



# Trends of Opioid Utilisation in Denmark: A Nationwide Study

Søren Kabell Nissen<sup>1</sup> · Anton Pottegård<sup>2</sup> · Jesper Ryg<sup>1,3</sup>

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## Abstract

**Background** Opioid use has more than doubled over recent decades, and Denmark occupies fifth place in the global ranking. These increases have been partly attributed to the ageing population.

**Objective** Our objective was to assess the impact of age over time on utilisation of the most commonly used opioids in Denmark.

**Methods** We retrieved nationwide sales data on opioid sales in Denmark from 1999 to 2017. We investigated utilisation trends in age groups for the four opioids with the highest use. We used three volume-based metrics (defined daily doses/1000/day, oral morphine equivalents/1000/day, and packages dispensed/year) and one person-based metric (users/1000/year).

**Results** The four opioids selected according to users/1000/year were tramadol (46.1), codeine and combination products (12.4 for codeine, 3.7 for codeine and acetylsalicylic acid, and 4.2 for codeine and paracetamol), morphine (17.0), and oxycodone (12.1). Overall utilisation according to volume and person metrics increased for all except codeine and combination products. Tramadol doses or strength increased, albeit less with increasing age. Oxycodone doses or strength decreased for all age groups but were nearly unchanged for the age group  $\geq 80$  years.

**Conclusion** Tramadol is the most utilised opioid in Denmark and was prescribed at increasing doses or strengths over the study period, particularly in the younger ( $< 80$  years) age groups. Overall, oxycodone was prescribed at decreasing doses or strengths over time but remained unchanged for the age group  $\geq 80$  years. There is a need to address the pharmacological treatment of pain in terms of age, with tramadol and oxycodone being possible targets for regulatory efforts.

## Key Points

We found age-dependent differences in utilisation patterns for oxycodone and tramadol.

Tramadol is the preferred opioid in all age groups, suggesting tramadol is an important drug to monitor, though oxycodone cannot be ignored.

## 1 Introduction

The prevalence of chronic pain is high and affects 12–30% of all Europeans, with a considerable impact on self-reported quality of life, posing a major international healthcare issue [1]. For some patients, opioids are used to treat chronic pain, and the total use of opioids more than doubled from 1999 to 2016 worldwide [2].

Denmark currently occupies fifth place in global opioid consumption rankings, with approximately twice the consumption of similar healthcare systems in Norway and Sweden [3, 4]. This high ranking is alarming in light of the recently publicised “opioid epidemic” in the USA involving significantly more deaths from unintentional drug overdoses, likely driven by opioid misuse [5, 6].

In 2016, the Danish Health Authority mapped the use of opioids in Denmark and demonstrated an increasing consumption of opioids in general and tramadol in particular. Notably, unlike in Norway and Sweden, tramadol was omitted from prescription monitoring in Denmark until 2017 [3]. Treatment with opioids was more prevalent in the older population; hence, at least part of the increase was explained by the aging population [3].

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✉ Søren Kabell Nissen  
Soren.Kabell.Nissen@rsyd.dk

<sup>1</sup> Department of Geriatric Medicine, Odense University Hospital, J. B. Winsløvsvej 4, 5000 Odense C, Denmark

<sup>2</sup> Department of Public Health, University of Southern Denmark, Clinical Pharmacology and Pharmacy, J. B. Winsløvsvej 19, 3, 5000 Odense C, Denmark

<sup>3</sup> Department of Clinical Research, University of Southern Denmark, J. B. Winsløvsvej 19, 3, 5000 Odense C, Denmark

In 2010, it was estimated that 70% of costs related to the use of opioids in Denmark was for the indication chronic non-cancer pain in the primary healthcare sector [11]. Recently, Denmark implemented a national guideline for the management of chronic ( $\geq 3$  months) non-cancer pain, adapted from the Canadian guideline [7–10]. The guideline does not advocate any specific weak or strong opioid for initiation of analgesic treatment but recommends an opioid trial, provided other pharmacological and non-pharmacological treatments have been tested and shown to be ineffective.

Both guidelines emphasise using oral morphine equivalents (OMEQs) for comparison of opioid doses, calculated from defined daily doses (DDD) in milligrams. OMEQs might provide better comparison of opioids of varying potency, as DDDs are based on the formal indications of the World Health Organization (WHO) [12–15].

