evaluating the quality of drug therapy for older people include drug-specific indicators. The national indicators were first published in 2004, and were updated in 2010 and 2017.¹⁷ In 2015, a European PIM list was developed by experts from 7 countries in the European Union. This screening tool is used to identify and compare prescription patterns across Europe. The EU(7)-PIM list originates from the different explicit tools, e.g., the German PRISCUS-list, the French Laroche list, the American AGS Beers Criteria, and the Canadian McLeod list, and was further developed and expanded to reach a total of 282 medications, i.e. the final EU(7)-PIM list.⁸ The American Geriatric Society (AGS) Beers Criteria is an American guideline consisting of 5 lists developed to identify PIMs among the elderly. These 5 lists are categorized as medications that should be avoided by most older people, medications that should be avoided by older people with specific conditions, medications that should be avoided in combination with one another, medications that should be used with caution, and medications that should be dosed differently due to decline in renal elimination capacity. These criteria were approved by the AGS and are continuously updated.¹⁸

Previous studies have addressed PIM prescription as a problem among the elderly, e.g., one study found that the prevalence of older people using PIMs varied between 16 and 24% when different explicit criteria were used as PIM identification tools.¹⁹ When the EU(7)-PIM list was used, 41% of the elderly with cognitive impairment included in the study, had one or more PIMs prescribed.²⁰ This raises the question about the appropriateness, validity, and feasibility of the different tools in use. As far as is known, no register-based study has been conducted comparing the prevalence of PIM use according to different PIM lists among a nationwide population of older people diagnosed with major NCD.

The purpose of the study is therefore to investigate and compare the use of PIMs among the elderly aged 65 years or older with major NCD, using 3 different explicit criteria. Furthermore, the study aims to investigate associated factors for using PIMs.

2. Methods

2.1. Setting and study design

This nationwide register-based study included people aged 65 years or older, registered in the Swedish registry for cognitive/dementia disorders (SveDem), and diagnosed with major NCD between May 01, 2007 and June 30, 2017. Data from the cause of death register was used to exclude the deceased up to December 31, 2017. People without a personal identity number and consequently lack of information about prescribed drugs collected at Swedish pharmacies, were also excluded

(n = 26). Therefore, the final study population comprised 35,212 people.

2.2. Definitions and data extraction

PIM use was defined as having collected a minimum of one PIM according to the used explicit criterion, at least once during the time period July 01 – December 31, 2017. Information about PIM use among the study population was gained from the Swedish Prescribed Drug Register (SPDR), by linking the SPDR with SveDem through the individual's personal identity number. Three different explicit criteria were used to identify PIMs: the Swedish quality indicators for good drug therapy among the elderly, from the Swedish National Board of Health and Welfare 2017,¹⁷ the EU(7)-PIM list,⁸ and the AGS Beers Criteria from 2019.¹⁸ The World Health Organization (WHO) Anatomical Therapeutic Index (ATC) drug classification system was used to identify the PIMs in the data file. Substances still registered on the Swedish market on December 31, 2017 were included in the study. The complete list of PIMs included on the basis of 3 lists of explicit criteria is listed in [Appendix 1](#). Information regarding sex was collected from SPDR. Age, Mini Mental Test (MMT) score (0–30; lower score indicates more severe cognitive impairment) and type of major NCD diagnosis were collected from SveDem. Data was anonymized before the research team gained access to it.

2.2.1. The Swedish indicators

The Swedish quality indicators comprises 2 parts, i.e., drug-specific and diagnosis-specific indicators. The drug-specific indicators are further divided into 9 parts, for which “*medications that should be avoided if not specific reasons to use them are present*”, and parts of “*substances for which correct and current indication often is missing or indefinite*”, are used in the present study. All drugs and drug classes listed in the first part, i.e., long-acting benzodiazepines, anticholinergic drugs, codeine, tramadol, propiomazine, and glibenclamide were included, as were NSAIDs and antipsychotics from the second part, with the exception of lithium due to its association with severe side effects.¹⁷ Altogether, 77 substances were included in the analysis.

