

# Declining Use of Potentially Inappropriate Medication in People with Dementia from 2000 to 2015: A Repeated Cross-Sectional Nationwide Register-Based Study

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## Abstract.

**Background:** Studies have shown declining use of potentially inappropriate medication (PIM), medication where risks associated with use outweigh potential benefits in older people. However, the trend in people with dementia remains unknown.

**Objective:** To test the hypothesis that the use of PIM has decreased in people with dementia in line with the declining use in the general older population.

**Methods:** Repeated cross-sectional register-based study of the entire Danish population aged  $\geq 65$  years (2000: N = 802,106; 2015: N = 1,056,476). PIM was identified using the Danish “Red-yellow-green list”. Changes in the use of PIM were examined by calculating the annual prevalence of filling prescriptions for at least one PIM in older people with and without dementia. Characteristics of the study population were examined annually including comorbidity.

**Results:** From 2000 to 2015, the prevalence of PIM use decreased from 54.7% to 43.5% in people with dementia and from 39.5% to 28.8% in people without dementia; the decrease was significant across all age groups and remained so in a sensitivity analysis where antipsychotics were removed. During the same period, comorbidity scores increased in people with and without dementia.

**Conclusion:** The declining use of PIM in people with dementia from 2000 to 2015 parallels the trend in the general older population. The use of PIM decreased despite increasing levels of comorbidity and was not solely attributable to the decreasing use of antipsychotics in people with dementia. However, PIM use remained more widespread in people with dementia who may be more vulnerable to the risks associated with PIM.

Keywords: Dementia, inappropriate prescribing, pharmacoepidemiology, potentially inappropriate medication, time trend

## INTRODUCTION

Potentially inappropriate prescribing, which is a major public health concern in older people, is

often defined as treatments where potential risks outweigh benefits [1, 2]. The concept has multiple aspects, including inappropriate drug choice, polypharmacy, drug-drug interactions, drug-disease interactions, or even treatment omissions [3]. Several explicit and implicit quality indicators have been developed to identify inappropriate prescribing. Explicit indicators are criteria-based; most focus mainly or solely on drugs that should be avoided in all

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44 older people—often termed potentially inappropriate  
45 medication (PIM). The most widely known criteria  
46 are the Beers Criteria, first published in 1991 in the  
47 United States and since then updated several times [4,  
48 5]. Due to the great variability in available drugs and  
49 prescribing practices, many countries have developed  
50 their own lists of PIM. In Denmark, the Institute for  
51 Rational Pharmacotherapy published its list of PIM  
52 in 2011 called the Red-yellow-green list [6].

53 The use of PIM has been associated with sev-  
54 eral adverse outcomes including increased risk of  
55 falls, fractures, hospitalizations, and mortality [7–9].  
56 Potentially inappropriate prescribing is of particular  
57 concern in people with dementia who may be more  
58 susceptible to the adverse effects associated with  
59 PIM, and in whom widespread polypharmacy, frailty,  
60 multimorbidity, and changing goals of care due to  
61 the progressive nature of dementia further complicate  
62 pharmacological management [10–12]. Additionally,  
63 cognitive decline can negatively influence adherence  
64 to treatment regimens and the ability to report adverse  
65 effects and make people with dementia more suscep-  
66 tible to the adverse effects of specific drugs, e.g.,  
67 anticholinergics [13]. In a Swedish study, 41% of  
68 acute hospitalizations of people with dementia were  
69 determined to be drug-related [14]. Nonetheless, PIM  
70 is widespread in people with dementia, with a preva-  
71 lence ranging from 14–64% in a recent review [15].  
72 In our previous study in Denmark, we found that 45%  
73 of people with dementia had filled at least one pre-  
74 scription for PIM in 2014 compared to 30% of people  
75 without dementia [16].

76 A review of existing literature revealed that the use  
77 of PIM in older people has been decreasing since the  
78 mid 1990s in the western world [17–23]. However,  
79 the time trend in people with dementia has not been  
80 investigated. The aim of this nationwide study was to  
81 investigate changes in the use of PIM in older people  
82 with dementia from 2000 to 2015. We hypothesized  
83 that the use of PIM had decreased in people with  
84 dementia in line with the documented decrease in the  
85 general older population.

## 86 METHODS

### 87 *Study design*

88 We conducted a repeated-measures cross-sectional  
89 study utilizing nationwide Danish registers to exam-  
90 ine changes in the use of PIM in people with and  
91 without dementia from 2000–2015. The study was  
92 approved by the Danish Data Protection Agency (ID

no.: 2007-58-0015/30-0667), Statistics Denmark, 93  
and the Danish Health and Medicines Authority (ID 94  
no.: 6-8011-907/1). According to Danish law, it is 95  
not required to obtain ethics committee approval for 96  
register-based studies. 97