Neither the Danish nor the Canadian guidelines contain recommendations relating to age, even though the prevalence of chronic non-cancer pain increases with age [16]. Furthermore, the use of opioids is an acknowledged risk factor for geriatric syndromes such as falls and delirium [17].

The Danish Health Data Authority provides public access to registers linking anonymized individual-level data with nationwide drug sale statistics [18], allowing for investigation of opioid sales trends on a national level [19]. Specifically, by combining volume metrics with the number of users receiving prescribed opioids, it is possible to investigate trends in opioid utilisation over time, as previously done by Karanges et al. [20].

We aim to assess utilisation trends in relation to age for the most commonly prescribed opioids in Denmark by combining volume-level metrics with person-level metrics and investigating the proportionality of these over time.

## 2 Methods

This study was conducted using national Danish data from 1 January 1999 to 31 December 2017.

### 2.1 Setting

Denmark has tax-supported universal healthcare with equal and free access. A reimbursement system provides standardised partial refunds on most prescribed drugs, including opioids.

### 2.2 Data Sources

Data on opioid use were retrieved from the Danish Health Data Authority, public access to which is provided via the web service Medical Statistics (MEDSTAT) [18, 19].

The MEDSTAT database provides on-demand nationwide aggregate statistics on drug use with linkage to individual-level prescription data in the primary care sector (since 1996) and in the hospital sector (since 1999), for all registered drugs sold in Denmark. The study ended in 2017 as the MEDSTAT database is updated annually, with a backlog of about 12 months.

Drug sales are registered according to anatomical therapeutic chemical (ATC) classification code.

It is possible to provide linkage at an individual level for prescription opioids, as a valid civil registration number is a prerequisite for obtaining prescription medicine.

Opioids administered while patients are in hospitals are not registered by prescriptions; instead, prescriptions for opioids are written at discharge or at ambulatory visits and dispensed at community pharmacies, thus captured in the MEDSTAT data source. Hence, age-linked data are only available for primary sector prescription dispensing [21].

Data on users collecting any prescription have been considered reliable since 1999 [18]. Sales data on drugs available over the counter (OTC) are also captured in the MEDSTAT database, albeit without linkage to individual-level data as these are not registered for OTC sales.

When calculating the prevalence proportion of users for specific age groups, the denominator is not provided by MEDSTAT; instead, data on population size were retrieved from Statistics Denmark [22], also used by the MEDSTAT database, employing the same cut-off date of 1 January each year.

### 2.3 Opioids

We compiled data on opioid sales, divided into weak and strong potency subcategories [14].

All opioids are dispensed on prescription, except for some codeine and acetylic acid combination products (N02AJ07), which are also available OTC. It is not possible to age stratify OTC sales since these are not linked to a prescription.

The group of weak opioids encompassed codeine and paracetamol combination products (N02AJ06), codeine and acetylsalicylic acid combination products (N02AJ07), codeine (R05DA04), tramadol (N02AX02), and dextropropoxyphene (N02AC04). In 2009, the European Medicines Agency recommended the gradual withdrawal of dextropropoxyphene from the market [23], and no Danish dispensing has been registered since 2012.

Codeine and acetylsalicylic acid combination products (N02AJ07) are also sold OTC under the following conditions: Packages containing 20 tablets of paracetamol 500 mg + codeine 9.6 mg are available for OTC sale in pharmacies provided the customer is aged  $> 18$  years. Sales of packages containing ten tablets of paracetamol

500 mg + codeine 9.6 mg are not restricted to pharmacies. Any dose, package size, or combination other than the above is prescription only.

The group of strong opioids included morphine (N02AA01), hydromorphone (N02AA03), nicomorphine (N02AA04), oxycodone (N02AA05), oxycodone and naloxone combination products (N02AA55), pethidine (N02AB02), fentanyl (N02AB03), buprenorphine (N02AE01), and ketobemidone and antispasmodic combination products (N02AG02).

No prescriptions were registered in the study period for morphine combinations (N02AA51) or pethidine and psycholeptic combination products (N02AB72). For fentanyl, only ATC group N02 was included, as N01 is reserved for anaesthetics.

## 2.4 Data Analysis

Opioid sales were studied in the period from 1999 to 2017. Utilisation patterns were investigated by comparing relative changes of three volume-based metrics and one person-based metric as previously done by Karanges et al. [20]. We selected the four most commonly prescribed opioids in 2017 and stratified sales data according to year and age group for the users (0–64, 65–79, and  $\geq 80$  years). Utilisation patterns for prescription dispensing and OTC sales are presented separately.

