ORIGINAL RESEARCH ARTICLE

Potentially Inappropriate Medications Pre- and Post-Diagnosis of Major Neurocognitive Disorders Among Older People in Sweden: A Register-Based, 6-Year Longitudinal Study

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Abstract

Objective The aim of the present study was to investigate how potentially inappropriate medication usage and anti-dementia drug use change from 3 years prior to, up until 3 years post-diagnosis of major neurocognitive disorders among older people living in Sweden.

Methods People registered in the Swedish registry for cognitive/dementia disorders from 1 July, 2008 to 31 December, 2017, and aged 68 years or older at diagnosis, were included ($n = 67{,}226$). Data were combined with the Swedish Prescribed Drug Registry to obtain information about drugs collected in 6-month periods at Swedish pharmacies from 3 years pre-diagnosis until 3 years post-diagnosis. Potentially inappropriate medications were identified according to Swedish national guidelines. A generalised estimating equation regression model and estimated marginal means were used.

Results Of the 67,226 people included in the study population, 59.2% were women and the mean age $\pm$ standard deviation was 81.5 ± 6.4 years, 47.0% lived together with a spouse or partner, and 88.9% were living at home at the time of diagnosis. The proportions of people using potentially inappropriate medications continuously decreased pre- and post-diagnosis, except for antipsychotic drug use, which continuously increased both pre- and post-diagnosis. Moreover, anticholinergic drug use increased pre-diagnosis and declined post-diagnosis. When comparing the periods pre- and post-diagnosis date, the adjusted proportion of people using potentially inappropriate medications was significantly lower post-diagnosis compared with pre-diagnosis, except for the adjusted proportion using antipsychotics, which was significantly higher post-diagnosis, 10.6%, compared with the period before, 3.1% (adjusted odds ratio 3.71; 95% confidence interval 3.59–3.83). The adjusted proportion of people using anticholinergic drugs was significantly lower post-diagnosis, 7.2%, compared with the pre-diagnosis period, 8.9% (adjusted odds ratio 0.80; 95% confidence interval 0.78–0.82). Anti-dementia drug use was significantly higher post-diagnosis, 52.6%, when compared with the pre-diagnosis period, 3.5% (adjusted odds ratio 30.13; 95% confidence interval 29.19–31.10).

Conclusions Overall, the prevalence of people using potentially inappropriate medications decreased and was significantly lower post-diagnosis of major neurocognitive disorders, except for antipsychotics. This indicates that potentially inappropriate medication use should be noticed and reviewed among all older people. The small decrease in the prevalence of anticholinergic drug users and the increasing proportions of people using antipsychotic drugs post-diagnosis are of special concern because of the adverse drug reactions associated with these types of potentially inappropriate medications. Consequently, it is important to identify and regularly question anticholinergic and antipsychotic drug treatment to prevent unnecessary and serious adverse drug reactions among a vulnerable group of people.

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Key Points

The proportion of people using potentially inappropriate medications declined both pre-diagnosis and post-diagnosis of major neurocognitive disorder and was significantly lower post-diagnosis compared with the pre-diagnosis period, except for antipsychotic drug use.

Potentially inappropriate medication use, especially anticholinergic and antipsychotic drug treatment, should be regularly evaluated among all older people to minimise the risk of adverse drug reactions associated with this type of drug treatment.

1 Introduction

It is well known that older people with major neurocognitive disorders are vulnerable to drug effects [1]. Nevertheless, the medication burden is often high and potentially inappropriate medications (PIMs) are prescribed to these individuals even when this type of drug use is associated with adverse drug reactions (ADRs) [2–7], which are preventable [8].

The increased sensitivity to drugs is partly due to the ageing process, which affects the pharmacokinetic and pharmacodynamic profile of drugs [8]. One example is glibenclamide, which has active metabolites that are cleared by the kidneys. If prescribed dosages are not properly adjusted, use of glibenclamide in an older patient with declining renal function can lead to hypoglycaemia and consequently delirium [3–5]. Another example is the prolonged half-life of long-acting benzodiazepines, which leads to residual sedation and therefore increases the risk for fall accidents in older people. The use of long-acting benzodiazepines is also associated with an increased risk for ADRs such as cognitive decline among the elderly [8, 9]. Moreover, treatment with non-steroidal anti-inflammatory drugs (NSAIDs) may cause gastrointestinal bleeding owing to the inhibition of the prostaglandin synthesis, which leads to impaired protection of the gastric mucosa and an increased risk for lesions [3, 5, 10].

Ageing is also associated with a decreased number of cholinergic neurons in the central nervous system. The decline in acetylcholine levels is even more pronounced among older individuals with major neurocognitive disorders compared with older people without this disorder. Additionally, decreased levels of serotonin, noradrenaline, and dopamine contribute to the symptoms found among people with this disorder, which includes the following

subtypes: Alzheimer's disease (AD), vascular dementia, Lewy body dementia, Parkinson's disease dementia, and frontotemporal dementia. Moreover, the coexistence of different subtypes is common [11]. Additionally, it is found that the blood–brain barrier changes among people with AD, which enhances the entrance of central nervous system-active drugs. Altogether, these changes may lead to an even more increased sensitivity for and enhanced effects from drugs among people with major neurocognitive disorders [12]. For example, anticholinergic drugs may increase already existing cognitive impairments and antipsychotic drugs may lead to severe ADRs such as fall accidents, cerebrovascular events, or even death [13–16]. Even if this is known, antipsychotics are commonly used among people with major neurocognitive disorders because of the behavioural and psychological symptoms with dementia (BPSD) that often arise among these people [17]. However, cholinesterase inhibitors, approved for the treatment of symptoms that arise as a result of major neurocognitive disorders, may also have positive effects on BPSD [18]. Moreover, the use of cholinesterase inhibitors and memantine is found to reduce the risk of psychotropic drug use among people with major neurocognitive disorders when compared with people with this disorder who do not use anti-dementia drugs [19]. Nevertheless, a higher prevalence of PIMs has been reported among those with major neurocognitive disorders compared with those without this disorder [7]. Different studies have found that 27–64.4% of people with major neurocognitive disorders have at least one PIM prescribed, depending on the study settings and type of PIM criteria being used [2, 15, 20–23].

The onset of major neurocognitive disorders may start decades before symptoms arise [11]. Moreover, the diagnosis is made after the onset of neurodegeneration and after symptoms have arisen [24]. Consequently, an increased sensitivity for drug effects may start before the major neurocognitive disorders are identified and classified. To optimise drug treatment and diminish risks for ADRs among this vulnerable group of people, we need more knowledge about how the prevalence of PIM use changes pre-diagnosis and post-diagnosis. A previous study, comprising 2448 participants, found that the prevalence of people with major neurocognitive disorders using PIMs had increased at 1-year and 2-year post-diagnosis of major neurocognitive disorders when compared with the prevalence of PIM users at diagnosis [25]. Another study, comprising 2418 people, found that the odds for PIM exposure was lower at 1-year pre-diagnosis compared with at 1-year diagnosis (adjusted odds ratio [aOR] 0.83, 95% confidence interval [CI] 0.75–0.91). Additionally, the odds for PIM exposure continued to increase 1-year post-diagnosis (aOR 1.17, 95% CI 1.05–1.32) [26]. Previous studies have also found an increasing prevalence of antipsychotic drug use, 10 years pre-diagnosis until 4 years

post-diagnosis of major neurocognitive disorders [27], and from the onset of diagnosis and onwards [28].