2.2.2. EU(7)-PIM list

The EU(7)-PIM list was adapted to the Swedish pharmaceutical market, i.e., substances not approved on the Swedish market were excluded (n = 126). Duration (n = 12), dose (n = 13) and regimen-dependent drugs (i.e., sliding scale insulins), as well as formulation-dependent PIMs (n = 2) were also excluded due to limited information in register data, resulting in a list comprising 131 substances.

2.2.3. AGS Beers Criteria

AGS Beers Criteria comprises 5 parts. The first part i.e., “*medications that are potentially inappropriate in most older adults*” was used to identify PIMs in the present study. Drugs not approved on the Swedish market were excluded (n = 118) as were duration-dependent PIMs (n = 13), dose-dependent PIMs (n = 2), regimen-dependent PIMs (e.g., sliding scale insulins), and formulation-dependent PIMs (n = 3). The final list contained 70 substances.

2.3. Data analysis

Descriptive statistics were used to summarize the data. Proportions were calculated for dichotomous variables, mean values with standard deviation (SD) were calculated for age and interquartile range (IQR), and range for MMT value. Simple logistic regression analyses were conducted to investigate the association between people with and without PIMs, according to the 3 different criteria. PIM use was set as the dependent variable and possible associated factors; age, sex, MMT value and major NCD diagnosis (categorized as Alzheimer's disease (AD), both early and late onset, Vascular dementia (VaD), Frontotemporal

dementia (FTD), and Lewy body dementias (LBD), including dementia with Lewy bodies (DLB), and Parkinson’s disease dementia (PDD)), were included as independent variables in the model. Consequently, data for 20,071 people was included in the simple logistic regression models. A multiple logistic regression analysis was conducted, including all variables from the simple model. Results are presented as odds ratio (OR) with 95% confidence interval (CI). A p-value of <0.05 was considered statistically significant. All statistical calculations were performed using SPSS version 26.

Ethical approval

The Regional Ethical Review Board in Umeå, Sweden, approved the study. Registration number 2017/256-31.

3. Results

Basic characteristics of the study population are presented in Table 1. A total of 35,212 people were included in the study, 61.8% of whom were women. The mean age was 82.7 ± 6.6 years, and IQR (range) for MMT value was 19–25 (0–30). The most common major NCD diagnosis according to the ICD codes registered in SveDem was AD (both early and late onset), 34.8%. Moreover, 18.0% were diagnosed with VaD, 1.7% of the population were diagnosed with LBD, and 1.3% of individuals were diagnosed with PDD and FTD. More than every fifth individual had an unknown diagnosis, 18.4% were diagnosed with mixed dementia (AD/VaD) and 2.5% had other types of major NCD.

A total of 9226 PIMs were identified among 21.7% (n = 7629) of the study population according to the Swedish quality indicators. When the EU(7)-PIM list was used as an identification tool, 15,741 PIMs were found among 33.6% (n = 11,838) of individuals, and according to AGS Beers Criteria, 15,941 PIMs were identified among 34,1% (n = 12,002) of the study population.

Table 2 summarizes the 3 most frequently used PIM classes, and the most common drug substance within each drug class among the study population. According to Swedish quality indicators, the most frequently used PIM class was antipsychotics (n = 4323), with risperidone as the most common PIM within that drug class, used by 2653 people. According to the EU(7)-PIM list, the most frequently used PIM class was antithrombotic agents (n = 3570) and apixaban was the most commonly used PIM (2208 people). When AGS Beers Criteria were applied, the most frequently used PIM class was anxiolytics (n = 8357).

Table 1
Characteristics of the study population.

