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Research Article

Frequent use of opioids in patients with dementia and nursing home residents—A study of the entire elderly population of Denmark

Christina Jensen-Dahm[a,*], Christiane Gasse[b], Aske Astrup[b], Preben Bo Mortensen[b,c,d], Gunhild Waldemar[a]

[a]*Department of Neurology, Danish Dementia Research Centre (DDRC), Rigshospitalet–University of Copenhagen, Copenhagen, Denmark*
[b]*National Centre for Register-based Research, Aarhus University, School of Business and Social Sciences, Aarhus, Denmark*
[c]*Centre for Integrated Register-Based Research, CIRRAU, Aarhus University, Aarhus, Denmark*
[d]*The Lundbeck Foundation Initiative for Integrative Psychiatric Research, iPSYCH, Aarhus, Denmark*

Abstract

Background: Pain is believed to be undertreated in patients with dementia; however, no larger studies have been conducted. The aim was to investigate prevalent use of opioids in elderly with and without dementia in the entire elderly population of Denmark.

Method: A register-based cross-sectional study in the entire elderly (≥65 years) population in 2010 was conducted. Opioid use among elderly with dementia (N = 35,455) was compared with elderly without (N = 870,645), taking age, sex, comorbidity, and living status into account.

Results: Nursing home residents (NHRs) used opioids most frequently (41%), followed by home-living patients with dementia (27.5%) and home-living patients without dementia (16.9%). Buprenorphine and fentanyl (primarily patches) were commonly used among NHRs (18.7%) and home-living patients with dementia (10.7%) but less often by home-living patients without dementia (2.4%).

Conclusions: Opioid use in the elderly Danish population was frequent but particularly in patients with dementia and NHR, which may challenge patient safety and needs further investigation.

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Keywords: Dementia; Opioids; Elderly; Buprenorphine; Fentanyl; Pain

1. Introduction

Elderly patients with dementia often suffer from multimorbidity, and pain-causing conditions are frequent [1]. Thus, appropriate use of drugs and treating comorbidity represent an important public health issue. Currently, pain is believed to be undertreated in the elderly and especially in people with dementia [2,3], an assumption corroborated by a number of small case-control studies [4–9]. Reasons for undertreatment are not well understood. Assessment of pain in patients with dementia is challenging, which may

lead to undertreatment. On one hand, careful prescribing may be appropriate as elderly have an increased risk of side effects and severe adverse drug reactions [10]. Opioids may be particularly problematic in patients with dementia because of sedation and their association with a reduction in mental health functioning [11]. On the other hand, pain is associated with lower quality of life [12] and impairment of working memory [13] and should be treated efficiently. Furthermore, results have indicated that treatment of pain can improve behavioral symptoms in patients with dementia [14].

Studies examining data collected before 2000 have consistently reported that patients with dementia were less likely to receive analgesics [5,7,8]. However, more recent reports have shown a more varied picture, with some

studies reporting that patients with dementia are more likely to receive paracetamol [15,16] and opioids, although the association of opioid use in dementia was not significant in a multivariate analysis [15]. Over the past 10 to 15 years, however, several countries have reported increasing opioid use in the general population [17–19], and recent results could indicate that prescription patterns in patients with dementia may have changed. Consequently, we conducted a nationwide register-based study in the entire elderly population of Denmark, comparing 2010 opioid prescription patterns in home-dwelling and nursing home elderly with and without dementia. Our hypothesis was that frail elderly such as patients with dementia and/or nursing home residents were less likely to receive opioids and particularly strong opioids.

2. Methods

2.1. Registry data sources

Denmark has a tax-financed health care system that provides equal access to all residents. Because individuals are given a permanent personal civil registration number at the time of birth or immigration, nationwide registries allow data retrieval at individual level [20]. This study linked individual-level data from national registries using the civil registration number. The National Patient Registry contains all hospitalizations and invasive procedures registered since 1978, and since 1995, data from hospital-based outpatient clinics and emergency departments have been registered [21,22]. The Psychiatric Central Research Registry includes data on all psychiatric inpatient admissions in Denmark since April 1, 1969, and outpatient contacts since 1995 [23]. Information comprises dates and discharge diagnosis, registered using WHO *International Classification of Diseases* (ICD) codes. ICD-8 was used from 1970 to 1993 [24] and ICD-10 from 1994 and onward [25]. ICD-9 was never used. The Danish National Prescription Registry [26] has registered dispensed prescriptions consecutively since 1995 according to the Anatomical Therapeutic Chemical (ATC) classification system [27], including data on amount and strength of dispensed tablets and dispensing dates [22].