According to our knowledge, no previous study has investigated longitudinal patterns of PIM use pre- and post-diagnosis of major neurocognitive disorders among older people living in Sweden. The aim of the present study was therefore to investigate how PIM usage changes from 3 years prior to, up until 3 years post-diagnosis of major neurocognitive disorders among older people living in Sweden. Longitudinal patterns of anti-dementia drug use were investigated as well.

2 Methods

2.1 Settings and Study Design

This longitudinal study includes people aged 68 years or older at the diagnosis date of major neurocognitive disorders, registered in the Swedish registry for cognitive/dementia disorders (SveDem) between 1 July, 2008 and 31 December, 2017 ($n = 67,226$). All participants included in SveDem are registered after diagnosis and the diagnosis date is the date when the participant is informed about the diagnosis. The data registered in SveDem are validated through different methods to ensure good data quality [29]. The study population, collected from SveDem, was combined with data from the Swedish Prescribed Drug Register (SPDR), which contains information about all the drugs collected at Swedish pharmacies [30]. Data from the SPDR made it possible to identify PIM use and anti-dementia drug use among the study population from 1 July, 2005 until 31 December, 2017. Moreover, data from the Cause of Death Register [31] were applied to obtain information about people who died within 3 years post-diagnosis date. All individuals who are registered in the Swedish Population Register are given a personal identity number, which makes it possible to retrieve and link information between different registries. All data were, however, anonymised before the researcher gained access to the data file.

## 2.2 Data Extraction and Definitions

Information about sex was collected from the SPDR and the information about diagnosis date, age at diagnosis date, Mini-Mental State Examination (MMSE) score, type of major neurocognitive disorder, type of residence, and living status at the baseline registration was collected from SveDem. Moreover, the diagnosis year was extracted from the diagnosis date and the degree of cognitive impairment, according to the MMSE, was categorised into the following four categories: no impairment (24–30), mild impairment (16–23), moderate impairment (8–15), or severe impairment (0–7).

2.2.1 Time Periods Pre- and Post-Diagnosis Date of Major Neurocognitive Disorders

To investigate how PIM use was associated with the period pre- and post-diagnosis of major neurocognitive disorders, the diagnosis date was identified for each individual. Based on this date, 12 6-month periods were identified and coded for each participant. Six periods were identified pre-diagnosis and six periods post-diagnosis. The first 6-month period post-diagnosis included the diagnosis date. The six periods pre-diagnosis were further categorised into one pre-diagnosis period and the six periods post-diagnosis were categorised into one post-diagnosis period. The procedure is shown in Fig. 1.

2.2.2 PIMs

Potentially inappropriate medications were defined according to the explicit and drug-specific part of quality indicators published by the Swedish National Board of Health and Welfare. This is a Swedish national guideline developed by Swedish experts. The drug-specific part consists of nine parts; drugs inappropriate for older people regardless of indication, drugs for which correct and current indication are important, inappropriate dose regimes, inappropriate doses, polypharmacy, potentially inappropriate drug combinations, drugs that should be adjusted based on renal function, PIMs based on specific conditions and symptoms, respectively, and psychotropic drugs [3]. Compared to the
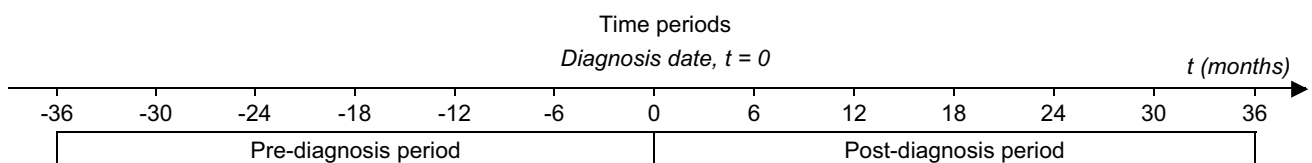
Fig. 1 Twelve time periods identified pre- and post-diagnosis date ($t = 0$) of major neurocognitive disorders for each individual in the study population. Six 6-month periods were identified pre-diagnosis and formed the pre-diagnosis period. Six 6-month periods were identified post-diagnosis and formed the post-diagnosis period. The diagnosis date was included in the first 6-month period post-diagnosis

explicit STOPP criteria, the STOPP criteria is an international PIM list, which includes 65 criteria listing drugs that should be withdrawn among certain groups of patients or certain diseases developed by 19 experts from 13 European countries [32, 33]. The Beers criteria, in contrast, are an American explicit PIM list developed to detect PIMs that should be avoided by people aged 65 years or older, in most circumstances or in certain conditions or diseases [4]. The Anatomic Therapeutic Chemical classification code specified in the indicators was used to identify PIMs. The PIMs were categorised according to the classification in the quality indicators, i.e. as drugs inappropriate for older people regardless of indication: long-acting benzodiazepines, anticholinergic drugs, tramadol, propiomazine, codeine, and glibenclamide. Antipsychotic drugs and NSAIDs were also included in accordance with previous studies, although information about indications was not available [34, 35]. Correct and current indications are important according to the indicators [3], nevertheless, these PIM classes were included because of the many side effects associated with this type of drug treatment [10, 13]. Table 1 specifies the Anatomic Therapeutic Chemical classification codes for the different PIMs and PIM classes, respectively. M.S. and E.S. extracted the data about PIMs from the datafile 4 April, 2020 using SAS Enterprise Guide 7.1.

2.2.3 PIM Use

To be classified as a tramadol, propiomazine, codeine or glibenclamide user, a person had to collect at least one of the PIMs, respectively, at least once during a 6-month period. If a person collected at least one of the specified PIMs included in a PIM class, i.e. at least one long-acting benzodiazepine, anticholinergic drug, NSAID or antipsychotic drug, at least once, the person was classified as a user of that specified PIM class, during a 6-month period. Moreover, the PIM total was classified as having collected at least one of the PIMs specified in Table 1, regardless of PIM or PIM class, at least once during a 6-month period. People without any identified PIM were defined as non-users for that specific 6-month period. However, to be dichotomised as a PIM user or non-user within a 6-month period, one prerequisite was that full collection data from SPDR should be available for that 6-month period. Consequently, people with a diagnosis date between 1 January, 2015 and 31 December, 2017 received missing PIM use data within each of the 6-month periods with incomplete collection data from 1 January, 2018 and onwards. In addition, people who died within 3 years post-diagnosis received missing PIM use data for the 6-month period in which the death occurred and onwards. However, all people alive at the diagnosis date were included in the study. The number of people who were alive and had complete collection data during the 3-year period post-diagnosis is specified for each 6-month period in Fig. 2.

2.2.4 Anti-Dementia Drug Use

Anti-dementia drug use was defined and identified in the same way as PIM use, i.e. having collected at least one anti-dementia drug within Anatomic Therapeutic Chemical code N06D, i.e. cholinesterase inhibitors and memantine, at least once during a 6-month period.

2.3 Statistical Analyses

Descriptive statistics were used to describe the study population. Continuous variables are presented as the mean with standard deviation and categorical variables as frequencies. A generalised estimating equation (GEE) regression model with an exchangeable within-person correlation and a logit link function was used to estimate the aOR, and the estimated marginal means (EMM) was used to estimate adjusted proportions for using a PIM, PIM class, PIM total, or anti-dementia drug pre- and post-diagnosis of major neurocognitive disorders. Potentially inappropriate medication and anti-dementia drug use were set as the dependent variable in each analysis, respectively. Time, dichotomised as pre- or post-diagnosis of major neurocognitive disorders, was used as the independent variable. The model was adjusted for sex, age (categorised into 68–77, 78–87, or 88–105 years, respectively), and year of diagnosis (categorised into 2008–9, 2010–11, 2012–13, 2014–15, or 2016–17, respectively). Moreover, EMM was used to estimate unadjusted proportions for using a PIM, PIM class, PIM total, or anti-dementia drug within each of the 12 time periods. The proportions were plotted against the time periods. The prevalence of PIM users, excluding those who died post-diagnosis and those without complete data from the SPDR, was calculated for comparison purposes.