Total study sample, n	35,212
Sex (n, %)	
Female	21,746 (61.8)
Male	13,456 (38.2)
n/a	10 (.0)
Age (mean ± SD)	82.7 (6.6)
MMT ^a (mean ± SD)	21.5 (4.7)
MMT ^a IQR, (range)	19-25, (0–30)
Type of major NCD (n, %)	
AD (early onset)	683 (1.9)
AD (late onset)	11,569 (32.9)
Mixed dementia (AD/vascular)	6470 (18.4)
VaD	6325 (18.0)
LBD	605 (1.7)
PDD	444 (1.3)
FTD	445 (1.3)
UNS major NCD	7796 (22.1)
Other type of major NCD	875 (2.5)

^a n = 33,622 due to missing values. SD=Standard deviation, MMT = Mini Mental Test, IQR=Interquartile range, NCD=Neurocognitive disorder, AD = Alzheimer’s disease, VaD = Vascular dementia, LBD = Lewy Body dementia, PDD=Parkinson’s disease dementia, FTD=Fronto-temporal dementia, UNS=Unspecified.

Table 2

Prevalence of the most commonly used PIM class and PIM within each class among the study population (n = 35,212) according to the Swedish quality indicators, the EU(7)-PIM list, and AGS Beers Criteria.

Swedish Indicators	EU(7)-PIM	AGS Beers Criteria
Antipsychotics (N05A)	Antithrombotic agents (B01A)	Anxiolytics (N05B)
4323 (12.3)	3570 (10.1)	8357 (23.7)
Risperidone (N05AX08)	Apixaban (B01AF02)	Oxazepam (N05BA04)
2653 (7.5)	2208 (6.3)	7289 (20.7)
NSAIDs (M01A)	Sedatives and hypnotics (N05C)	Antipsychotics (N05A)
941 (2.7)	1948 (5.5)	4323 (12.3)
Naproxen (M01AE02)	Clomethiazole (N05CM02)	Risperidone (N05AX08)
380 (1.1)	1452 (4.1)	2653 (7.5)
Urologic agents (G04B)	Laxatives (A06A)	Sedatives and hypnotics (N05C)
559 (1.6)	1500 (4.3)	879 (2.5)
Solifenacin (G04BD08)	Sodium picosulfate (A06AB08)	Zolpidem (N05CF02)
241 (0.7)	1490 (4.2)	879 (2.5)

PIM=Potentially inappropriate medication, EU(7)-PIM=European Union (7 European countries) potentially inappropriate medication, AGS = American Geriatric Society, NSAIDs = non-steroidal anti-inflammatory drugs.

Oxazepam was the most frequently used PIM within that drug class, used by 7289 people. Table 3 presents the 10 most commonly used PIMs among the study population, depending on which explicit criteria are being used as the PIM identification tool. The complete list of identified PIMs is available in Appendix 1.

Table 4 presents the results from the regression analyses investigating factors possibly associated to PIMs according to the Swedish quality indicators. The probability of using PIMs decreased with

Table 3

Prevalence of the 10 most common PIMs identified among the study population (n = 35,212) according to each PIM list. Complete list of identified PIMs is available in Appendix 1.

PIMs according to Swedish Indicators, n (%)	PIMs according to EU (7)-PIM list, n (%)	PIMs according to AGS Beers Criteria, n (%)
Risperidone (N05AX08)	Apixaban (B01AF02)	Oxazepam (N05BA04)
2653 (7.5)	2208 (6.3)	7289 (20.7)
Quetiapine (N05AH04)	Sodium picosulfate (A06AB08)	Risperidone (N05AX08)
633 (1.8)	1490 (4.2)	2653 (7.5)
Haloperidol (N05AD01)	Clomethiazole (N05CM02)	Zolpidem (N05CF02)
533 (1.5)	1452 (4.1)	879 (2.5)
Olanzapine (N05AH03)	Rivaroxaban (B01AF01)	Quetiapine (N05AH04)
502 (1.4)	985 (2.8)	633 (1.8)
Hydroxyzine (N05BB01)	Digoxin (C01AA05)	Haloperidol (N05AD01)
467 (1.3)	906 (2.6)	533 (1.5)
Diazepam (N05BA01)	Venlafaxine (N06AX16)	Olanzapine (N05AH03)
397 (1.1)	642 (1.8)	502 (1.4)
Naproxen (M01AE02)	Hydroxyzine (N05BB01)	Hydroxyzine (N05BB01)
380 (1.1)	467 (1.3)	467 (1.3)
Codeine with paracetamol (N02AJ06)	Sitagliptin (A10BH01)	Diazepam (N05BA01)
374 (1.1)	459 (1.3)	397 (1.1)
Propiomazine (N05CM06)	Diazepam (N05BA01)	Amitriptyline (N06AA09)
352 (1.0)	397 (1.1)	314 (0.9)
Amitriptyline (N06AA09)	Pramipexol (N04BC05)	Metoclopramide (A03FA01)
314 (0.9)	357 (1.0)	254 (0.7)