### *Data*

98 All Danish residents are provided a unique 99  
personal identification number at birth or upon immi- 100  
gration. This facilitates individual-level linkage of 101  
data across nationwide registers including the Dan- 102  
ish National Patient Register, the Danish Psychiatric 103  
Central Research Register, and the Danish National 104  
Prescription Registry [24–27]. The National Patient 105  
Register contains information on admission and dis- 106  
charge dates as well as discharge diagnoses from 107  
all hospitalizations and invasive procedures since 108  
1978 and hospital-based outpatient clinics and emer- 109  
gency departments since 1995 [24]. The Psychiatric 110  
Central Research Register contains data on all psychi- 111  
atric inpatient admissions since 1969 and outpatient 112  
contacts since 1995. The Danish National Prescrip- 113  
tion Registry contains information on all dispensed 114  
prescription medication since 1995; including pre- 115  
scriptions to older people residing in nursing homes. 116  
The data on dispensed prescriptions include data on 117  
the type of drug according to the Anatomical Ther- 118  
apeutic Chemical (ATC) system as well as strength, 119  
amount, and date of dispensing [26]. 120

### *Study population*

121 The study population was defined annually on Janu- 122  
ary 1 from 2000 to 2015 (index date) and included 123  
all residents in Denmark aged  $\geq 65$  years. People with 124  
dementia were identified as individuals registered 125  
with a dementia diagnosis as an in- or outpatient (spe- 126  
cific diagnosis codes available in the Supplementary 127  
Material) and/or as individuals who had filled at least 128  
one prescription for anti-dementia medication (ATC: 129  
N06D) before the index date. Anti-dementia drugs 130  
are not approved, nor to our knowledge, prescribed 131  
for any other indication in Denmark. Individuals were 132  
excluded if they had been diagnosed with dementia 133  
and/or filled their first prescription for anti-dementia 134  
medication before age 60 as previous research has 135  
found early diagnoses to be unreliable in the regis- 136  
ters [28, 29]. Characteristics of the study population 137  
including age, sex, marital status, and comorbid- 138  
ity status were examined to facilitate comparisons 139  
between the groups and changes within the study 140

141 period. Comorbidity status was assessed using the  
142 Charlson Comorbidity Index, which was calculated  
143 without dementia as one of the items [30].

#### 144 *Potentially inappropriate medication (PIM)*

145 The Danish Red-yellow-green list has three cate-  
146 gories: the green category lists drugs where evidence  
147 regarding long-term effects is limited; the yellow cat-  
148 egory lists drugs where the indication and dosage  
149 should be reassessed regularly, i.e., to use with care;  
150 and lastly, the red category lists drugs that should  
151 be avoided in people aged 65 years or above unless  
152 under special circumstance [6]. In this study, the red  
153 and the yellow categories were examined; however,  
154 only the red category, which matches the general def-  
155 inition, was used to define PIM. Most drugs from the  
156 red and the yellow categories are included in sev-  
157 eral other criteria including the Beers Criteria [4].  
158 The red category contains 28 drugs and drug classes  
159 (for specific drugs, see Fig. 3). The yellow cate-  
160 gory contains 10 drugs or drug classes (included  
161 drugs available in the Supplementary Material).  
162 Both the red and yellow categories are divided into  
163 subgroups based on indication: digestive, cardiovas-  
164 cular, urological, analgesics, hypnotics/anxiolytics,  
165 antipsychotics, and antidepressants. Two drugs were  
166 excluded from our study as recommendations were  
167 dependent on dosage information (acetylsalicylic  
168 acid and a combination containing dipyridamole and  
169 acetylsalicylic acid).

170 The Danish red-yellow-green list was first pub-  
171 lished in 2011 and since updated in 2016, the original  
172 2011 edition was used in this study. The most sig-  
173 nificant changes in the 2016 edition were that all  
174 antipsychotics, all benzodiazepines and similar drugs  
175 (z-drugs), and all antidepressants were considered  
176 red, some of which were not included in the 2011  
177 edition or considered yellow [31].

#### 178 *Statistics*

179 To examine changes in the use of PIM from 2000  
180 to 2015 in people with and without dementia, we  
181 calculated the following measures annually: 1) The  
182 percentage of PIM users, defined as people filling at  
183 least one prescription for a PIM within a given cal-  
184 endar year, 2) the percentage of new PIM users in a  
185 given year, defined as filling a prescription for a sub-  
186 group of the red category for which the individual  
187 had not filled a prescription in the previous calendar  
188 year. New use was determined by subgroup and not

189 by specific drugs as this allowed substitution within  
190 groups without this being registered as the initiation  
191 of a new treatment, 3) the percentage of PIM users fill-  
192 ing prescriptions for multiple different PIM, defined  
193 as filling prescriptions for  $\geq 2$  different PIM within  
194 a given calendar year, and 4) utilization patterns per  
195 subgroup of the red and yellow categories, done by  
196 calculating the percentage who filled prescriptions  
197 for drugs from each subgroup of the red and yellow  
198 categories within a given calendar year.

199 The use of antipsychotics in the management  
200 of behavioral symptoms associated with dementia  
201 has decreased following national and international  
202 warnings on adverse events including increased mor-  
203 tality associated with such use [32–35]. In Denmark,  
204 the use of antipsychotics in people with dementia  
205 decreased from 31% to 20% from 2000 to 2012  
206 [36]. The red category of the Red-yellow-green list  
207 includes eight antipsychotics. Therefore, a sensitiv-  
208 ity analysis was conducted excluding antipsychotics  
209 from the analyses to discern whether a potential  
210 decline in the use of PIM was driven solely by the  
211 established decline in the use of antipsychotic medi-  
212 cation.