Additionally, simple and multiple logistic regression analyses were conducted to investigate the association between using at least one PIM regardless of the classification at diagnosis and the following 6 months and age, sex, MMSE score, use of anti-dementia drugs, and type of residence. All statistical analyses were made using IBM SPSS Statistics (Armonk, NY, USA) version 26.

3 Results

The mean age (± standard deviation) in the study population was 81.5 (6.4) years, with a range between 68 and 105 years at the diagnosis date of major neurocognitive disorders and the majority, 59.2% (n = 39,803), were female. Almost half of those with a reported MMSE score at registration in the

Table 1 List of drugs, identified according to the ATC code specified below, and included in each of the PIM classes according to the Swedish quality indicators for good drug therapy among the elderly [3]

PIM/PIM class	ATC code
Long-acting benzodiazepines	
Diazepam	N05BA01
Nitrazepam	N05CD02
Flunitrazepam	N05CD03
Anticholinergic drugs	
Gastrointestinal agents, anticholinergic	
Glycopyrronium	A03AB
Atropine, hyoscyamine	A03BA
Butylscopolamine, methylscopolamine	A03BB
Anticholinergic antiemetics	
Scopolamine	A04AD
Antiarrhythmics class 1A	
Disopyramide	C01BA
Urinary antispasmodics (excluding G04BD12)	
Oxybutynin, tolterodine, solifenacin, darifenacin, fesoterodine	G04BD excluding G04BD12
Muscle-relaxing agents, other centrally acting	
Orphenadrine	M03BC01
Orphenadrine, combinations	M03BC51
Opiates and opioids in combination with antispasmodics	
Morphine, ketobemidone and hydromorphone combined with antispasmodics	N02AG
Anticholinergic anti-Parkinsonian drugs	
Trihexyphenidyl, biperiden	N04A
Antipsychotic drugs	
Levomepromazine	N05AA02
Prochlorperazine	N05AB04
Chlorprothixene	N05AF03
Clozapine	N05AH02
Anxiolytics	
Hydroxyzine	N05BB01
Antidepressants, non-selective monoamine reuptake inhibitors	
Clomipramine, amitriptyline, nortriptyline, maprotiline	N06AA
Antihistamines	
Dimenhydrinate	R06AA02
Clemastine	R06AA04
Dexchlorpheniramine, chlorphenamine	R06AB
Alimemazine, promethazine, tiethylperazine	R06AD
Meklozine	R06AE05
Cyproheptadine	R06AX02
Tramadol	N02AX02
Propiomazine	N05CM06
Codeine	N02AJ06
	N02AJ09
	R05DA04
Glibenclamide	A10BB01
NSAIDs (COX inhibitors)	M01A excluding M01AX05
Antipsychotic drugs	N05A excluding N05AN

ATC Anatomical Therapeutic Chemical, *COX* cyclooxygenase, *NSAIDs* non-steroidal anti-inflammatory drugs, *PIM* potentially inappropriate medication

Time periods

Diagnosis date, t = 0

t (months)

	-36	-30	-24	-18	-12	-6	0	6	12	18	24	30	36
People alive (n):							67,226	64,834	61,932	59,073	56,051	52,998	50,085
People alive and with complete data collection (n):							67,226	61,877	55,216	49,107	42,519	36,576	30,497

Fig. 2 Number of people alive and with complete data collection at the diagnosis date and within each 6-month interval post-diagnosis of major neurocognitive disorders

SveDem, 49.1% (*n* = 33,029), had mild cognitive impairment at diagnosis and the mean MMSE score (± standard deviation) was 20.7 (5.0). The most common major neurocognitive disorder was late-onset AD, which was registered for 28.7% (*n* = 19,303) of individuals. Moreover, the majority of the study population lived at home, 88.9% (*n* = 59,790), and lived together with a spouse or a partner, 47.0% (*n* = 31,625). Basic characteristics for the study population are presented in Table 2. Table 3 presents the results from the simple and multiple regression analyses investigating factors associated with PIM use at the time of diagnosis and the following 6 months. In the multiple regression analysis, it was found that PIM use was significantly higher among women (aOR 1.14; 95% CI 1.09–1.18) and among those living in nursing homes (aOR 1.77; 95% CI 1.66–1.90). Moreover, PIM use decreased with increasing age (aOR 0.98; 95% CI 0.97–0.98) and was significantly lower among people using anti-dementia drugs (aOR 0.84; 95% CI 0.80–0.87).

Figure 3a–i show the unadjusted proportions of people using PIMs within each 6-month period, 3 years pre-diagnosis until 3 years post-diagnosis. The proportions of PIM users decreased for the PIMs, PIM classes, and PIM total shown in Figs. 3a, c–g, and 3i, respectively. However, based on the unadjusted proportions shown in Fig. 3b, the proportion of people using anticholinergic drugs increased slightly, from 9.2% to 9.4%, within the year prior to diagnosis. Moreover, antipsychotic drugs increased both pre- and post-diagnosis, Fig. 3h. This also applies for the proportion of people using anti-dementia drugs, which is shown in Fig. 3j. When excluding those who died post-diagnosis and those without complete data from the SPDR, it was found that the unadjusted proportions of PIM users (data not shown) only differed to a small extent when compared with the proportions presented in Fig. 3.

The results from the GEE and EMM analyses are presented in Table 4. The adjusted proportions of people using antipsychotic drugs were significantly higher post-diagnosis, 10.6%, compared with the period before, 3.1% (aOR 3.71; 95% CI 3.59–3.83). For all other PIMs, PIM classes, and PIM total, the adjusted proportion of PIM users was significantly lower post-diagnosis compared with the period pre-diagnosis of major neurocognitive disorders

(long-acting benzodiazepines: 1.6% vs 2.5%; aOR 0.64; 95% CI 0.62–0.67, anticholinergics: 7.2% vs 8.9%; aOR 0.80; 95% CI 0.78–0.82, tramadol: 1.1% vs 3.0%; aOR 0.37; 95% CI 0.35–0.38, propiomazine: 1.9% vs 3.0%; aOR 0.64; 95% CI 0.62–0.67, codeine: 1.9% vs 3.0%; aOR 0.63; 95% CI 0.61–0.66, glibenclamide: 0.7% vs 1.4%; aOR 0.51; 95% CI 0.48–0.54, NSAIDs: 3.6% vs 7.0%; aOR 0.50; 95% CI 0.48–0.51 and PIM total: 23.9% vs 25.8%; aOR 0.90; 95% CI 0.89–0.92). The adjusted proportion of people using anti-dementia drugs was significantly higher post-diagnosis, 52.6%, when compared with the time period pre-diagnosis, 3.5% (aOR 30.13; 95% CI 29.19–31.10).

Moreover, it was found that the use of at least one PIM regardless of classification, and the majority of PIMs and PIM classes were significantly more common among women than among men (long-acting benzodiazepines: 2.4% vs 1.6%; aOR 1.54; 95% CI 1.41–1.68, anticholinergics: 8.8% vs 7.2%; aOR 1.24; 95% CI 1.19–1.29, tramadol: 2.2% vs 1.5%; aOR 1.44; 95% CI 1.34–1.54, propiomazine: 2.7% vs 2.2%; aOR 1.26; 95% CI 1.16–1.36, codeine: 2.8% vs 2.1%; aOR 1.29; 95% CI 1.22–1.37, NSAIDs: 5.7% vs 4.5%; aOR 1.27; 95% CI 1.22–1.31, PIM total: 26.7% vs 23.0%; aOR 1.22; 95% CI 1.19–1.25). The use of anti-dementia drugs was also significantly more common among women than among men (17.6% vs 16.0%; aOR 1.12; 95% CI 1.08–1.17).