The four opioids most commonly prescribed were identified according to the person-based metric prevalence proportion of users, defined as number of users dispensed at least one prescription per 1000 per year (users/1000/year).

The three volume-based metrics include packages dispensed per 1000 inhabitants per year (packages dispensed/1000/year), DDD per 1000 inhabitants per day (DDD/1000/day), and OMEQ per 1000 inhabitants per day (OMEQ/1000/day). The latter two metrics reflect standardised changes in utilisation (DDD) and corrected standardised changes according to potency (OMEQ). Utilisation data are presented according to opioid potency in two groups (weak and strong).

DDDs were converted to OMEQs, using best estimates of equianalgesic ratios for available formulations [3, 13, 14, 20], e.g. transdermal, per oral, parenteral, rectal, and suppository. The OMEQ value presented represents an aggregate of individually calculated OMEQs depending on the type of formulation of a given opioid [Table 1 in the Electronic Supplementary Material (ESM)].

For sales of codeine and acetylsalicylic acid combination products (N02AJ07), the share of prescription dispensing and OTC sales was retrieved. The majority of these sales reflected OTC sales, not linked to individual data, presented and analysed separately from prescription dispensing data.

## 3 Results

### 3.1 Utilisation of Weak and Strong Opioids, Not Stratified by Age

The most commonly prescribed opioids in 2017 according to users/1000/year were tramadol (46.1 users/1000/year), codeine including combination drugs (12.4 users/1000/year for codeine, 3.7 users/1000/year for codeine and acetylsalicylic acid, 4.2 users/1000/year for codeine and paracetamol), morphine (17.0 users/1000/year), and oxycodone (12.1 users/1000/year) (Fig. 1). The fifth most commonly prescribed opioid, a comparatively much lower figure, was fentanyl (3.3 users/1000/year) (Table 2 in the ESM). These numbers do not account for users obtaining more than one opioid or multiple prescriptions for the same opioid in a given year.

During the study period, utilisation of weak opioids increased by 44% according to OMEQ/1000/day and decreased by 26% according to DDD/1000/day (Table 2 in the ESM). This contrast is caused by the increasing use of tramadol holding more weight in the calculation of OMEQs because of its higher potency than codeine and codeine combinations (Fig. 1; Table 2 in the ESM). Metrics in Fig. 1 do not include OTC sales of codeine and acetylsalicylic acid combination products.

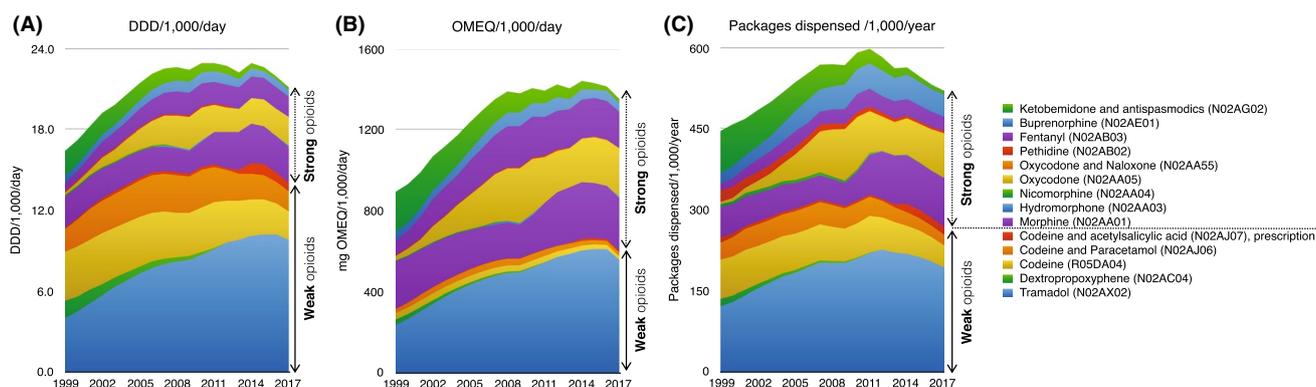
Utilisation of strong opioids increased by 33% according to OMEQ/1000/day and 25% according to DDD/1000/day (Table 2 in the ESM). The difference is caused by oxycodone and fentanyl both increasing substantially (1152% and 157%, respectively) and both being more potent than morphine (Fig. 1; Table 1 in the ESM).