The study was approved by the Danish Data Protection Agency (ID no: 2007-58-0015/30-0667), Statistics Denmark, and the Danish Health and Medicine Authority (ID no: 6-8011-907/1). Danish law did not require ethic committee approval or informed patient consent.

2.2. Study population

All permanent residents aged ≥65 years alive on January 1, 2010, were identified using the Central Population Registry [28]. Individuals with dementia were identified as those who had been registered in the National Patient Registry or Psychiatric Central Research Registry before January 1, 2010, with a dementia diagnosis as the main or secondary diagnosis during admission or at an outpatient visit (Supplementary Table A1 for diagnostic codes) and/or who had filled an antidementia prescription (ATC: N06D). The individuals had to be ≥60 years at the time of diagnosis and/or first prescription, as prior research has shown low validity of the dementia diagnosis in those <60 years [29]. The remaining individuals formed the group without dementia.

2.3. Opioid treatment

In Denmark, opioids are only available by prescription from a physician and can only be dispensed once per prescription. Opioid users were defined as individuals who had redeemed at least one opioid prescription (ATC: N02A) in 2010. We grouped morphine analogues (N02AA01-04), oxycodone (N02AA05-55), pethidine (N02AB02), fentanyl (N02AB03), buprenorphine (N02AE01), and ketobemidone (N02AG02) as strong opioids, whereas codeine (N02AA59), dextropropoxyphene (N02AC04), and tramadol (N02AX02) were grouped as weak opioids.

2.4. Comorbidity and demographic information

Comorbidity was evaluated at baseline (January 1, 2010). We evaluated potentially pain-causing diseases (cancer, osteoporosis, arthritis, and recent fracture) and comorbidity (diabetes, vascular, pulmonary, renal and liver disease) that may affect opioid use (Supplementary Table A2). Statistics Denmark provided information about living status (home living and nursing home).

2.5. Statistical analysis

Our descriptive analysis showed that opioid use patterns differed depending on living status, and the two groups were evaluated separately. Frequency of comorbidity and percentage of opioid users were compared using Pearson's chi-squared test. A logistic regression analysis was performed initially to evaluate the effect of covariates independently (crude analysis) and then in a multivariate logistic regression analysis (adjusted analysis), where age, sex, pain-causing disorders, and comorbidity were included as these covariates have been shown to be potential confounders [4,15].

To evaluate treatment intensity, we computed the number of prescriptions and equivalent doses of oral morphine and total dose for each user. Equivalent doses of oral morphine were calculated as the number of defined daily dosages redeemed in 2010 multiplied by a factor, which was based on content of one defined daily dosage and equianalgesic effects (Appendix Table A3). To calculate duration of use, a daily dose of 30 mg was assumed. Differences were evaluated using a nonparametric test (Wilcoxon).

Data analysis was performed using SAS statistical software, version 9.3 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Study population

On January 1, 2010, Denmark had 908,418 residents aged ≥65 years, representing 16.36% of the Danish population. We excluded 2318 people (0.26%) who had received a dementia diagnosis before the age of 60 years, leaving 906,100 individuals, 35,455 (3.91%) of whom were diagnosed with dementia before January 1, 2010. This left a population without dementia of N = 870,645 (Fig. 1). Table 1 lists the characteristics of the study population stratified by dementia diagnosis and living status. Home-living patients with dementia were older and suffered from more comorbidity than the population without dementia, whereas the nursing home residents without dementia suffered from more comorbidity than the patients with dementia, with the exception of fractures.