PIMs = Potentially inappropriate medications, EU(7)-PIM=European Union (7 European countries) potentially inappropriate medication, AGS = American Geriatric Society.

Table 4

Results from the simple and multiple regression analyses investigating factors possibly associated with using PIMs, identified with the Swedish quality indicators.

Patient characteristics	Swedish Indicators		Simple OR (95% CI)	Multiple OR (95% CI)
	With PIM(s), n = 4330	Without PIM(s), n = 15,741		
Age, years				
65-74	821 (26.7)	2252 (73.3)	Ref.	Ref.
75-84	2063 (21.9)	7337 (78.1)	0.771 (0.702–0.847)	0.781 (0.709–0.860)
85-94	1386 (19.3)	5798 (80.7)	0.656 (0.594–0.724)	0.659 (0.594–0.731)
95-104	60 (14.5)	354 (85.5)	0.465 (0.350–0.618)	0.456 (0.339–0.613)
Sex ^a				
Men	1629 (21.1)	6099 (78.9)	Ref.	Ref.
Women	2701 (21.9)	9636 (78.1)	1.049 (0.979–1.125)	1.133 (1.053–1.219)
MMT value ^b	21.6 ± 4.7	21.8 ± 4.6	0.989 (0.982–0.996)	0.987 (0.980–0.994)
Diagnosis				
AD (early and late onset)	2497 (20.4)	9755 (79.6)	Ref.	Ref.
VaD	1386 (21.9)	4939 (78.1)	1.096 (1.018–1.181)	1.121 (1.038–1.212)
LBD/PDD	325 (31.0)	724 (69.0)	1.754 (1.528–2.013)	1.710 (1.480–1.977)
FTD	122 (27.4)	323 (72.6)	1.476 (1.193–1.826)	1.402 (1.122–1.751)

^a n = 20,065 due to lack of data for 6 individuals.

^b n = 19,288 due to lack of data. PIM; Potentially inappropriate medication, OR; Odds ratio, CI; Confidence interval, AD = Alzheimer's disease, VaD = Vascular dementia, LBD; Lewy body dementia, PDD=Parkinson's disease dementia, FTD=Frontotemporal dementia.

increasing age. PIMs were, however, more common among women than among men, according to the results from the multivariable analysis. Moreover, an association was found between lower MMT score and using one or more PIMs, and PIMs were found to be more common among those with VaD, LBD/PDD and FTD, compared to people with AD.

Table 5 shows that PIM use was less common among those aged 85–104 compared to younger individuals when the EU(7)-PIM list was used as the PIM identification tool. Moreover, an association was found between use of PIMs and having VaD or LBD/PDD, when compared to AD.

The results from the regression analyses, investigating factors possibly associated to PIMs according to the AGS Beers Criteria, are presented in Table 6. PIM use was more common among women than men, and using one or more PIMs was associated with more severe deterioration in cognitive function. PIMs were also more common among people with VaD and LBD/PDD, when compared to AD.