### 3.2 Utilisation Trends of Most Prescribed Opioids, Not Stratified by Age

Prescribed morphine, oxycodone, tramadol, and codeine with acetylsalicylic acid increased by all metrics, whereas codeine and codeine with paracetamol decreased by all metrics (Table 1; Fig. 1).

The percentage difference between DDD/1000/day and OMEQ/1000/day was either zero or negligible (+0.3 percentage points for morphine) for all four opioids, as almost all registered sales of these drugs were exclusively for the oral formulation (Table 1 in the ESM); consequently, changes in OMEQ/1000/day are not displayed in Table 1.

Prescription dispensing of codeine and acetylsalicylic acid increased according to DDD/1000/day, with a concomitant decrease in DDD/1000/day for the OTC portion of sales (Fig. 1 in the ESM). This correlates with a limitation of OTC availability given the legal restrictions on package size imposed in 2013 in Denmark.



**Fig. 1** Prescription dispensing trends of all opioids investigated, listed in layered two-dimensional diagrams according to analgesic potency (weak below and strong above) in **a** DDD/1000/day, **b** OMEQ/1000/day, and **c** packages dispensed/1000/year [18]. DDD defined daily dose, OMEQ oral morphine equivalents. Metrics do not include over-the-counter sales of codeine and paracetamol combination products

### 3.3 Utilisations Trends of Selected Opioids, Age-Stratified

For tramadol, increased utilisation according to DDD/1000/day was not matched by an equally large increase in users/1000/year in any age group, with the relative change being less pronounced with increasing age (Table 1). As for tramadol, utilisation of codeine and acetylsalicylic acid combination products increased according to DDD/1000/day, with a smaller increase in users/1000/day, though the relative changes were more pronounced with increasing age (Table 1).

In contrast, oxycodone utilisation increased according to DDD/1000/year but with a larger increase in users/1000/year; the relative difference was smaller with increasing age (Table 1). Utilisation of morphine, like that of oxycodone, exhibited a larger increase according to users/1000/year than DDD/1000/day, but with nearly proportional relative changes of metrics when comparing age groups (Table 1).

Codeine utilisation diminished according to both metrics and did not display age-dependent differences, with nearly proportional relative changes of metrics in all age groups (Table 1).

Codeine and paracetamol combination products were utilised less according to DDD/1000/day, with a relatively larger decrease of users/1000/year; the difference was less pronounced with increasing age (Table 1).

Age-stratified metrics do not include OTC sales of codeine and acetylsalicylic acid combination products.

## 4 Discussion

This study demonstrated significant age-dependent trends in utilisation of select opioids in Denmark from 1999 to 2017. Further, it demonstrates an increasing utilisation of

day, and **c** packages dispensed/1000/year [18]. DDD defined daily dose, OMEQ oral morphine equivalents. Metrics do not include over-the-counter sales of codeine and paracetamol combination products

morphine, oxycodone, and tramadol, and codeine and acetylsalicylic acid combination products according to all metrics employed

### 4.1 Tramadol

Tramadol utilisation metrics suggested a trend towards an increasing proportion of the population being treated with a higher dose or strength, in similar quantities per dispensing when comparing changes in volume and person metrics. The volume metric DDD/1000/day increased the most (146%), followed by packages dispensed/1000/year (58%), which was nearly equal to the person metric users/1000/year (55%).

Stratifying for age, the proportional increase in volume-metric DDD/1000/year compared with the increase in person-metric users/1000/year was inversely correlated with increasing age, implying that, with decreasing age groups, there is a trend to prescribe tramadol to more users and at higher doses or strengths. There has been an increased focus on physical dependence on tramadol and reports of misuse of tramadol in some Middle Eastern and African countries [13, 24–26]. Further, the WHO expert committee on drug dependence has gradually acknowledged a potential for physical dependence on tramadol when used within the recommended dose range. The risk is still considered low compared with prototypical opioids [27], but it is likely to be dose related [24].