Table 4 shows that the adjusted proportions of people using anticholinergic drugs, tramadol, propiomazine, NSAIDs, PIM total, and anti-dementia drugs decreased continuously at higher ages and were significantly lower among those aged 78–87 years and 88 years or older, compared with those aged 68–77 years at the time of diagnosis. It was also found that the use of codeine was significantly lower among people aged 88 years or older compared with those aged 68–77 years. However, long-acting benzodiazepines and antipsychotic drug use were significantly higher among the oldest age group compared with the youngest group (2.4% vs 1.8%; aOR 1.35; 95% CI 1.19–1.52 and 6.3% vs 5.7%; aOR 1.11; 95% CI 1.03–1.20, respectively).

Finally, the GEE and EMM analyses found that the adjusted proportions of people using long-acting benzodiazepines and at least one PIM regardless of classification continuously decreased and were significantly lower for

Table 2 Basic characteristics of the study sample ($n = 67{,}226$) at baseline registration

Characteristics	n (%)
Sex	
Female	39,803 (59.2)
Male	27,423 (40.8)
Age at diagnosis date (years), mean ± SD, range	81.5 ± 6.4, 68–105
MMSE[a], mean ± SD	20.7 ± 5.0
Degree of cognitive impairment at registration[a]	
No impairment[b]	20,265 (30.1)
Mild impairment[c]	33,029 (49.1)
Moderate impairment[d]	8484 (12.6)
Severe impairment[e]	860 (1.3)
Type of major neurocognitive disorder	
AD, early onset	672 (1.0)
AD, late onset	19,303 (28.7)
AD and VD	13,117 (19.5)
VD	13,183 (19.6)
LBD	1383 (2.1)
FTD	726 (1.1)
PDD	968 (1.4)
Dementia UNS	16,345 (24.3)
Other	1529 (2.3)
Diagnosis year	
2008	1431 (2.1)
2009	4462 (6.6)
2010	5689 (8.5)
2011	7006 (10.4)
2012	8209 (12.2)
2013	8357 (12.4)
2014	8847 (13.2)
2015	8296 (12.3)
2016	7928 (11.8)
2017	7001 (10.4)
Type of residence[f]	
Living at home	59,790 (88.9)
Nursing home	7216 (10.7)
Unknown	219 (0.3)
Living status[g]	
Lives alone	30,146 (44,8)
Lives with spouse or partner	31,625 (47.0)
Unknown	707 (1.1)

AD Alzheimer's disease, *FTD* frontotemporal dementia, *LBD* Lewy body dementia, *MMSE* Mini-Mental State Examination, *PDD* Parkinson disease dementia, *SD* standard deviation, *UNS* unspecified, *VD* vascular dementia

[a]$n = 62{,}638$ because 2762 not tested and 1826 not available for testing

[b]MMSE score 24–30

[c]MMSE score 16–23

[d]MMSE score 8–15

[e]MMSE score 0–7

[f]$n = 67{,}225$ because 1 missing

[g]$n = 62{,}478$ because 4748 missing

those with diagnosis years 2010–11, 2012–13, 2014–15, and 2017–18, respectively, compared with those with diagnosis years 2008–9 (data shown in Table 4). Moreover, the adjusted proportions of people using propiomazine and NSAIDs were significantly lower and decreased continuously for those with diagnosis years 2012–13, 2014–15, and 2016–17 compared with those diagnosed in 2008–9. Tramadol, glibenclamide, anticholinergic, and antipsychotic drug use were also significantly lower among people diagnosed in years 2014–15 and 2016–17 compared with those diagnosed 2008–9.

4 Discussion

Overall, we found that the use of the majority of PIMs and PIM classes in the present study declined among the study population, and the proportion of users was significantly lower post-diagnosis compared with the period before. The decreasing proportions might indicate an awareness of the ADRs associated with PIMs and consequently a cautious approach when prescribing these types of drugs among older people. Increasing contact with prescribers at the time of, and subsequent to, diagnosis of major neurocognitive disorders, may result in more regular medication reviews. This may, however, also lead to the capture of more symptoms, which accordingly could lead to increased drug use. The decreasing proportions of PIM users among the present study population is opposite to a previous study where the proportions of PIM users increased from nearly two-thirds at diagnosis, to 75.2% 2 years post-diagnosis of major neurocognitive disorders [25]. The result in the present study is also in contrast to an American study where a continuous increase of PIM use was found 1-year pre-diagnosis until 1-year post-diagnosis [26]. The study populations in these studies were, however, smaller and Beers criteria were used to identify PIMs, which could explain the conflicting results. Moreover, the proportion of people using at least one PIM regardless of classification was lower post-diagnosis in the present study compared with the proportion reported in earlier studies, with a range between 27.0 and 64.4% among people with major neurocognitive disorders [2, 15, 20–23]. The difference found between the result in the present study and the other studies may be due to the use of other guidelines, e.g. the EU(7)-PIM list and STOPP indicators, which include a higher number of medications compared with the Swedish guidelines, or because different parts from the Swedish guidelines were utilised. Moreover, different drug markets in varying countries or other inclusion criteria may have contributed to the lower prevalence found in the present study. However, the decrease was small when comparing the proportion of PIM users post-diagnosis with the proportion pre-diagnosis. This is partly explained

Table 3 Simple and multiple logistic regression analyses investigating the association between different factors at baseline registration and the usage of at least one PIM 6 months following diagnosis of major neurocognitive disorders

	PIM use (n = 15,225)	No PIM use (n = 46,652)	Simple OR (95% CI)	Multiple OR (95% CI)
Sex[a], n (%)				
Male	5906 (38.8)	19,096 (40.9)	Ref	Ref
Female	9319 (61.2)	27,556 (59.1)	1.09 (1.05–1.14)	1.14 (1.09–1.18)
Age[a], years, mean ± SD	80.9 ± 6.4	81.5 ± 6.4	0.99 (0.98–0.99)	0.98 (0.97–0.98)
MMSE[a,b], mean ± SD	20.7 ± 5.1	20.9 ± 4.9	0.99 (0.99–1.00)	1.00 (0.99–1.00)
Anti-dementia drug				
Without, n (%)	6673 (43.8)	18,194 (39.0)	Ref	Ref
With, n (%)	8552 (56.2)	28,458 (61.0)	0.82 (0.79–0.85)	0.84 (0.80–0.87)
Type of residence[a,c], n (%)				
Living at home	12,863 (84.8)	42,434 (91.3)	Ref	Ref
Nursing home	2311 (15.2)	4064 (8.7)	1.88 (1.78–1.98)	1.77 (1.66–1.90)

CI confidence interval, *MMSE* Mini-Mental State Examination, *OR* odds ratio, *PIM* potentially inappropriate medication, *Ref* reference, *SD* standard deviation, *SPDR* Swedish Prescribed Drug Register

[a]n = 2392 who died during the 6-month period following diagnosis of major neurocognitive disorders, n = 2957 with diagnosis date between 1 July, 2017 and 31 December, 2017 and a lack of data from the SPDR during the 6-month period following diagnosis. Total study sample in analysis, n = 61,877