213 Logistic regression was used to compare the annual  
214 prevalence of filling one or more prescriptions for  
215 PIM in 2015, 2010, 2005, and 2000 (reference year).  
216 To obtain the independent observations necessary for  
217 the analyses, the population was divided into 5-year  
218 age groups (age 65–69, 70–74, 75–79, 80–84, 85–89,  
219 90–94, and 95–99), so that an individual would not  
220 be represented at more than one time point in the  
221 same group. Logistic regression was done separately  
222 for people with and without dementia. First, a crude  
223 logistic regression was conducted with the calen-  
224 dar year as the independent variable. Second, sex  
225 was included in a multivariable logistic regression as  
226 potential confounders. Third, as a sensitivity analy-  
227 sis, the Charlson Comorbidity Index was added to  
228 the multivariable analysis. Odds ratios (OR) were  
229 presented with 95% confidence intervals (CI). A *p*-  
230 value of  $< 0.5$  was considered statistically significant.  
231 The data analysis was performed using SAS statisti-  
232 cal software, version 9.4 (SAS Institute Inc., Cary,  
233 NC, USA).

## 234 **RESULTS**

### 235 *Characteristics of the study population*

236 On January 1, 2000, we identified 19,062 peo-  
237 ple  $\geq 65$  years with dementia (2.4%) and 781,056

Table 1  
Characteristics of the study population in 2000 and 2015 stratified by dementia status

	2000		2015	
	Dementia N = 19,062 (100 %)	No dementia N = 781,056 (100%)	Dementia N = 36,031 (100%)	No dementia N = 1,018,015 (100%)
Sex (female)	12,865 (67.5)	452,944 (58.0)	22,789 (63.3)	551,093 (54.1)
Married <sup>1</sup>	5,832 (30.6)	382,946 (49.8)	12,726 (35.3)	583,822 (57.7)
Age groups				
65–69	1,070 (5.6)	221,119 (28.3)	2,031 (5.6)	351,056 (34.5)
70–74	2,266 (11.9)	195,146 (25.0)	4,167 (11.6)	269,962 (26.5)
75–79	4,236 (22.2)	165,670 (21.2)	6,468 (18.0)	180,439 (17.7)
80–84	4,661 (24.5)	107,665 (13.8)	8,589 (23.8)	113,720 (11.2)
85–89	4,491 (23.6)	63,072 (8.1)	8,723 (24.2)	66,100 (6.5)
90–94	1,930 (10.1)	23,108 (3.0)	4,878 (13.5)	28,827 (2.8)
95–99	388 (2.0)	4,809 (0.6)	1,064 (3.0)	6,991 (0.7)
CCI score <sup>2</sup>				
0	8,632 (45.3)	484,636 (62.1)	11,931 (33.1)	512,375 (50.3)
1	4,929 (25.9)	137,353 (17.6)	8,451 (23.5)	183,425 (18.0)
2	2,875 (15.1)	94,073 (12.0)	6,415 (17.8)	159,420 (15.7)
≥3	2,626 (13.8)	64,994 (8.3)	9,234 (25.6)	162,795 (16.0)

CCI, Charlson Comorbidity Index. <sup>1</sup>data missing on civil status: 11,767 in 2000 and 6,245 in 2015.

<sup>2</sup>Calculated without dementia as one of the items. Numbers are given as n (%) and median (25–75% interquartile range), as appropriate.

without dementia (97.6%). In 2015, this had increased to 36,031 (3.4%) individuals with dementia and 1,018,015 individuals without dementia (96.6%). Table 1 lists the characteristics of the study population in 2000 and 2015. In both years, people with dementia were older, more likely to be female, and had higher comorbidity scores. From 2000 to 2015, the age distribution in the two groups remained largely the same over time, while the comorbidity scores increased in people with and without dementia.

### Prevalence of PIM

Figure 1 shows the annual proportion of people with and without dementia filling at least one prescription for one or more drugs from the red category of the Red-yellow-green list which was used to identify PIM. As seen in Fig. 1, the use of PIM was continuously more widespread in people with dementia from 2000 to 2015. In people with dementia, the prevalence decreased from 54.7% to 43.5% from 2000 to 2015, whereas it decreased from 39.5% to 28.8% in people without dementia. Figure 2 shows the results of the logistic regression comparing 2000 to 2015 in 5-year age groups stratified by dementia status and adjusted for sex. The use of PIM was significantly less likely in 2015 compared to 2000 in all age groups in both people with and without dementia. The most marked decrease was found in people aged 85–89 where the likelihood of PIM use in 2015