3.2. Opioid use in 2010

Fig. 2 shows the 2010 frequency of opioid use stratified by dementia, age, and living status. Home-living patients with dementia received more opioids than the reference population (patients vs. reference: 27.5%, 95% confidence interval [CI], 26.8%–28.1% vs. 16.9%, 95% CI, 16.8%–17.0%; $P < .001$ for all age groups except for 95+ years, where $P = .007$). Nursing home residents used opioids even more frequent, but patients with dementia received fewer opioids than those without (37.8% [37.0%–38.5%] vs. 43.0% [42.4%–43.6%], $P < .001$ for all age groups except for age 90–94 years, where $P = .12$, and 95+ years, where $P = .22$).

Table 2 lists the results of the logistic regression analysis for those receiving "any opioid" in 2010 according to living status. Home-living patients with dementia had a crude odds ratio (OR; 95% CI) of 1.86 (1.80–1.92) for receiving an opioid, which after adjustment for age and sex decreased to 1.43 (1.38–1.47), and further decreased to 1.27 (1.22–1.31) after additional adjustment for comorbidity. In contrast, nursing home residents with dementia were 20% less likely to receive an opioid (crude OR, 0.80 [0.77–0.84]), and there was minimal effect from adjustment for age, sex, and comorbidity (adjusted OR, 0.83 [0.80–0.87]). Use of opioids increased with age, but this was especially pronounced for the home living. Comorbidity was associated with increased ORs, which was also the case for potential contraindications such as pulmonary or renal disease. When we excluded those who died in 2010, the overall pattern did not change, but the frequency decreased by 1.2% to 6.7% (Supplementary Figure A1).

Table 3 lists the distribution of opioid subtypes and overall results of logistic regression analysis (for detailed results, see Supplementary Table A1A–G). The crude analysis showed that home-living patients with dementia received all subtypes of opioid more frequent, but after adjusting for age, sex, and comorbidity, they were less likely to receive weak opioids. The crude analysis showed that home-living patients with dementia had a fivefold increased OR for buprenorphine and a fourfold OR for fentanyl, which after adjustment decreased to 2.57 (2.41–2.74) and 2.32 (2.15–2.50), respectively. Use of buprenorphine and fentanyl was highly dependent on age, and the 95+ group had, compared with the 65- to 69-year-old group, a crude OR of 17.24 (15.41–19.30) for buprenorphine use (Supplementary Table A4D). The pattern was similar for fentanyl, although the OR was lower (95+: crude OR, 10.46 [9.17–11.93]). For both buprenorphine and fentanyl, the estimates diminished with adjustment for age, sex, and comorbidity but remained high at 11.18 (9.95–12.55) and 7.10 (6.20–8.13), respectively (Supplementary Table A4C).

Comparing nursing home residents and home living, 27.9% (27.5%–28.4%) of nursing home residents used strong opioids in contrast with 7.1% (7.1%–7.2%) of the home living without dementia and 17.4% (16.9%–17.9%) of the home living with dementia, but the difference was especially pronounced for buprenorphine and fentanyl. The age dependency in the home-living population for buprenorphine (95+: crude OR, 2.58 [2.06–3.23]) and fentanyl (95+: crude OR, 1.74 [1.38–2.19]) was less pronounced in nursing home residents (Supplementary Table 4AC–D). The pattern differed for nursing home residents with no significant difference between groups for strong opioids but less frequent use of weak opioids in those with dementia. Fentanyl and buprenorphine were mainly used as transdermal formulations, that is, patches.

3.3. Treatment intensity

Home-living patients with dementia were more likely to receive more than one opioid prescription than those without (75.6% [74.5%–76.8%] vs. 70.8% [70.6%–71.0%],
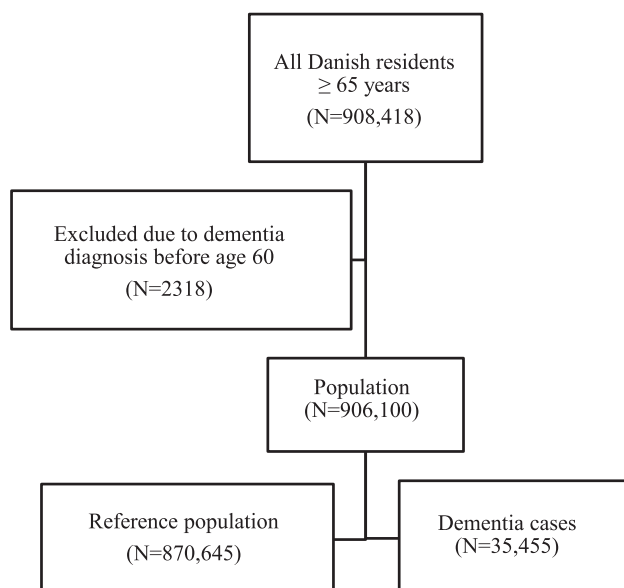