[b]n = 4131 with missing MMSE

[c]n = 204 with unknown residency and n = 1 with missing values
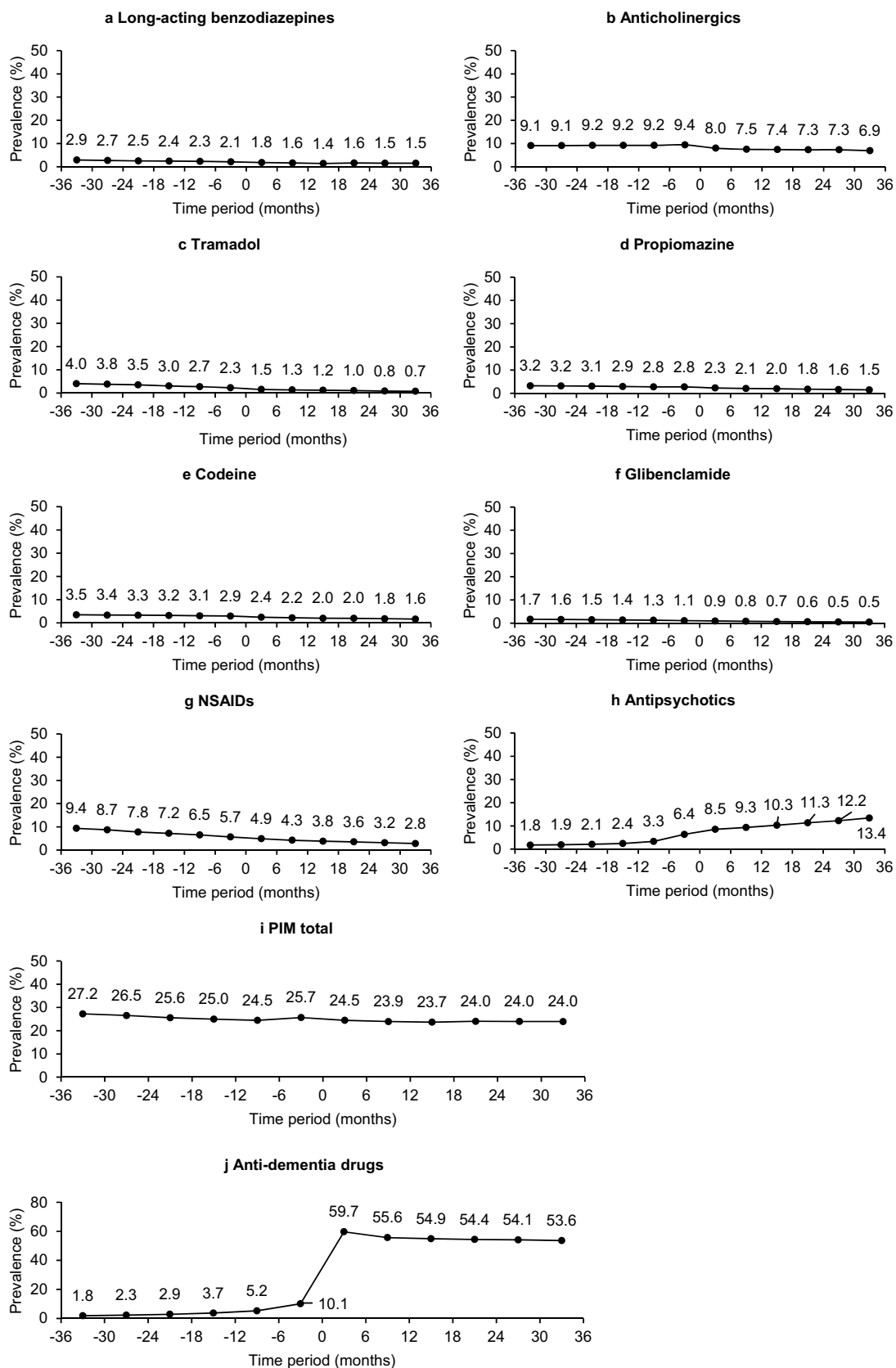
by the increasing proportion of people using antipsychotic drugs post-diagnosis.

The proportions of people using antipsychotic drugs, which almost doubled within the year preceding diagnosis, is an alarming result in the present study. The proportion then continued to increase, which is worrying because of the serious side effects associated with this type of drug treatment [13, 14]. Moreover, the longitudinal analysis found that antipsychotic drug use was significantly more common among people aged 88 years or older. These results might reflect the occurrence of BPSD that is associated with the progression of major neurocognitive disorders [36], and it has been found that BPSD, e.g. hallucinations and aggression, may arise pre-diagnosis [37–40], which might explain the increase in antipsychotic drug use prior to diagnosis found in the present study. The increasing trend of antipsychotic drug use pre- and post-diagnosis is found in other studies as well [27, 28]. The proportion of antipsychotic drug users 1-year post-diagnosis is also in line with a study conducted in Norway [37], but lower compared with other studies, which found proportions between 12.5 and 27%, depending on the study setting [14, 27, 41]. Nonetheless, the proportion of people using antipsychotic drugs was significantly higher post-diagnosis compared with the pre-diagnosis period. This is concerning and should be highlighted given the severe ADRs such as fall accidents, cerebrovascular adverse events such as stroke, and the increased mortality rate that antipsychotic drug use may lead to among older people with major neurocognitive disorders [13–16].

The proportions of people using anticholinergic drugs post-diagnosis also contributed to the high proportion of people using at least one PIM regardless of the classification post-diagnosis found among the study population. Even if the proportions continuously decreased post-diagnosis, the decrease was small and the proportions were higher compared with other PIMs or PIM classes identified in the present study. Additionally, the proportion of anticholinergic drug users increased pre-diagnosis, which could be linked with increased contact with healthcare because of experienced symptoms. Consequently, clinicians are able to note a constellation of symptoms, which may be followed by an increase in PIM use. These trends warrant concern because of the anticholinergic side effects that are particularly harmful among people with major neurocognitive disorders.

The statistical analysis found that the use of anti-dementia drugs was significantly higher post-diagnosis compared with the period before, which is in accordance with our expectations. The proportion of people using anti-dementia drugs 1-year post-diagnosis is in line with, but somewhat lower than another study [37]. The increase in anti-dementia drug use during the 6-month periods pre- and post-diagnosis of major neurocognitive disorders is, however, more than double compared with a German study [42]. The declining proportion of people using anti-dementia drugs 12 months post-diagnosis might reflect de-prescribing because of side effects and/or no initial effect. The multiple logistic regression analyses found that people using anti-dementia drugs had a lower odds of using PIMs at the time of diagnosis.

a Long-acting benzodiazepines

2.9 2.7 2.5 2.4 2.3 2.1 1.8 1.6 1.4 1.6 1.5 1.5

b Anticholinergics

9.1 9.1 9.2 9.2 9.2 9.4 8.0 7.5 7.4 7.3 7.3 6.9

c Tramadol

4.0 3.8 3.5 3.0 2.7 2.3 1.5 1.3 1.2 1.0 0.8 0.7

d Propiomazine

3.2 3.2 3.1 2.9 2.8 2.8 2.3 2.1 2.0 1.8 1.6 1.5

e Codeine

3.5 3.4 3.3 3.2 3.1 2.9 2.4 2.2 2.0 2.0 1.8 1.6

f Glibenclamide

1.7 1.6 1.5 1.4 1.3 1.1 0.9 0.8 0.7 0.6 0.5 0.5

g NSAIDs

9.4 8.7 7.8 7.2 6.5 5.7 4.9 4.3 3.8 3.6 3.2 2.8

h Antipsychotics

1.8 1.9 2.1 2.4 3.3 6.4 8.5 9.3 10.3 11.3 12.2 13.4

i PIM total

27.2 26.5 25.6 25.0 24.5 25.7 24.5 23.9 23.7 24.0 24.0 24.0

j Anti-dementia drugs

1.8 2.3 2.9 3.7 5.2 10.1 59.7 55.6 54.9 54.4 54.1 53.6

Fig. 3 Unadjusted proportions of people using at least one potentially inappropriate medication (PIM)/anti-dementia drug, at least once, within each 6-month period pre- and post-diagnosis date (*t* = 0) of major neurocognitive disorders. *NSAIDs* non-steroidal anti-inflammatory drugs