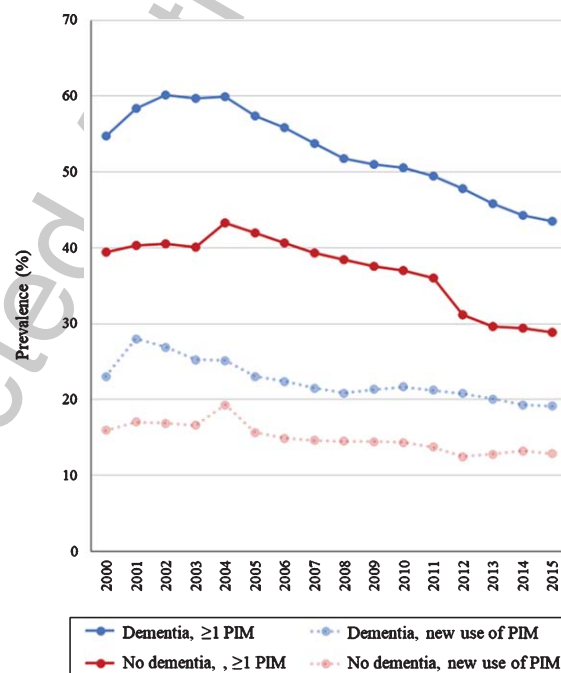


Fig. 1. Prevalence of potentially inappropriate medication (PIM), defined as the red category of the red-yellow-green list, in older people with dementia (blue line) and without dementia (red line) from 2000 to 2015. And the prevalence of new use of PIM in people with dementia (dashed transparent blue line) and without dementia (dashed transparent red line) from 2000 to 2015.

was almost half of what it had been in 2000 (adjusted ORs: dementia, 0.60 (0.55–0.64); no dementia: 0.52

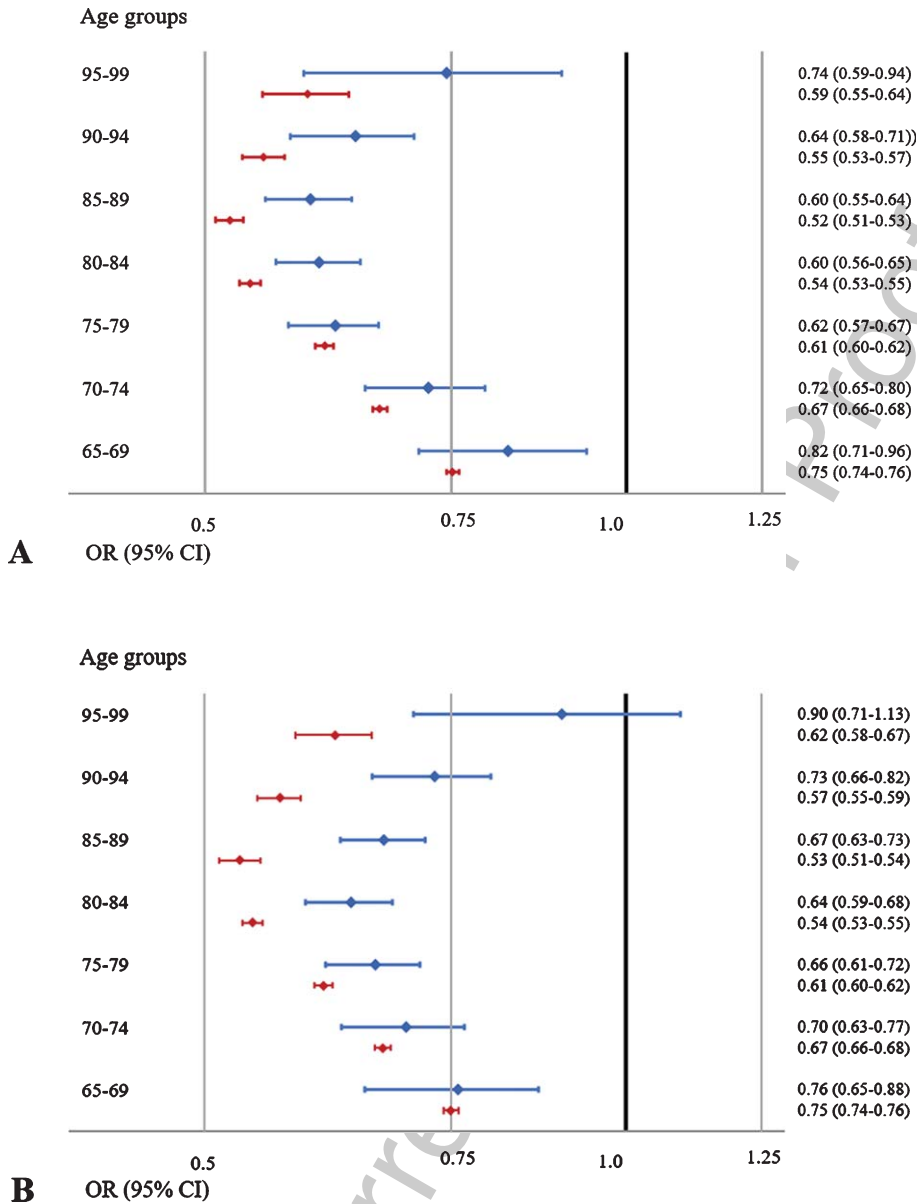


Fig. 2. Likelihood of potentially inappropriate medication (PIM), defined as drugs from the red category of the red-yellow-green list, use in 2015 versus 2000 in people with dementia (blue) and without (red) dementia. Panel A shows the results of logistic regression analyses comparing 2015 versus 2000 and Panel B shows the result of the sensitivity analysis where antipsychotics from the red category were excluded from the analysis in 5-year age groups displaying adjusted odds ratios (ORs) and 95% confidence intervals (CIs). Adjustments were made for sex.