4. Discussion

Different proportions of people using at least one PIM were identified when the 3 explicit criteria were applied in the present study. This might be due to the different number of PIMs that were included from the different PIM identification tools. Only 70 PIMs were included from the AGS Beers Criteria, since this tool was developed for the American drug market. Nevertheless, the prevalence of people using at least one PIM was almost the same as with the application of the EU(7)-PIM list, even if 131 PIMs were included from the EU(7)-PIM list. The number of PIMs included from the Swedish quality indicators was approximately the same as those included using the AGS Beers Criteria. Nevertheless, the prevalence of PIM users was lowest when the Swedish indicators were

Table 5

Results from the simple and multiple regression analyses investigating factors possibly associated with using PIMs, identified with the EU⁷-PIM list.

Patient characteristics	EU ⁷ -PIM		Simple OR (95% CI)	Multiple OR (95% CI)
	With PIM(s), n = 6622	Without PIM(s), n = 13,449		
Age, years				
65-74	1042 (33.9)	2031 (66.1)	Ref.	Ref.
75-84	3162 (33.6)	6238 (66.4)	0.988 (0.907–1.077)	0.968 (0.886–1.059)
85-94	2322 (32.3)	4862 (67.7)	0.931 (0.851–1.018)	0.900 (0.819–0.990)
95-104	96 (23.2)	318 (76.8)	0.588 (0.463–0.748)	0.573 (0.447–0.736)
Sex ^a				
Men	2686 (34.8)	5042 (65.2)	Ref.	Ref.
Women	3936 (31.9)	8401 (68.1)	0.879 (0.828–0.934)	0.971 (0.911–1.034)
MMT value ^b	21.8 ± 4.6	21.7 ± 4.6	1.003 (0.997–1.010)	1.003 (0.996–1.010)
Diagnosis				
AD (early and late onset)	3513 (28.7)	8739 (71.3)	Ref.	Ref.
VaD	2504 (39.6)	3821 (60.4)	1.630 (1.529–1.738)	1.632 (1.527–1.744)
LBD/PDD	470 (44.8)	579 (55.2)	2.019 (1.777–2.295)	1.926 (1.685–2.201)
FTD	135 (30.3)	310 (69.7)	1.083 (0.882–1.331)	1.060 (0.855–1.313)

^a n = 20,065 due to lack of data for 6 individuals.

^b n = 19,288 due to lack of data. PIM; Potentially inappropriate medication, OR; Odds ratio, CI; Confidence interval, AD = Alzheimer's disease, VaD = Vascular dementia, LBD; Lewy body dementia, PDD=Parkinson's disease dementia, FTD=Frontotemporal dementia.

applied as the PIM identification tool and indicates that the Swedish first-line options for drug treatment among the elderly are known and respected by health care professionals. The reasons for this might be due to a long tradition of independent drug information campaigns, guidelines, monetary reimbursement from Swedish authorities and medication reviews to promote rational prescribing and consequently decrease PIM use among elderly living in Sweden.^{17,21,22}

The differences in prevalence of PIM users might also be due to the different PIMs included in the lists. Antithrombotic agents were the most frequently used PIM class according to the EU(7)-PIM list, and apixaban was the most commonly used PIM. However, this medication is considered a PIM only in this particular list. In Sweden, apixaban is one of the first-line options for thromboembolic prophylactic treatment, which might contribute to the result.²³ Moreover, the most frequently identified PIM according to the Swedish indicators, was risperidone. However, according to the EU(7)-list, this medication class is considered a duration-dependent PIM, and was not identified when that criteria were applied as the identification tool, which consequently affected the indicated prevalence. Overall, the differences found indicate an inconsistency, and different perspectives regarding PIMs in the compilation of guidelines. The EU(7)-PIM list is considered a sensitive identification tool when identifying PIMs among older people.⁸ However, increased sensitivity may compromise specificity,²⁴ which is a reminder that explicit criteria can guide and support the prescribing physician when undertaking evaluations of the risk-benefit ratio for a medication, and PIMs prescriptions are being considered for older people with major NCD. Nevertheless, it is important to remember that explicit criteria cannot replace an individual assessment of an individual's clinical condition.