It has been proposed that the high utilisation of tramadol in Denmark is irrational, that the risk of physical dependence is not less than other opioids, and that tramadol is not superior in regards to analgesic or side effects [28]. This has likely prompted the recent monitoring of prescriptions of tramadol in Denmark. The high and increasing level of utilisation according to all metrics could also be a consequence of physician preference, which display significant national

**Table 1** Changes in opioid utilisation from 1999 to 2017 according to volume and person metrics, with interpretations of results based on relative changes [18]

	DDD/1000/day (% change)	Packages dispensed/1000/year (% change)	Users/1000/year (% change)	Comparison of metrics, interpretation
Morphine All age groups	16.0% ↑ <sub>Ref.</sub>	62.7% ↑↑↑ <sub>292%</sub>	159.3% ↑↑↑ <sub>897%</sub>	A larger increase in users and packages dispensed than DDD Suggests a trend to treat more patients, with lower doses or strengths
Age 0–64	21.9% ↑ <sub>Ref.</sub>		209.0% ↑↑↑ <sub>855%</sub>	A larger increase in users than DDD in the <65 years group
Age 65–79	–12.1% ↓ <sub>Ref.</sub>		78.1% ↑↑↑ <sub>747%</sub>	Suggests a trend to treat those aged ≥65 years with higher strengths and/or doses vs. the 0–64 years group
Age ≥80	–17.8% ↓ <sub>Ref.</sub>		112.9% ↑↑↑ <sub>734%</sub>	
Oxycodone All age groups	1151.9% ↑ <sub>Ref.</sub>	1974.6% ↑↑ <sub>71%</sub>	1734.6% ↑↑ <sub>51%</sub>	A smaller increase in DDD than packages dispensed and users Suggests a trend to treat more patients with slightly smaller doses and/or strengths <sup>a</sup>
Age 0–64	1262.3% ↑ <sub>Ref.</sub>		2054.7% ↑↑ <sub>63%</sub>	A smaller increase in DDD than users among the age group 0–79 years. Suggests a trend to treat those aged 0–79 years with lesser doses and/or strengths
Age 65–79	758.4% ↑ <sub>Ref.</sub>		1139.3% ↑↑ <sub>50%</sub>	vs. those aged ≥80 years. The overall increase in users was prompted by a likely trend to treat more patients aged 0–64 years
Age ≥80	1053.1% ↑ <sub>Ref.</sub>		1390.7% ↑ <sub>32%</sub>	
Tramadol All age groups	146.0% ↑↑↑ <sub>168%</sub>	58.4% ↑ <sub>7%</sub>	54.6% ↑ <sub>Ref.</sub>	A larger increase in DDD than users and packages dispensed Suggests a trend to treat more patients with higher doses and/or strengths
Age 0–64	171.7% ↑↑↑ <sub>176%</sub>		62.1% ↑ <sub>Ref.</sub>	A larger increase in DDD than users for all groups, though less pronounced with increasing age.
Age 65–79	80.6% ↑↑↑ <sub>215%</sub>		25.6% ↑ <sub>Ref.</sub>	Suggests a trend to treat those aged 0–79 years with higher doses and/or strengths vs. those aged ≥80 years
Age ≥80	44.8% ↑↑ <sub>136%</sub>		19.0% ↑ <sub>Ref.</sub>	
Codeine All age groups	–42.6% ↓ <sub>Ref.</sub>	–43.4% ↓ <sub>–2%</sub>	–44.4% ↓ <sub>–4%</sub>	Nearly equal decreases in DDDs, users, and packages dispensed Suggests a trend to treat fewer patients without a trend of changing doses and/or strengths
Age 0–64	–45.9% ↓ <sub>Ref.</sub>		–50.8% ↓ <sub>–11%</sub>	A larger decrease in DDD than users, similar for all age groups
Age 65–79	–43.9% ↓ <sub>–3%</sub>		–42.6% ↓ <sub>Ref.</sub>	Suggests no apparent age-related utilisation trends
Age ≥80	–53.3% ↓↓ <sub>–38%</sub>		–38.7% ↓ <sub>Ref.</sub>	
Codeine and ASA All age groups	466.3% ↑↑↑ <sub>994%</sub>	42.6% ↑ <sub>Ref.</sub>	264.2% ↑↑↑ <sub>520%</sub>	A larger increase in DDD than users and much smaller increase of packages dispensed than DDD. Suggests a trend to treat more patients with higher doses and/or strengths <sup>b</sup>
Age 0–64	582.5% ↑↑ <sub>70%</sub>		342.2% ↑ <sub>Ref.</sub>	A larger increase in DDD than users among those aged ≥80 years. Suggests a trend to treat those aged ≥80 years with higher doses and/or strengths than 0–79 years. The overall increase in users was prompted by a likely trend to treat more patients aged 0–79 years
Age 65–79	462.9% ↑↑ <sub>85%</sub>		250.3% ↑ <sub>Ref.</sub>	
Age ≥80	83.3% ↑↑↑ <sub>256%</sub>		23.4% ↑ <sub>Ref.</sub>	
Codeine and ASA, OTC All age groups	–77.9% ↓↓↓ <sub>–386%</sub>	–17.0% ↓ <sub>Ref.</sub>	N.A.	A larger decrease in DDD vs. packages dispensed. Suggests a trend to purchase smaller doses per package
Codeine and paracetamol All age groups	–9.5% ↓ <sub>Ref.</sub>	–37.6% ↓↓↓ <sub>296%</sub>	–64.8% ↓↓↓ <sub>–582%</sub>	A larger decrease in users than DDD, and larger decrease of packages dispensed than DDD. Suggests a trend to treat fewer patients with increasing doses and/or strengths