268 (0.51–0.53)) (detailed results available in the Sup-  
 269 plementary Material). In a sensitivity analysis, the  
 270 Charlson Comorbidity Index was added to the mul-  
 271 ti-variable logistic regression to adjust for changes in  
 272 comorbidity levels, this made the decreasing trend  
 273 slightly more marked across all age groups (detailed  
 274 results available in the Supplementary Material). In  
 275 a second sensitivity analysis excluding all antipsy-

chotics, the decrease remained significant across all  
 age groups in people with dementia (detailed results  
 available in the Supplementary Material).

The use of drugs from the yellow category was also  
 studied: Use of drugs from the yellow category was  
 also continuously more widespread in people with  
 dementia compared to people without dementia. In  
 people with dementia, the prevalence of filling at least

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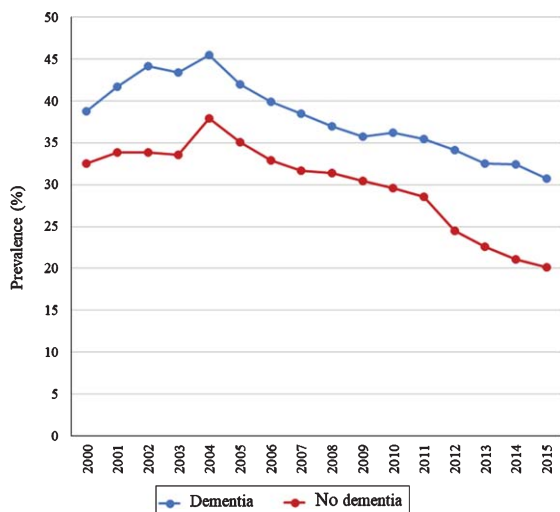


Fig. 3. Proportion of users of potentially inappropriate medication (PIM), defined in this study as drugs from the red category of the red-yellow-green list, filling prescriptions for  $\geq 2$  different PIM from 2000–2015 in people with (blue) and without (red) dementia.

one prescription for drugs from the yellow category, drugs to use with caution, decreased from 56.2% in 2000 to 43.7% in 2015. In people without dementia, the prevalence decreased from 29.8% to 25.4%.

#### *New use of PIM*

Figure 1 also shows the percentage of new users of PIM from 2000–2015. In people with dementia from 2000 to 2015, the percentage of new users of PIM decreased from 23.0 to 19.1%, whereas it decreased from 15.9% to 12.8% in people without dementia.

#### *Use of multiple PIM*

Most users of PIM, irrespective of dementia status, only filled prescriptions for one potentially inappropriate drug. Figure 3 shows the proportion of users who filled prescriptions for multiple PIM, which peaked in 2004 (dementia: 45.5%; no dementia: 34.1%). Overall, the proportion of PIM users who filled prescriptions for multiple different PIM decreased from 38.7% to 30.7% in people with dementia and from 32.5% to 20.2% in people without dementia from 2000 to 2015.

#### *Subgroups of PIM*

Figure 4 shows the annual proportion of people with and without dementia filling prescriptions for the various subgroups of the red category and Fig. 5

shows the annual proportion of people with and without dementia filling prescriptions for the various subgroups of the yellow category. The largest decrease in people with and without dementia was in the use of drugs for “hypnotics and anxiolytics”: red category (dementia: from 10.3% in 2000 to 5.1% in 2015); no dementia (11.2% to 2.1%) and yellow category (dementia: 30.3% to 12.8%; no dementia: 14.7% to 11.7%). Use of drugs from the various yellow subcategories also decreased from 2000–2015; however, an important exception was the analgesics category (including oxycodone, ketobemidone in combination with antispasmodics, and morphine) which increased from 9.2% to 13.5% in people with dementia and 5.0% to 6.2% in people without dementia. The use of morphine specifically increased from 5.2% to 10.1% in people with dementia and from 2.5% to 4.1% in people without dementia.

## DISCUSSION

To our knowledge, this is the first study to examine the time trend of PIM use in people with dementia. First, in line with our hypothesis, we found a decrease in the use of PIM in people with dementia that paralleled the documented decrease in the general older population. Second, this decrease was not attributable to the declining use of antipsychotics alone. Third, the decreasing use of PIM from 2000 to 2015 was observed despite increasing comorbidity scores in older people both with and without dementia. Last, throughout the study period, the use of PIM was more widespread in people with dementia compared to people without dementia.