Despite the differences between the identification tools, there are also similarities between the criteria. For example, several types of

Table 6
Results from the simple and multiple regression analyses investigating factors possibly associated with using PIMs, identified with the AGS Beers Criteria.

Patient characteristics	Beers Criteria		Simple OR (95% CI)	Multiple OR (95% CI)
	With PIM(s), n = 6680	Without PIM(s), n = 13,391		
Age, years				
65-74	1012 (32.9)	2061 (67.1)	Ref.	Ref.
75-84	3063 (32.6)	6337 (67.4)	0.984 (0.903–1.074)	0.986 (0.902–1.079)
85-94	2470 (34.3)	4714 (65.6)	1.067 (0.976–1.167)	1.039 (0.946–1.142)
95-104	135 (32.6)	279 (67.4)	0.985 (0.792–1.226)	0.890 (0.708–1.118)
Sex ^a				
Men	2331 (30.2)	5397 (69.8)	Ref.	Ref.
Women	4349 (35.3)	7988 (64.7)	1.261 (1.186–1.340)	1.286 (1.206–1.371)
MMT ^b	21.4 ± 4.8	21.9 ± 4.6	0.975 (0.969–0.981)	0.976 (0.970–0.983)
Diagnosis				
AD (early and late onset)	3915 (32.0)	8337 (68.0)	Ref.	Ref.
VaD	2170 (34.3)	4155 (65.7)	1.112 (1.043–1.186)	1.125 (1.052–1.203)
LBD/PDD	440 (41.9)	609 (58.1)	1.539 (1.353–1.749)	1.729 (1.511–1.977)
FTD	155 (34.8)	290 (65.2)	1.138 (0.933–1.388)	1.216 (0.978–1.498)

^a n = 20,065 due to lack of data for 6 individuals.

^b n = 19,288 due to lack of data. PIM; Potentially inappropriate medication, OR; Odds ratio, CI; Confidence interval, AD = Alzheimer's disease, VaD = Vascular dementia, LBD; Lewy-body dementia, PDD=Parkinson's disease dementia, FTD=Frontotemporal dementia.

neuroleptics, sedatives and anxiolytics are included in the 3 lists of explicit criteria. Among the PIMs identified from the Swedish quality indicators, antipsychotics was the dominant PIM class, in which risperidone was the most frequently used medication. According to AGS Beers Criteria, antipsychotic agents was the second most frequently occurring class of PIM, and the most common PIM was risperidone. Antipsychotics are regarded as inappropriate for the elderly in general, and among people with major NCD in particular. Since their blood brain barrier (BBB) function is often impaired, people with major NCD are consequently more prone to adverse effects from CNS-active agents e.g., antipsychotic drugs. However, in Sweden, risperidone is the first line choice in the pharmacologic treatment of BPS among people with major NCD.¹⁷ However, for individuals with LBD, antipsychotic medication should be avoided due to the possibility of worsening of symptoms.²⁵ Hypnotic and sedative agents represented the second most frequently collected PIM class, and clomethiazole the most common PIM within this class when the EU(7)-PIM list was used as the PIM identification tool. The most commonly identified PIM class was anxiolytics, and oxazepam the most common PIM when AGS Beers Criteria were applied. Anxiolytic agents can contribute to an increased risk of e.g., falling and delusions among the elderly,^{26,27} and especially among older people with major NCD due to their increased sensitivity to CNS-active medications. However, when treating people with major NCD in Sweden, oxazepam is recommended as the first-line choice among anxiolytic agents¹⁷ due to its shorter half-life and lack of active metabolites.^{28,29} Anxiolytic agents might also be used as hypnotics among the elderly with major NCD. Moreover, clomethiazole is recommended as temporary treatment among older people with major NCD if the circadian rhythm is severely disturbed and agitation is present.¹⁷ Accordingly, these recommendations increase the possibility of identifying this type of drug treatment among this specific study population.