**Table 1** (continued)

	DDD/1000/day (% change)	Packages dispensed/1000/year (% change)	Users/1000/year (% change)	Comparison of metrics, interpretation
Age 0–64	1.7% ↑ <sub>Ref.</sub>		–66.9% ↓↓↓ <sub>–3973%</sub>	A larger decrease in users than DDD, less pronounced with increasing age. Suggests the trend to treat fewer patients with increasing doses and/or strengths is more pronounced with decreasing age
Age 65–79	–26.1% ↓ <sub>Ref.</sub>		–65.5% ↓↓↓ <sub>–151%</sub>	
Age ≥ 80	–46.7% ↓ <sub>Ref.</sub>		–66.7% ↓ <sub>–43%</sub>	

Arrows approximate the relative changes within one row, i.e. one type of opioid or one age group, the reference for relative change is the metric with the *least* change during the period. Relative change is calculated by: Relative change in percent =  $\frac{x-x_{ref}}{|x_{ref}|} \times 100$ . Relative change and which metric represents the reference ( $x_{ref}$ ) is denoted beside the arrows in subscript. Arrows visually indicate relative change according to the following parameters: ↑ indicates 0–50%, ↑↑ indicates 50–150%, ↑↑↑ indicates > 150%; ↓ indicates –50 to 0%, ↓↓ indicates –150 to –50%, ↓↓↓ indicates < –150%

ASA acetylsalicylic acid, DDD defined daily dose, OTC over-the counter

<sup>a</sup>Oxycodone has a DDD/median dose in non-cancer populations of 1.9 vs. 1.3 for morphine and 1.0 for tramadol [15], hence DDD/1000/day for oxycodone underestimates the use vs. morphine and tramadol [20]

<sup>b</sup>For codeine and ASA, the proportion sold on prescription increased from 3 to 24% in 2017

differences and seem to change over time [29], or tramadol might simply be the opioid physicians know best.

## 4.2 Codeine and Combination Products

For codeine, the changes in utilisation trends were proportional, nearly equal, for all metrics and when stratified for age (Table 1). This suggests a trend of decreasing utilisation, with no change in treatment- or prescription-related factors, and no obvious age-dependent trends to consider.

Utilisation of codeine and paracetamol combination products displayed a pattern of relative changes with primarily declining person metrics, users/1000/year (–65%), followed by packages dispensed/1000/year (–38%) and DDD/1000/day (–9.5%) (Table 1). This suggests a trend of treating fewer with higher doses or strengths and higher quantities per dispensing. Age stratification revealed a trend of reduced doses with increasing age groups.

Prescription of codeine and acetylsalicylic acid combination products is linked to OTC sales. Utilisation according to DDD/1000/day stagnated for OTC sales, and the prescribed volume increased and stagnated after the introduction of limitations on OTC sales in 2013 (Fig. 1 in the ESM). For prescription dispensing, utilisation according to packages dispensed increased much less than all other metrics (Table 1). This suggests a trend to treat more with higher doses or strengths, in much higher quantities per dispensing, compatible with the introduction of limitations on OTC sales, as users previously relying on OTC sales, are likely to instead obtain codeine and paracetamol on prescription.

Overall, the utilisation of codeine and combinations is declining, despite observed increases in prescriptions for codeine and acetylsalicylic acid combination products.