To the best of our knowledge, this was the first time-trend study of the use of PIM specifically in people with dementia. However, several studies have examined the time trend of PIM as measured by various explicit criteria in the general older population: differences in national settings, study periods, selection of the study population, and, in particular, differences between the various explicit quality indicators used, impede direct comparisons. Nevertheless, in line with our findings, most reported a decrease [18–20, 22, 37–40], while three reported either a slight increase [41] or a stable prevalence [42, 43]. Two out of these three used subsets of the STOPP-criteria, indicating that the observed decrease may not apply to all measures of potentially inappropriate medication. In our study, the use of PIM decreased from 55% to 44% in people with dementia

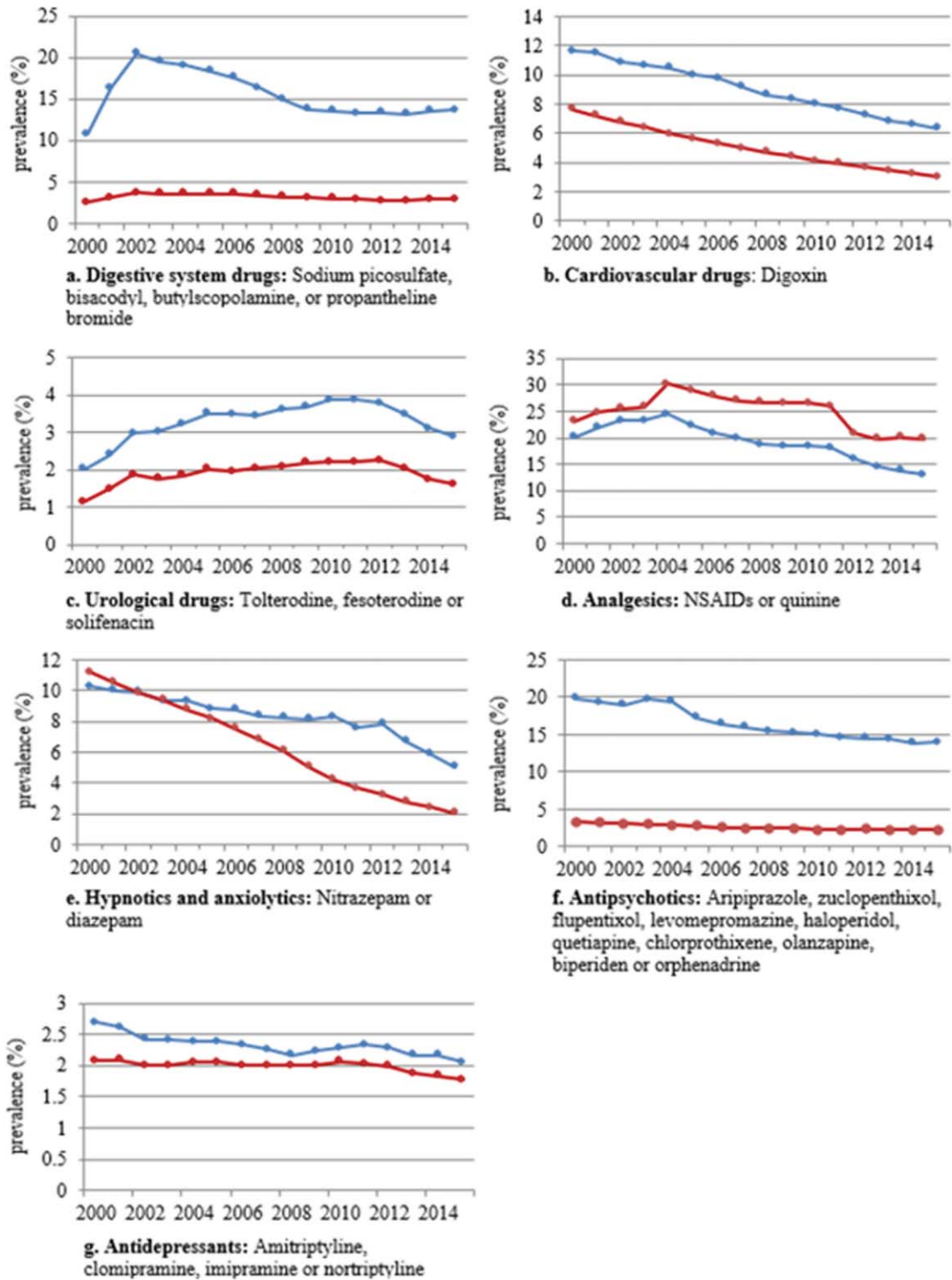


Fig. 4. Annual prevalence of potentially inappropriate medications (PIM), defined as the red category of the red-yellow-green list, use from 2000 to 2015 in people with (blue) and without dementia (red) per subgroup of the red category.