When the Swedish quality indicators and AGS Beers Criteria were used as PIM identification tools, it was found that PIM use was more common among women compared to men. Different patterns were also found when the association between age and use of one or more PIM was investigated. According to the Swedish quality indicators and the EU(7)-PIM list, PIM use was less likely with increasing age.

The results were more consistent when the association between type of diagnosis and the use of one or more PIMs was investigated. PIM use was more common among people with LBD/PDD and VaD, compared to people with AD, according to all three criteria. The probability differed, however, and PIM use was almost twice as common among people with LBD/PDD compared to AD, when the EU(7)-PIM list was used. Overall, the association between PIM use among people with LBD/PDD is alarming, since people with DLB are significantly more vulnerable to side effects from antipsychotics, and experience worsening of symptoms when using these types of drugs. Antipsychotics were commonly used among the total study population when the Swedish quality indicators and AGS Beers Criteria were used, which may explain the association found in the present study. When prescribing medication for people with LBD/PDD, it is especially important to evaluate the risk-benefit ratio.

Both similarities and differences are found when the results in the present study are compared with the results in other studies. Although the prevalence of PIM users was high when the EU(7)-PIM list was used, the prevalence was lower overall compared to previous studies using the same criteria to identify PIMs in the elderly.^{20,30–32} This indicates that a large proportion of PIMs from the EU(7)-PIM list was not identified among the study population. However, the low prevalence of PIM users found when the Swedish indicators was applied as the PIM identification tool was in line with an earlier study.³⁰ Moreover, in accordance with the present study, PIM use has been found to be significantly more common among women than men in another study.³³ It has also been found that women more commonly use psychotropic drugs,³⁴ which could explain the significance found according to two of the criteria, but not when the EU(7)-PIM list was used given the most commonly used drugs identified among the study population. Another study also found an increased risk of PIM use among people with LBD compared to people with AD.³⁵ A previous study found that antipsychotic drug use was higher among people with LBD compared to people with other diagnosis of major NCD.³⁶ Altogether, the results may be due to the different PIMs included from the lists and accordingly identified among the study population. Moreover, it is important to remember that the diverse result found in different studies might be due to different settings, study designs and methods.

Some important limitations of the present study should be kept in mind. The exclusion of those who died might have contributed to a healthy survivor effect which could have affected the found prevalence of PIMs. Insulins were excluded, since dosage protocols were required to evaluate appropriateness with this type of drug treatment. However, this type of data was not available. Furthermore, medications considered to be PIMs when certain doses or recommended treatment duration is exceeded, were also excluded due to lack of data. Accordingly, this has lowered the sensitivity to identify PIMs and the prevalence of people using at least one of the identified PIMs might be higher, since this type of drug treatment was excluded. In addition, nothing can be said about adherence or whether the PIM was actually used by the individual. Moreover, given that antipsychotics are mainly prescribed for BPS and this information was unknown among the study population, some of the drug treatment might have been clinically motivated. Strengths of the present study are the large study population, and the use of three explicit criteria from different geographic locations, which increases the possibility of generalizing the results.

5. Conclusions

The diverse results indicate the different perspectives on PIMs among explicit criteria, and differences in prevalence and included PIMs make

it difficult to compare the results. However, psychotropic drug use was common, and PIM use was more common among people with LBD/PDD and VaD compared to AD, according to all 3 lists of explicit criteria. Given the vulnerability of this group of people, this is alarming and should be further highlighted.

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Author contributions

Eva Sönerstam: Conceptualization, Methodology, Formal analysis, Investigation, Writing – Original Draft. Frida Harlin: Conceptualization, Formal analysis, Writing – Original Draft. Maria Gustafsson: Conceptualization, Methodology, Writing – Review & Editing, Supervision.

Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.sapharm.2023.01.010>.

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