Fig. 1. Population selection.

Table 1
Characteristics of the study population stratified by living status and dementia diagnosis

Characteristic	Home living (N = 863,809)		Nursing home (N = 42,291)	
	Reference (N = 844,402)	Dementia (N = 19,407)	Reference (N = 26,243)	Dementia (N = 16,048)
Female	463,414 (54.9)	11,782 (60.7)*	18,110 (69.0)	11,452 (71.4)*
Age groups (y)				
65–69	296,622 (35.1)	1547 (8.0)*	1490 (5.7)	528 (3.3)*
70–74	211,647 (25.1)	2647 (13.6)	2232 (8.5)	1192 (7.4)
75–79	150,591 (17.8)	3974 (20.5)	3311 (12.6)	2283 (14.2)
80–84	103,524 (12.3)	5035 (25.9)	5265 (20.1)	4091 (25.5)
85–89	57,972 (6.9)	4094 (21.1)	6633 (25.3)	24,696 (29.3)
91–94	19,358 (2.3)	1676 (8.6)	4913 (18.7)	2533 (15.8)
95+	4688 (0.6)	434 (2.2)	2399 (9.1)	725 (4.5)
Time since diagnosis, y	NA	2.3 (0.9–4.5)	NA	3.3 (1.5–5.6)
Antidementia treatment	NA	8060 (41.5)	NA	6333 (39.5)
Living alone	326,929 (39.0)	11,058 (57.0)	NA	NA
Comorbidity				
Cancer	118,575 (14.0)	2992 (15.4)*	4418 (16.8)	2275 (14.2)*
Osteoporosis	90,407 (10.7)	3330 (17.2)*	5234 (19.9)	2864 (17.9)*
Arthritis	134,254 (15.9)	3973 (20.5)*	5921 (22.6)	2996 (18.7)*
Recent fracture	22,357 (2.7)	1303 (6.7)*	2234 (8.5)	1557 (9.7)*
Diabetes	79,166 (9.4)	2249 (11.6)*	3381 (12.9)	1691 (10.5)*
Vascular	169,001 (20.0)	7443 (38.4)*	11,760 (44.8)	6210 (38.7)*
Pulmonary	75,533 (9.0)	2315 (11.9)*	3664 (14.0)	1639 (10.2)*
Renal	17,443 (2.1)	663 (3.4)*	1202 (4.6)	470 (2.9)*
Liver	8426 (1.0)	323 (1.7)*	434 (1.7)	223 (1.4)*

Abbreviation: NA, not applicable.
NOTE. Numbers are given as n (%) or median (25% quartile to 75% quartile) as appropriate.
*$P < .001$.

respectively, $P < .0001$). Half of the home-living patients with dementia had a duration of use exceeding 93 days (25%–75% interquartile range, 27–288 days), compared with 70 days (19–272 days; $P < .0001$) for those without. Among nursing home residents, approximately 80% received more than one opioid prescription, but patients with dementia were less likely to receive more than one prescription than those without dementia (78.8% [77.8%–79.9%] vs. 82.7% [82.0%–83.4%], respectively, $P < .0001$). Likewise, patients with dementia at nursing

homes were treated for a shorter period, as half of patients with dementia had a duration of use exceeding 112 days (32–331 days), compared with 153 days (40–454 days; $P < .0001$) for those without.