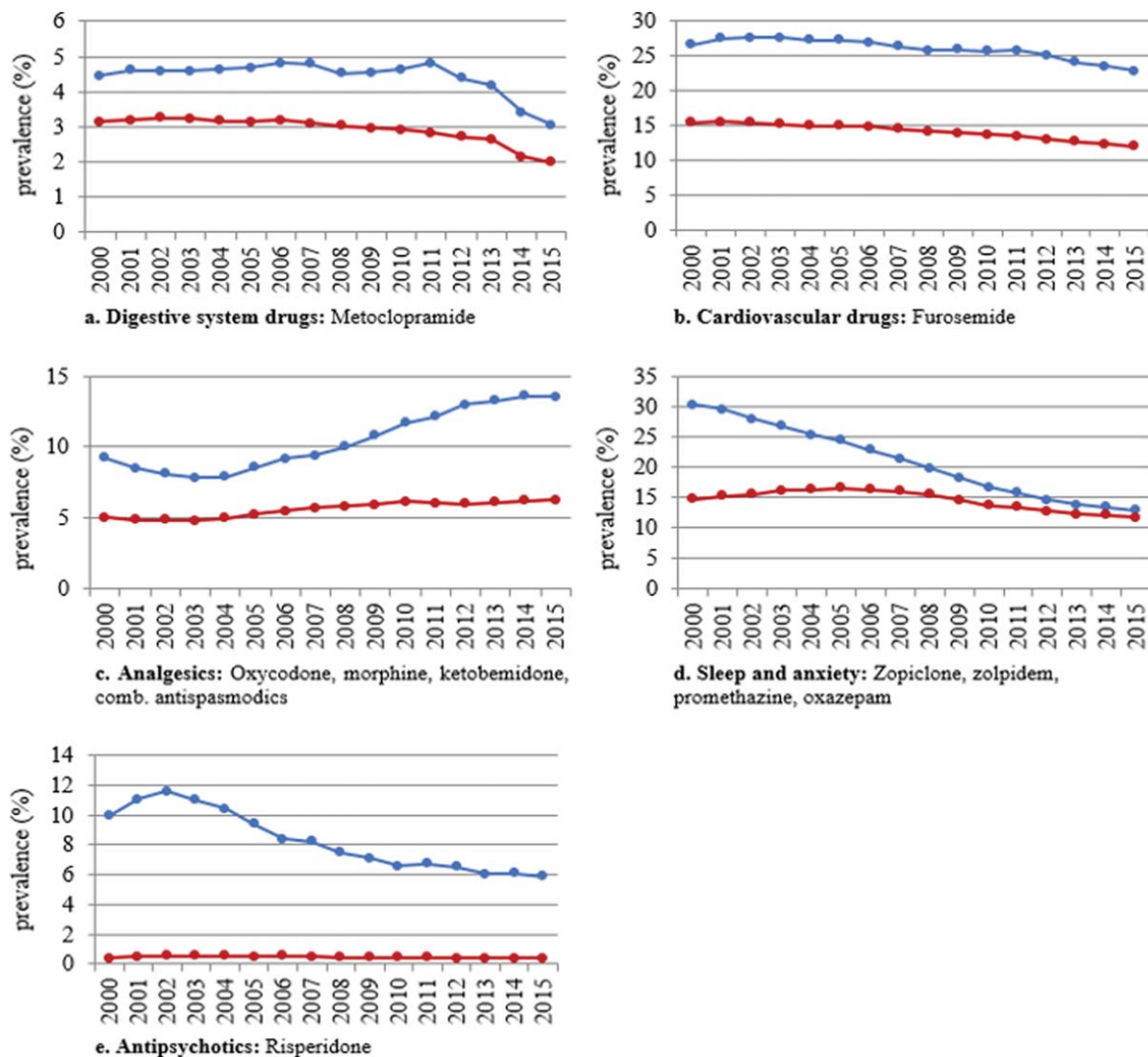


Fig. 5. Annual prevalence of drugs from the yellow category of the red-yellow-green list use from 2000 to 2015 in people with (blue) and without dementia (red) per subgroup of the yellow category.

358 and from 39% to 29% in older people without dementia  
 359 from 2000 to 2015. Using the Beers criteria  
 360 to define PIM, other studies have found compar-  
 361 able declines: in Australia, PIM use declined from  
 362 45% in 1993 to 40% in 2005 [40]; a US study  
 363 reported a decline from 46% to 41% from 2006  
 364 to 2012 [20]. While we found no studies examin-  
 365 ing the time trend in PIM use specifically in people  
 366 with dementia, a study investigated the Swedish  
 367 drug-specific recommendations in geriatric care units  
 368 where approximately 70% of the residents were cog-  
 369 nitively impaired [21]. They found a decrease from  
 370 44% to 26% from 2007 to 2013 which, though more  
 371 marked, is in line with our findings [21].

In our study, there was a small increase in the use  
 of PIM in the initial years of study. A possible expla-  
 nation could be that some of the drugs included in  
 the red category of the red-yellow-green list were  
 newly introduced to the market at the beginning of  
 the study period, e.g., quetiapine (N05AH04). How-  
 ever, the initial increasing use of quetiapine was accom-  
 panied by a simultaneous decrease in other drugs from  
 the same drug class indicating substitution rather than  
 novel use.

One possible explanation for the declining use of  
 PIM could be the growing attention to potential risks  
 associated with the use of PIM in older people. As evi-  
 dent from the steady rate of publications of criteria for

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386 PIM, guidelines on pharmacotherapy, and warnings  
387 from, for instance, the FDA, efforts to improve the  
388 quality and safety of prescribing for the older popu-  
389 lation have intensified [4, 44, 45]. Our study indicates  
390 that these efforts have also influenced the quality  
391 of prescribing for people with dementia. As is evi-  
392 dent by our results, the decreasing trend identified in  
393 this study preceded the publication and, subsequently,  
394 indicates an underlying trend which the publication  
395 of the list itself was a result of [6].