Table 4 Estimated marginal means and generalised estimating equation analyses investigating the association between different factors and the use of PIMs, PIM classes, PIM total and anti-dementia drugs, respectively, during the period pre- and post-diagnosis of major neurocognitive disorder among the study population, n = 67,226. Results are presented as adjusted proportions and aOR

PIM (group) %; (95% CI)	Long-acting benzodiazepines	Anticholinergic drugs	Tramadol	Propiomazine	Codeine	Glibenclamide	NSAIDs	Antipsychotic drugs	PIM total	Anti-dementia drugs
Time period										
Pre-diagnosis	2.5; Ref	8.9; Ref	3.0; Ref	3.0; Ref	3.0; Ref	1.4; Ref	7.0; Ref	3.1; Ref	25.8; Ref	3.5; Ref
Post-diagnosis	1.6; 0.64 (0.62–0.67)	7.2; 0.80 (0.78–0.82)	1.1; 0.37 (0.35–0.38)	1.9; 0.64 (0.62–0.67)	1.9; 0.63 (0.61–0.66)	0.7; 0.51 (0.48–0.54)	3.6; 0.50 (0.48–0.51)	10.6; 3.71 (3.59–3.83)	23.9; 0.90 (0.89–0.92)	52.6; 30.13 (29.19–31.10)
Sex										
Male	1.6; Ref	7.2; Ref	1.5; Ref	2.2; Ref	2.1; Ref	1.1; Ref	4.5; Ref	5.8; Ref	23.0; Ref	16.0; Ref
Female	2.4; 1.54 (1.41–1.68)	8.8; 1.24 (1.19–1.29)	2.2; 1.44 (1.34–1.54)	2.7; 1.26 (1.16–1.36)	2.8; 1.29 (1.22–1.37)	0.9; 0.81 (0.71–0.94)	5.7; 1.27 (1.22–1.31)	5.8; 0.99 (0.94–1.04)	26.7; 1.22 (1.19–1.25)	17.6; 1.12 (1.08–1.17)
Age, years										
68–77	1.8; Ref	9.3; Ref	2.1; Ref	2.7; Ref	2.6; Ref	0.9; Ref	6.8; Ref	5.7; Ref	27.3; Ref	25.8; Ref
78–87	1.9; 1.05 (0.95–1.16)	8.1; 0.86 (0.82–0.90)	1.8; 0.87 (0.81–0.94)	2.3; 0.86 (0.79–0.94)	2.5; 0.97 (0.91–1.03)	1.1; 1.26 (1.05–1.50)	5.3; 0.77 (0.74–0.80)	5.4; 0.94 (0.88–0.99)	24.7; 0.87 (0.85–0.90)	18.7; 0.66 (0.63–0.69)
≥ 88	2.4; 1.35 (1.19–1.52)	6.8; 0.70 (0.66–0.75)	1.5; 0.72 (0.65–0.80)	2.2; 0.81 (0.72–0.91)	2.2; 0.82 (0.75–0.89)	1.0; 1.15 (0.92–1.44)	3.6; 0.50 (0.48–0.53)	6.3; 1.11 (1.03–1.20)	22.6; 0.78 (0.75–0.81)	9.3; 0.29 (0.28–0.31)
Year of diagnosis										
2008–9	2.8; Ref	8.4; Ref	2.2; Ref	3.2; Ref	2.4; Ref	1.2; Ref	6.0; Ref	6.4; Ref	29.2; Ref	16.5; Ref
2010–11	2.5; 0.77 (0.67–0.89)	8.6; 1.02 (0.95–1.10)	2.3; 1.01 (0.90–1.14)	2.8; 0.87 (0.76–1.00)	2.4; 0.94 (0.89–1.11)	1.5; 1.13 (0.85–1.51)	5.9; 0.99 (0.92–1.06)	6.5; 0.99 (0.90–1.10)	28.1; 0.95 (0.90–0.99)	15.0; 0.81 (0.74–0.87)
2012–13	2.1; 0.63 (0.54–0.72)	8.1; 0.96 (0.89–1.03)	2.3; 1.04 (0.93–1.17)	2.5; 0.80 (0.70–0.91)	2.7; 1.10 (0.99–1.23)	1.2; 0.90 (0.68–1.20)	5.1; 0.85 (0.80–0.91)	6.1; 0.93 (0.85–1.03)	25.2; 0.82 (0.78–0.85)	15.3; 0.82 (0.76–0.89)
2014–15	1.6; 0.48 (0.42–0.56)	7.6; 0.89 (0.83–0.96)	1.7; 0.74 (0.66–0.84)	2.2; 0.68 (0.59–0.78)	2.5; 1.04 (0.94–1.16)	0.8; 0.60 (0.45–0.81)	4.7; 0.78 (0.73–0.83)	5.6; 0.85 (0.77–0.93)	22.4; 0.70 (0.67–0.73)	18.2; 1.01 (0.94–1.09)
2016–17	1.3; 0.39 (0.33–0.46)	7.3; 0.86 (0.79–0.93)	1.0; 0.43 (0.37–0.49)	1.7; 0.54 (0.47–0.62)	2.2; 0.92 (0.82–1.03)	0.5; 0.39 (0.28–0.53)	3.9; 0.65 (0.60–0.69)	4.6; 0.69 (0.63–0.77)	19.8; 0.60 (0.57–0.63)	19.1; 1.07 (0.99–1.16)

aOR adjusted odds ratio, CI confidence interval, NSAIDs non-steroidal anti-inflammatory drugs, PIM potentially inappropriate medication, Ref reference

This result is supported by a previously mentioned study, which found an association between a lower odds of psychotropic drug use when anti-dementia drugs were used [19]. The declining trend in anti-dementia drug use post-diagnosis is therefore worth highlighting.

An association was found between living in nursing homes and using PIMs in the multiple logistic regression analysis. Multi-morbidity and high numbers of medications are common in nursing homes [43] and it has been found that PIM use is associated with a higher number of medications [44]. This might explain the findings in the present study. Moreover, PIM use was more common among women at the time of diagnosis and the following 6 months. This trend was found in the longitudinal model as well, except for glibenclamide and antipsychotic drug use.

Finally, higher age was significantly associated with lower PIM use according to the multiple logistic regression and longitudinal analyses. This trend was found for all PIMs and PIM classes except for long-acting benzodiazepines and antipsychotic drug use. The association between lower PIM usage and a higher age was opposite to the results in a previously mentioned study [45]. Overall, PIM use decreased over the years and PIM use was less common among people with a diagnosis date between 2014 and 2017 compared with those with a diagnosis in 2008 or 2009. A previous study found that PIM use had decreased in 2013 compared with 2007 [34]. The trend of decreasing PIM use over the years and declining PIM use at higher ages is positive and might imply an increasing awareness of the inappropriateness of PIMs among older people.