## 4.3 Morphine

We found a larger increase in users/1000/year (159%) than both packages dispensed/1000/year (63%) and DDD/1000/day (16%) (Table 1), suggesting an overall trend to treat more with morphine but likely with smaller doses or strengths. Only 5.2% of all dispensing in the period was for parenteral morphine, which has a conversion factor of 0.9 and therefore does not have a significant impact on this interpretation (Table 1 in the ESM). There does not seem to be significant age-related utilisation trends, though the relative change when comparing users/1000/year with DDD/1000/day was slightly larger for the age groups ≥ 65 years. This suggests a minor trend to treat these groups at higher doses or strengths than for the age group 0–64 years.

## 4.4 Oxycodone

Comparing non-age stratified metrics for oxycodone, the most prominent increase was for packages dispensed/1000/year (1974%), followed by users/1000/day (1734%). This indicates an overall trend to prescribe oxycodone to more patients, but likely at lower quantities per dispensing.

A comparatively small increase of DDD/1000/day (1151%) suggests lesser average prescribed dosing or strength compared with 1999. But it should be considered that oxycodone has a DDD/median dose in the non-cancer population of 1.9 compared with 1.3 for morphine and 1.0 for tramadol [15]. We thus risk *underestimating* the utilisation of oxycodone in comparison with these opioids.

This drug was first synthesised a century ago but, in the observed period, the increase in oxycodone utilisation according to the reference metric DDD/1000/day reflected the introduction of Oxycontin and Oxynorm. Since 2010,

these two products have gradually been replaced by other oxycodone products. Comparing oxycodone with morphine, the two drugs seem to “switch”, in terms of both volume and person metrics for all age groups around 2008. The Danish Health Authority considers this to be the consequence of an effort in regional health districts and hospital management to reduce oxycodone utilisation due to high relative pricing [30].

Stratifying for age, there is a trend of decreasing doses or strength with decreasing age and nearly no change over time in dosing or strength per user among those aged  $\geq 80$  years.

#### 4.5 Global Ranking According to the Defined Daily Dose (DDD) Metric

Given the high global ranking for legal sales of opioids in 2017 [2], it might be tempting to conclude irrational prescriber behaviour for opioids in Denmark. However, the global comparison includes use of opioids in animals, use for anaesthesia, and pharmaceutical production and does not solely reflect the use of opioids for analgesic treatment [2, 3]. The UN does not monitor analgesics, but does monitor narcotic drugs, according to the 1961 Convention for Drug Control [31], and as such, their data are not optimal for use in arguments about prescriber behaviour. All Nordic countries except Finland are included in the global top 20, indicating that a high ranking might simply reflect financial prosperity and access to sufficient, not necessarily irrational, amounts of opioids [4, 32].

#### 4.6 Aging

The prevalence of pain is closely linked to the age composition of the population [34], compatible with the higher utilisation metrics for both volume and people with increasing age observed in Fig. 2.

Opioids seem to be effective against diseases that are highly prevalent in old age, i.e. osteoarthritis, vertebral fractures, herpes zoster, and rheumatoid arthritis [1], though studies on older populations are insufficient [35]. The recent national guideline has little focus on age and the complexities this brings [9, 35], likely due to lack of evidence. Currently, tramadol seems to be the de-facto first-choice opioid, utilised significantly more according to both volume and users/1000/year, and comprises a prime target for regulatory efforts on prescriber behaviour. This has been set in motion nationally by monitoring prescriptions and publishing new guidelines [9], and internationally by critical review by the WHO [27]. Assessing the effects of introducing a pain management guideline on utilisation would require year-long follow-up, as practical de-escalation of medications for chronic or severe pain requires multiple re-evaluations

by the prescriber [10]. Furthermore, maintaining adherence to pain management guidelines might be more difficult in an environment where opioids are affordable [33]. In the near future, the method of analysis employed in this study could be utilised as one aspect in the evaluation of guidelines.

The fact that a decline in the use of tramadol in both DDD/1000/day and users/1000/year was seen between 2016 and 2017 (Figs. 1, 2) indicates that part of the population might have been prescribed too much tramadol, regardless of age. For the older population, the high utilisation of opioids is probably ameliorated by attitudes towards pain changing with increasing age. In a qualitative study regarding back pain among older patients with a median age of 83 years, respondents had negative attitudes towards the use of analgesics, accepting pain as an inevitability of old age [36].