4. Discussion

This is the first study to investigate an entire elderly population's use of opioids. Contrary to our hypothesis, the frequency of opioid use rose steadily with age and was
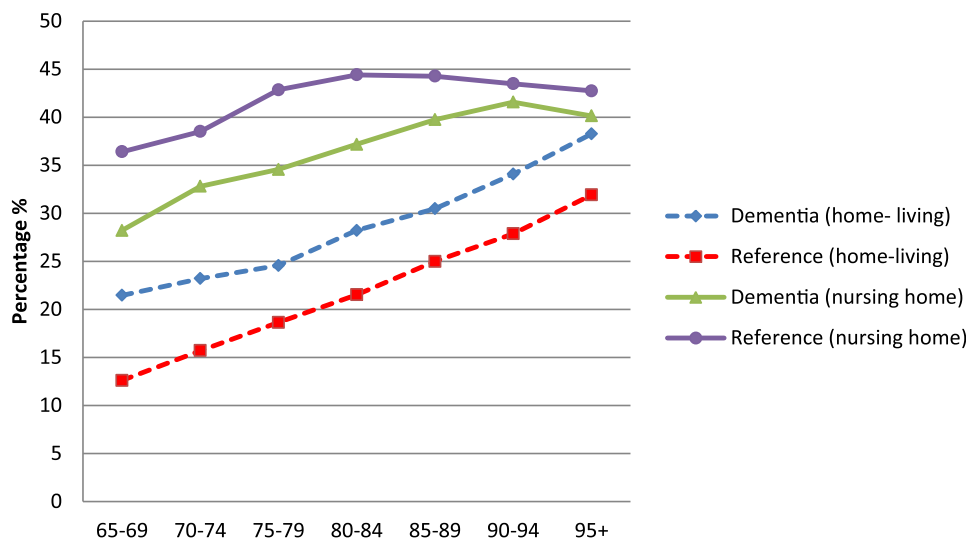

Fig. 2. Percentage receiving an opioid in 2010 stratified by dementia, age group, and living status.

Table 2
Opioid drug use in 2010

Characteristic	Home living		Nursing home	
	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
Dementia	1.86 (1.80–1.92)	1.27 (1.22–1.31)	0.80 (0.77–0.84)	0.83 (0.80–0.87)
Sex (females)	1.51 (1.49–1.53)	1.39 (1.38–1.41)	1.41 (1.35–1.47)	1.27 (1.21–1.32)
Age groups (y)				
65–69	1.0	1.0	1.0	1.0
70–75	1.30 (1.28–1.32)	1.18 (1.16–1.20)	1.11 (0.99–1.25)	1.11 (0.99–1.25)
75–80	1.60 (1.57–1.63)	1.31 (1.29–1.34)	1.28 (1.15–1.42)	1.22 (1.09–1.36)
80–85	1.94 (1.90–1.97)	1.48 (1.46–1.51)	1.36 (1.23–1.51)	1.27 (1.15–1.41)
85–90	2.36 (2.31–2.41)	1.73 (1.70–1.77)	1.43 (1.29–1.58)	1.31 (1.18–1.45)
90–95	2.77 (2.68–2.86)	2.06 (1.99–2.13)	1.46 (1.32–1.62)	1.34 (1.20–1.49)
95+	3.33 (3.14–3.54)	2.58 (2.42–2.74)	1.42 (1.26–1.59)	1.34 (1.18–1.51)
Comorbidity				
Cancer	1.73 (1.71–1.76)	1.56 (1.53–1.58)	1.39 (1.32–1.47)	1.35 (1.28–1.42)
Osteoporosis	2.59 (2.55–2.63)	1.84 (1.81–1.87)	2.14 (2.04–2.25)	1.83 (1.74–1.93)
Arthritis	2.86 (2.82–2.90)	2.35 (2.32–2.39)	1.76 (1.68–1.84)	1.59 (1.51–1.67)
Recent fracture	2.44 (2.37–2.50)	1.81 (1.76–1.87)	1.73 (1.62–1.85)	1.60 (1.50–1.72)
Diabetes	1.54 (1.51–1.57)	1.40 (1.38–1.43)	1.03 (0.97–1.10)	1.04 (0.98–1.11)
Vascular	1.89 (1.86–1.91)	1.55 (1.53–1.57)	1.15 (1.11–1.20)	1.14 (1.09–1.19)
Pulmonary	2.20 (2.17–2.24)	1.74 (1.71–1.77)	1.37 (1.29–1.45)	1.23 (1.16–1.31)
Renal	2.26 (2.19–2.33)	1.44 (1.39–1.49)	1.33 (1.20–1.47)	1.22 (1.10–1.35)
Liver	2.11 (2.02–2.21)	1.74 (1.66–1.82)	1.26 (1.08–1.47)	1.27 (1.09–1.50)

Abbreviations: OR, odds ratio; CI, confidence interval.