The following limitations should be considered when interpreting these results. Because of the large study sample, there is a possibility that small differences become significant [46]. We do not know if the medicines were actually used, neither did we have information about the indication for which the PIMs were prescribed, nor the length of treatment or the prescribed doses. Some medicines may therefore be appropriate to use according to the patient's clinical condition. Moreover, Swedish guidelines were used to identify PIMs which, compared to international criteria, include a smaller number of PIMs. Additionally, some of the substances included in the Swedish quality indicators are deregistered from the Swedish drug market, e.g. prochlorperazine, which is currently utilised against nausea in special cases. Moreover, not all people with major neurocognitive disorders seek medical advice. Consequently, the approximated completeness rate for SveDem ranged between 15 and 41% in 2008–17 [29]. Finally, the use of SveDem was more common among specialised memory clinics compared with community healthcare when the registry was set up in 2007. Selection might therefore have influenced the result.

The strengths of the present study that should be highlighted include the large study population, as data are nationally representative, including all Swedish counties, and comprise information about people registered in SveDem over 9.5 years. Additionally, those who died or had missing data from the SPDR within 3 years post-diagnosis were included. Moreover, SveDem is validated through different methods to ensure good data quality [29].

5 Conclusions

Overall, the proportions of people using PIMs were significantly lower post-diagnosis of major neurocognitive disorders. This indicates that PIM use should be noticed and reviewed among all older people. The small decrease in proportions of anticholinergic drug users and the increasing proportions of people using antipsychotic drugs post-diagnosis are of special concern because of the ADRs associated with these types of PIMs. Consequently, anticholinergic and antipsychotic drug treatment needs to be identified and regularly questioned to prevent unnecessary and serious ADRs among a vulnerable group of people.

Declarations

Conflicts of Interest/Competing Interests Hugo Lövheim is a member of the Swedish Registry for Cognitive/Dementia Disorders, SveDem's Steering Committee. Eva Sönnerstam, Maria Gustafsson and Maria Sjölander have no conflicts of interest that are directly relevant to the contents of this study.

Ethics Approval This study was approved by the Regional Ethical Review Board in Umeå (registration number 2017/256-31) and conducted in accordance with the ethical standards stated by the Declaration of Helsinki.

Consent to Participate The participants are voluntarily registered in SveDem after being informed that collected data will be used for research purposes, including group-level analyses, as well as quality improvement activities, and that they have the right to deny registration.

Consent for Publication Not applicable.

References

1. Eshetie TC, Nguyen TA, Gillam MH, Kalisch Ellett LM. A narrative review of problems with medicines used in people with dementia. Expert Opin Drug Saf. 2018;17(8):825–36. https://doi.org/10.1080/14740338.2018.1497156.

2. Sönnerstam E, Sjölander M, Gustafsson M. An evaluation of the prevalence of potentially inappropriate medications in older people with cognitive impairment living in Northern Sweden using the EU(7)-PIM list. Eur J Clin Pharmacol. 2017;73(6):735–42. https://doi.org/10.1007/s00228-017-2218-2.

3. The National Board of Health and Welfare. Indikatorer för god läkemedelsterapi hos äldre 2017 [Indicators of good drug therapy in the elderly 2017]. Available from: www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/ovrigt/2017-6-7.pdf. Accessed 11 Jun 2021.

4. American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2019 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2019;67(4):674–94. https://doi.org/10.1111/jgs.15767.

5. Renom-Guiteras A, Meyer G, Thürmann PA. The EU(7)-PIM list: a list of potentially inappropriate medications for older people consented by experts from seven European countries. Eur J Clin Pharmacol. 2015;71(7):861–75. https://doi.org/10.1007/s00228-015-1860-9.

6. Hukins D, Macleod U, Boland JW. Identifying potentially inappropriate prescribing in older people with dementia: a systematic review. Eur J Clin Pharmacol. 2019;75(4):467–81. https://doi.org/10.1007/s00228-018-02612-x.

7. Park HY, Park JW, Song HJ, Sohn HS, Kwon JW. The association between polypharmacy and dementia: a nested case-control study based on a 12-year longitudinal cohort database in South Korea.

8. PLoS ONE. 2017;12(1): e0169463. https://doi.org/10.1371/journal.pone.0169463.

8. Davies EA, O'Mahony MS. Adverse drug reactions in special populations: the elderly. Br J Clin Pharmacol. 2015;80(4):796–807. https://doi.org/10.1111/bcp.12596.

9. Picton JD, Marino AB, Nealy KL. Benzodiazepine use and cognitive decline in the elderly. Am J Health Syst Pharm. 2018;75(1):e6-12. https://doi.org/10.2146/ajhp160381.

10. Langman MJ, Weil J, Wainwright P, Lawson DH, Rawlins MD, Logan RF, et al. Risks of bleeding peptic ulcer associated with individual non-steroidal anti-inflammatory drugs. Lancet. 1994;343(8905):1075–8. https://doi.org/10.1016/s0140-6736(94)90185-6.

11. Ames D, O'Brien JT, Burns A. Dementia. 5th ed. New York: CRC Press Taylor & Francis Group; 2017. p. 915.

12. Mehta D, Short J, Hilmer S, Nicolazzo J. Drug access to the central nervous system in Alzheimer's disease: preclinical and clinical insights. Pharm Res. 2015;32(3):819–39. https://doi.org/10.1007/s11095-014-1522-0.

13. Gill SS, Bronskill SE, Normand SL, Anderson GM, Sykora K, Lam K, et al. Antipsychotic drug use and mortality in older adults with dementia. Ann Intern Med. 2007;146(11):775–86. https://doi.org/10.7326/0003-4819-146-11-200706050-00006.

14. Kolanowski A, Fick D, Waller JL, Ahern F. Outcomes of antipsychotic drug use in community-dwelling elders with dementia. Arch Psychiatr Nurs. 2006;20(5):217–25. https://doi.org/10.1016/j.apnu.2006.04.004.

15. Renom-Guiteras A, Thürmann PA, Miralles R, Klaaßen-Mielke R, Thiem U, Stephan A, et al. Potentially inappropriate medication among people with dementia in eight European countries. Age Ageing. 2018;47(1):68–74. https://doi.org/10.1093/ageing/afx147.

16. van Iersel MB, Zuidema SU, Koopmans RT, Verhey FR, Olde Rikkert MG. Antipsychotics for behavioural and psychological problems in elderly people with dementia: a systematic review of adverse events. Drugs Aging. 2005;22(10):845–58. https://doi.org/10.2165/00002512-200522100-00004.

17. Lövheim H, Sandman PO, Kallin K, Karlsson S, Gustafson Y. Relationship between antipsychotic drug use and behavioral and psychological symptoms of dementia in old people with cognitive impairment living in geriatric care. Int Psychogeriatr. 2006;18(4):713–26. https://doi.org/10.1017/S1041610206003930.

18. Cummings J, Lai TJ, Hemrungrojn S, Mohandas E, Yun Kim S, Nair G, et al. Role of donepezil in the management of neuropsychiatric symptoms in Alzheimer's disease and dementia with Lewy bodies. CNS Neurosci Ther. 2016;22(3):159–66. https://doi.org/10.1111/cns.12484.

19. Suzuki Y, Sakakibara M, Shiraishi N, Komiya H, Akishita M, Kuzuya M. Use of anti-dementia drugs reduces the risk of potentially inappropriate medications: a secondary analysis of a nationwide survey of prescribing pharmacies. Dement Geriatr Cogn Disord. 2020;49(5):526–32. https://doi.org/10.1159/000512043.

20. Sköldunger A, Fastbom J, Wimo A, Fratiglioni L, Johnell K. Impact of inappropriate drug use on hospitalizations, mortality, and costs in older persons and persons with dementia: findings from the SNAC Study. Drugs Aging. 2015;32(8):671–8. https://doi.org/10.1007/s40266-015-0287-4.