396 The use of antipsychotics in people with dementia  
397 has been associated with increased mortality risk,  
398 and several guidelines regarding this issue have been  
399 published [46–48]. Thus, in recent years, the use of  
400 antipsychotics in the treatment of behavioral symp-  
401 toms associated with dementia has decreased [36].  
402 Consequently, another explanation for the declining  
403 use of PIM in older people with dementia could be  
404 the decrease in the use of antipsychotics. However,  
405 in this study, we found that the decline in the use of  
406 PIM in people with dementia could not be attributed  
407 to the decrease in the use of antipsychotics alone.

408 Another possible explanation for the decreasing  
409 use of PIM could be a change in the demographics  
410 of the population and thus a lower prevalence of risk  
411 factors for PIM. Age is a risk factor for PIM [49], but  
412 the mean age remained largely unchanged through-  
413 out the study period. Polypharmacy also increases  
414 the risk of PIM [49, 50]; but in a previous study,  
415 we found an increase in polypharmacy from 2000  
416 to 2011, and thereafter, a relatively stable prevalence  
417 until 2014 [51]. Additionally, increasing levels of  
418 comorbidity heighten the risk of PIM use [52], but  
419 despite an increase in comorbidity within the study  
420 period, the use of PIM decreased. Furthermore, in a  
421 sensitivity analysis, we adjusted for the comorbid-  
422 ity levels, which made the decreasing trend slightly  
423 more marked. Thus, changes in demographics do  
424 not explain the decrease in the use of PIM. Conse-  
425 quently, the use of PIM decreased despite increasing  
426 polypharmacy and comorbidity, indicating greater  
427 awareness of PIM and greater caution when prescrib-  
428 ing to older people and people with dementia. While  
429 the decline in the use of PIM demonstrated in this  
430 study is a positive find, the study also identified poten-  
431 tial implications to the safety of patient: First, the  
432 use of PIM was continuously more widespread in  
433 people with dementia who could be more suscepti-  
434 ble to the adverse effects associated with the use of  
435 PIM. Secondly, while the use of drugs from most sub-  
436 groups of the Red-yellow-green list decreased in the  
437 study period, the use of analgesics from the yellow

438 category increased in people with dementia. This  
439 increase was mainly driven by the increasing use of  
440 morphine which was also observed in a recent study in  
441 the same population. In this study, a disproportionate  
442 increase in the use of opioids was observed in people  
443 with dementia. The authors speculated that a possi-  
444 ble explanation could be that opioids have replaced  
445 antipsychotics in the treatment of behavioral and psy-  
446 chological symptoms associated with dementia [53].

447 The greatest strength of the study is the use of  
448 complete nationwide data which makes it possible  
449 to identify individuals with dementia and follow  
450 them in the registers and examine real-life prescrip-  
451 tion patterns without risk of selection bias. However,  
452 this study also has some limitations: First, while  
453 the study was based on complete information on  
454 all filled prescriptions, we cannot ascertain whether  
455 the medication was actually consumed. Furthermore,  
456 information on over-the-counter sales, as well as  
457 treatment duration, and dosage, is not available in  
458 the registers. In Denmark, low-dose ibuprofen, which  
459 is in the red category, is available over the counter  
460 in limited quantities which could lead to an under-  
461 estimation of use. Secondly, while the validity of  
462 a dementia diagnosis in the Danish registers has  
463 previously proven to be high it is well known that  
464 dementia is underdiagnosed [29]. In 2015, we iden-  
465 tified 36,031 people aged 65 years or above who had  
466 been registered with a dementia diagnosis in the Dan-  
467 ish registers. However, based on the extrapolation  
468 from European population-based studies, Alzheimer  
469 Europe estimates that approximately 87,000 aged  
470 60 or above in Denmark are living with demen-  
471 tia [54]. Consequently, the reference group without  
472 dementia contains an unknown number of individu-  
473 als with undiagnosed or untreated dementia, which  
474 could have led to an underestimation of differences  
475 between people with and without dementia. Thirdly,  
476 using the Danish Red-yellow-green list rather than  
477 an internationally well-known indicator could limit  
478 generalizability. However, the majority of drugs in  
479 the red category is also included in other well-known  
480 explicit indicators. Furthermore, due to differences in  
481 prescribing practices, guidelines, and available med-  
482 ication, we believe the national Danish list is better  
483 suited to this setting.

484 This nationwide study found a decrease in the use  
485 of PIM from 2000 to 2015 in people with demen-  
486 tia comparable to the decrease found in the general  
487 older population. The decrease in the use of PIM  
488 in people with dementia was not attributable to the  
489 decreasing use of antipsychotics alone. Furthermore,  
490

the decrease was observed despite increasing levels of comorbidity in the same period. This indicates that efforts to improve prescribing practices in the older population also had an effect in people with dementia. However, the use of PIM remained continually more widespread in people with dementia compared to people without dementia which could have implications for patient safety and thus emphasizes the need for continued efforts to improve drug therapy especially in people with dementia.

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## SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: <https://dx.doi.org/10.3233/JAD-200627>.

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