NOTE. This table shows the logistic regression analysis comparing opioid users and nonopioid users according to living status. The results are given as OR (95% CI). The crude ORs for comorbidity and demographic variables are modeled for any opioids. The adjusted ORs include adjustment for age, sex, and comorbidity.

particularly pronounced among the most vulnerable patients, that is, patients with dementia (32%) and nursing home residents (41%). Home-living patients with dementia were more likely to receive multiple prescriptions and higher dosages than those without dementia. However, the highest percentage of use was found among nursing home residents. Our results also show that there are clear differences in treatment of patients with dementia in relation to living status, as nursing home residents without dementia were the most frequent users. This is surprising for two reasons. First, our findings are in opposition to the current belief that pain is undertreated in the elderly, especially those with dementia [2,3]. Second, frail elderly patients, and particularly patients with dementia, are much more prone to adverse

events associated with opioids, leading us to believe physicians would be reluctant to prescribe them.

Previous studies, which had limited sample size and generalizability, have found that among elderly, increasing age was associated with lower likelihood of receiving analgesics [30,31], which is opposite to our results, which showed that use of opioids rose steadily with age. Likewise, our results contrast with most studies on home-living patients with dementia, which have found that patients with dementia receive fewer analgesics [5–8]. Second, all the studies were published in 2004 or prior, and over the past 15 years, several countries have reported an increase in opioid prescriptions [17–19]. In Denmark, use of opioids in the entire population has increased by 34%

Table 3
Percentage of individuals receiving prescriptions for different kinds of opioids in 2010

Opioid	Home living (N = 863,809)				Nursing home (N = 42,291)			
	Dementia	Reference	Crude OR	Adjusted OR	Dementia	Reference	Crude OR	Adjusted OR
All opioids	27.5	16.9	1.86 (1.80–1.92)	1.27 (1.22–1.31)	37.8	43.0	0.80 (0.77–0.84)	0.83 (0.80–0.87)
Strong opioids	17.4	7.1	2.74 (2.64–2.85)	1.79 (1.72–1.86)	27.8	28.1	0.99 (0.94–1.03)	1.04 (0.99–1.08)
Morphine	5.0	2.6	1.98 (1.85–2.12)	1.35 (1.26–1.44)	6.8	8.6	0.77 (0.72–0.84)	0.82 (0.76–0.88)
Oxycodone	5.2	3.5	1.53 (1.43–1.63)	1.07 (1.01–1.15)	6.0	9.4	0.61 (0.57–0.66)	0.63 (0.58–0.68)
Fentanyl	4.4	1.1	4.07 (3.78–4.37)	2.28 (2.12–2.46)	7.9	8.4	0.94 (0.88–1.01)	0.99 (0.92–1.07)
Buprenorphine	6.3	1.3	5.15 (4.84–5.47)	2.57 (2.41–2.74)	12.3	9.5	1.34 (1.26–1.42)	1.38 (1.29–1.47)
Weak opioids	14.9	12.4	1.23 (1.18–1.28)	0.88 (0.85–0.92)	16.6	24.1	0.63 (0.59–0.66)	0.64 (0.61–0.67)
Tramadol	13.6	11.1	1.27 (1.21–1.32)	0.91 (0.87–0.95)	15.1	22.2	0.63 (0.59–0.66)	0.64 (0.61–0.67)

Abbreviation: OR, odds ratio.