21. Barry HE, Cooper JA, Ryan C, Passmore AP, Robinson AL, Molloy GJ, et al. Potentially inappropriate prescribing among people with dementia in primary care: a retrospective cross-sectional study using the enhanced prescribing database. J Alzheimers Dis. 2016;52(4):1503–13. https://doi.org/10.3233/JAD-151177.

22. Parsons C, Johnston S, Mathie E, Baron N, Machen I, Amador S, et al. Potentially inappropriate prescribing in older people with dementia in care homes: a retrospective analysis. Drugs Aging. 2012;29(2):143–55. https://doi.org/10.2165/11598560-000000000-00000.

23. Thorpe JM, Thorpe CT, Kennelty KA, Gellad WF, Schulz R. The impact of family caregivers on potentially inappropriate medication use in noninstitutionalized older adults with dementia. Am J Geriatr Pharmacother. 2012;10(4):230–41. https://doi.org/10.1016/j.amjopharm.2012.05.001.

24. Stahl SM. Stahl's essential psychopharmacology neuroscientific basis and practical applications. 4th ed. Cambridge: Cambridge University Press; 2013. p. 608.

25. Ramsey CM, Gnjidic D, Agogo GO, Allore H, Moga D. Longitudinal patterns of potentially inappropriate medication use following incident dementia diagnosis. Alzheimers Dement (N Y). 2018;4:1–10. https://doi.org/10.1016/j.trci.2017.10.008.

26. Gnjidic D, Agogo GO, Ramsey CM, Moga DC, Allore H. The impact of dementia diagnosis on patterns of potentially inappropriate medication use among older adults. J Gerontol A Biol Sci Med Sci. 2018;73(10):1410–7. https://doi.org/10.1093/gerona/gly078.

27. Martinez C, Jones RW, Rietbrock S. Trends in the prevalence of antipsychotic drug use among patients with Alzheimer's disease and other dementias including those treated with antidementia drugs in the community in the UK: a cohort study. BMJ Open. 2013. https://doi.org/10.1136/bmjopen-2012-002080.

28. Joling KJ, Koppel MT, van Hout HPJ, Onwuteaka-Philipsen BD, Francke AL, Verheij RA, et al. Psychotropic drug prescription rates in primary care for people with dementia from recorded diagnosis onwards. Int J Geriatr Psychiatry. 2021;36(3):443–51. https://doi.org/10.1002/gps.5442.

29. Svenska registret för kognitiva sjukdomar/demenssjukdomar, SveDem [Swedish Registry for Cognitive/Dementia Disorders]. www.ucr.uu.se/svedem/. Accessed 26 Mar 2021.

30. Wettermark B, Hammar N, Fored CM, Leimanis A, Otterblad Olausson P, et al. The new Swedish Prescribed Drug Register: opportunities for pharmacoepidemiological research and experience from the first six months. Pharmacoepidemiol Drug Saf. 2007;16(7):726–35. https://doi.org/10.1002/pds.1294.

31. The National Board of Health and Welfare. Dödsorsaksregistret [The Cause of Death Register]. www.socialstyrelsen.se/statistikoch-data/register/alla-register/dodsorsaksregistret/. Accessed 26 Mar 2021.

32. Hamilton H, Gallagher P, Ryan C, Byrne S, O'Mahony D. Potentially inappropriate medications defined by STOPP criteria and the risk of adverse drug events in older hospitalized patients. Arch Intern Med. 2011;171(11):1013–9. https://doi.org/10.1001/archinternmed.2011.215.

33. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age Ageing. 2015;44(2):213–8. https://doi.org/10.1093/ageing/afu145.

34. Gustafsson M, Sandman PO, Karlsson S, Isaksson U, Schneede J, Sjölander M, et al. Reduction in the use of potentially inappropriate drugs among old people living in geriatric care units between 2007 and 2013. Eur J Clin Pharmacol. 2015;71(4):507–15. https://doi.org/10.1007/s00228-015-1825-z.

35. Sönnerstam E, Gustafsson M, Lövheim H. Potentially inappropriate medications in relation to length of nursing home stay among older adults. BMC Geriatr. 2022;22(1):70. https://doi.org/10.1186/s12877-021-02639-3.

36. Lövheim H, Sandman PO, Karlsson S, Gustafson Y. Behavioral and psychological symptoms of dementia in relation to level of cognitive impairment. Int Psychogeriatr. 2008;20(4):777–89. https://doi.org/10.1017/S1041610208006777.

37. Vik-Mo AO, Giil LM, Borda MG, Ballard C, Aarsland D. The individual course of neuropsychiatric symptoms in people with Alzheimer's and Lewy body dementia: 12-year longitudinal cohort study. Br J Psychiatry. 2020;216(1):43–8. https://doi.org/10.1192/bjp.2019.195.

38. Vik-Mo AO, Giil LM, Ballard C, Aarsland D. Course of neuropsychiatric symptoms in dementia: 5-year longitudinal study. Int J Geriatr Psychiatry. 2018;33(10):1361–9. https://doi.org/10.1002/gps.4933.

39. Steinberg M, Shao H, Zandi P, Lyketsos CG, Welsh-Bohmer KA, Norton MC, et al. Point and 5-year period prevalence of neuropsychiatric symptoms in dementia: the Cache County Study. Int J Geriatr Psychiatry. 2008;23(2):170–7. https://doi.org/10.1002/gps.1858.

40. Spalletta G, Musicco M, Padovani A, Rozzini L, Perri R, Fadda L, et al. Neuropsychiatric symptoms and syndromes in a large cohort of newly diagnosed, untreated patients with Alzheimer disease. Am J Geriatr Psychiatry. 2010;18(11):1026–35. https://doi.org/10.1097/JGP.0b013e3181d6b68d.

41. Taipale H, Koponen M, Tanskanen A, Tolppanen AM, Tiihonen J, Hartikainen S. High prevalence of psychotropic drug use among persons with and without Alzheimer's disease in Finnish nationwide cohort. Eur Neuropsychopharmacol. 2014;24(11):1729–37. https://doi.org/10.1016/j.euroneuro.2014.10.004.

42. van den Bussche H, Kaduszkiewicz H, Koller D, Eisele M, Steinmann S, Glaeske G, et al. Antidementia drug prescription sources and patterns after the diagnosis of dementia in Germany: results of a claims data-based 1-year follow-up. Int Clin Psychopharmacol. 2011;26(4):225–31. https://doi.org/10.1097/YIC.0b013e328344c600.

43. Jokanovic N, Tan EC, Dooley MJ, Kirkpatrick CM, Bell JS. Prevalence and factors associated with polypharmacy in longterm care facilities: a systematic review. J Am Med Dir Assoc. 2015;16(6):535.e1-12. https://doi.org/10.1016/j.jamda.2015.03.003.

44. Lau DT, Mercaldo ND, Harris AT, Trittschuh E, Shega J, Weintraub S. Polypharmacy and potentially inappropriate medication use among community-dwelling elders with dementia. Alzheimer Dis Assoc Disord. 2010;24(1):56–63. https://doi.org/10.1097/WAD.0b013e31819d6ec9.

45. Muhlack DC, Hoppe LK, Stock C, Haefeli WE, Brenner H, Schöttker B. The associations of geriatric syndromes and other patient characteristics with the current and future use of potentially inappropriate medications in a large cohort study. Eur J Clin Pharmacol. 2018;74(12):1633–44. https://doi.org/10.1007/s00228-018-2534-1.

46. Thygesen LC, Ersbøll AK. When the entire population is the sample: strengths and limitations in register-based epidemiology. Eur J Epidemiol. 2014;29(8):551–8. https://doi.org/10.1007/s10654-013-9873-0.