NOTE. The cumulative percentage is higher than "all opioids" as a user may have used more than one opioid. This table also shows the OR (95% confidence interval) of the logistic regression analysis comparing those with dementia with those without dementia according to living status. The adjusted ORs include adjustment for age, sex, and comorbidity.

from 1999 to 2010 [32], which the high percentage of users in our study may reflect. More recent publications have reported results that were closer to our findings. In accordance with our study, a smaller Swedish study found that home-living patients with dementia used opioids more frequently (8.0% without dementia [N = 2199] and 14.3% with [N = 119]) [15]. A Finnish register-based study examining 2005 data found that home-living patients with Alzheimer's disease received opioids less frequently than those without (3.6% vs. 4.6%) but were more likely to receive strong opioids. However, the percentage of users is much lower than what we found (3.6% vs. 27.5% for home-living dementia patients), but the study has limited generalizability as they excluded nursing home residents and those with dementia due to other causes than Alzheimer's disease.

In our study, the highest percentage of use was found among the most fragile patients living at nursing homes. Forty-one percent of nursing home residents had used an opioid in comparison with 17% of the home living without dementia. To our knowledge, only one other study has compared home-living and nursing home residents and like-wise found that a higher percentage of nursing home residents received analgesics [15]. In our study, nursing home residents with dementia received opioids less frequently than residents without dementia (38% vs. 43%), but this was due to fewer receiving weak opioids. This finding is in accordance with a number of smaller studies, with limited generalizability, which have found that nursing home residents with dementia were less likely to receive pain medication compared with the cognitively intact [5,6,33,34]. In Denmark, dementia is the primary reason for nursing home placement, and most residents without dementia have severe physical disability [35], which could also explain the differences between the two groups. Our results also show that there are different treatment patterns of patients with dementia depending on living situation as nursing home residents with dementia received opioids less frequently than those without dementia. Nevertheless, opioid use was very common in nursing home residents and much more common than among home-living elderly.

This study raises an important question, whether the frequent opioid use in the elderly, and especially in patients with dementia and nursing home residents, is appropriate. On one hand, frailty and comorbidity have been associated with pain [36], and pain is frequent among nursing home residents [37,38]. On the other hand, the main limitations of opioid use are adverse reactions, which increase with age, frailty, dementia, and higher dosages [2,39]. The frequent opioid use is in sharp contrast to the fact that very few elderly of age >65 years have been included in analgesic trials and no trials have included patients with dementia or elderly of age >85 years [40] among which we found the most frequent use. At present, little data exist supporting evidence-based prescribing of opioids in dementia and frail elderly. Furthermore, most patients received multiple prescriptions, but the evidence for long-term use is limited

[41]. A recent Cochrane review concluded that the effect of strong opioids in osteoarthritis is outweighed by large increases in risk of adverse events and strong opioids should not be used routinely [42]. Guidelines for pain treatment in the elderly are few, but an expert consensus statement on opioids for treatment of chronic severe pain states that "in properly selected and monitored patients, opioid analgesics constitute a potentially effective treatment as part of a multi-modal strategy, but should only be prescribed on a trial basis with clearly defined therapeutic goals" [43]. One may question if 41% of nursing home residents constitute a properly selected group of patients.

Our analysis revealed that fentanyl and buprenorphine were used by 20% of nursing home residents with dementia, in contrast to 10% of home-living patients with dementia and 2% of the home-living reference population. Among the home living, those aged ≥95 years had, compared with the age group 65 to 69 years, a risk of receiving buprenorphine and fentanyl, which were 17 and 11 times higher, respectively. Although adjustment for age, sex, and comorbidity diminished the effect estimates, home living >95 years had an 11 and 7 times increased risk for receiving buprenorphine or fentanyl, respectively. The prevalent use of fentanyl and buprenorphine (i.e., patches) in nursing home residents, patients with dementia, and very old individuals is potentially problematic as it may pose a risk to patient safety. First, in 2005, the US Food and Drug Administration released a black box warning against using fentanyl patches in nonopioid–tolerant patients because of serious adverse events and deaths [44]. The elderly and those with cognitive impairment are the most susceptible to serious adverse events or death, and a recent study showed that initiation of transdermal fentanyl in opioid naïve persons was more frequent among those with advanced age and/or cognitive impairment [45]. Second, even palliation guidelines from the National Institute for Clinical Excellence in the United Kingdom do not recommend use of transdermal patch formulations as first-line maintenance treatment in patients for whom oral opioids are suitable [46]. Last, but not least, using drugs with potentially serious side effects in patients with dementia poses an ethical challenge as patients with dementia eventually lose the ability to consent to treatment.

One of the strengths of this study is that it investigates "real-life prescription patterns" in an entire elderly population eliminating problems of selection bias. The validity of registered dementia diagnoses at hospitals has previously been shown to be high [47], but most cases are registered as unspecified dementia. However, dementia is generally underdiagnosed, and previous research has shown that estimated 50% to 70% of cases are diagnosed and therefore captured by the Danish hospital registries [48]. Potential undiagnosed cases among the reference group could lead to an underestimation of differences. An additional strength is that we are able to distinguish between home-living and institutionalized individuals, which is not possible in several countries [4,49]. However, in some cases, patients or their caregivers may not report moving to a nursing home, and it has been

estimated that this leads to an underestimation of the number of nursing home residents by approximately 10% (information provided by Statistics Denmark). The Danish National Prescription Registry registers all prescriptions filled at pharmacies, and the information has proven to be accurate [22], but we cannot be certain that the patients consumed the drugs. However, between 73.8% and 82.7% of patients redeemed multiple prescriptions indicating that the majority did consume the medication. Furthermore, the exact indication for the prescriptions is unknown. In our analysis, we adjusted for a number of potential confounders (both indications and contraindications for opioid use), but not all pain-causing comorbidity can be accounted for in hospital registries, in particular disease states such as back pain, which are mainly treated by general practitioners. Our logistic regression analysis showed that the crude estimates for dementia were confounded by age, sex, and comorbidity, but age was the most important confounder. It is noteworthy that even conditions that must be considered relative contraindications for opioids (i.e., pulmonary, renal and liver disease) were associated with use of opioids, which was contrary to expected. However, we cannot rule out that unmeasured confounding could explain part of the remaining association between dementia and opioids. An alternative explanation could be that patients with dementia are more likely to receive opioids for other indications such as end-of-life treatment. We explored this by excluding those who died in 2010, which decreased the frequency of use to 1.2% to 6.7%, but the overall pattern remained unchanged, indicating that end-of-life treatment was not the explanation. An alternative explanation may be found in a recent study that showed that a systematic approach to pain treatment (though mainly paracetamol) leads to reduced agitation in people with moderate-to-severe dementia [14], and one may speculate if opioids in our population were used to treat behavioral symptoms and not pain.

5. Conclusions

In the entire elderly population of Denmark, we surprisingly found that use of opioids rose steadily with age and was particularly high for patients with dementia and nursing home residents. This study raises a number of questions, the first being if the frequent opioid use with increasing age, dementia, and/or nursing home residency may challenge patient safety? Future studies should explore potential consequences of opioid use in these groups to further assess this. As opioid use has been increasing in several countries, there are reasons to suspect that our findings apply outside Denmark. Our study also highlights the urgent need for more evidence to guide analgesic prescribing in the elderly and especially those who are frail and/or suffer from dementia.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jalz.2014.06.013.

RESEARCH IN CONTEXT

1. Systematic review: We searched PubMed using the keywords: "dementia," "opioid," "pain," "analgesics," and "nursing home." Articles published in English and from peer-reviewed journals were collected and reviewed. We specifically reviewed studies that had assessed use of analgesics in the elderly, dementia, and nursing home residents.

2. Interpretation: This study is the first to study opioid use in an entire elderly population, eliminating problems of selection bias. Contrary to expected, patients with dementia and nursing home residents were the most frequent users of opioids. However, clinical trials of analgesics have never included patients with dementia and nursing home residents, representing the frailest patient groups. Our findings highlight the urgent need for more evidence to guide analgesic prescribing in these groups.

3. Future directions: This study raises a number of questions, the first being if the frequent opioid use with increasing age, dementia, and nursing home residence may challenge patient safety, which should be explored in future studies. As opioid use has been increasing in several countries, there are reasons to suspect that our findings apply outside Denmark.

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