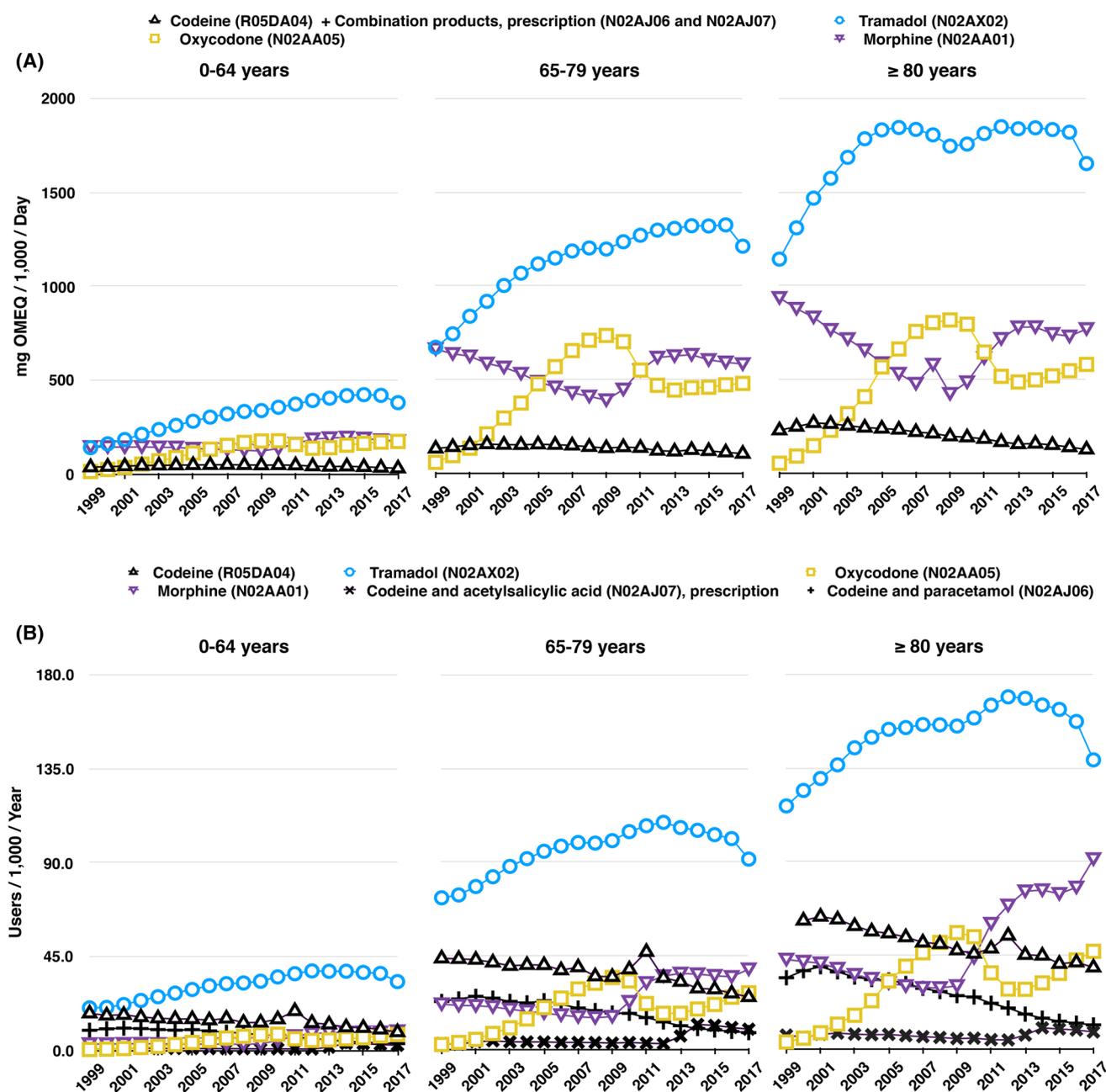
#### 4.7 Comparison to Other Studies on Opioid Utilisation Trends

Others have also found that tramadol is the most utilised opioid in terms of volume metrics, establishing that preferences for tramadol are similar in Norway and Sweden [29]. A report in Danish [37] also examined differences in volume- and person-metric trends from 2003 to 2013 using the same dataset as this study, though without comparison of proportional changes. Here, it was evident that tramadol, morphine, and oxycodone were increasingly popular among prescribers. It was speculated that the primary explanation for the increased opioid utilisation according to DDD/1000/day was an aging population and tramadol being prescribed instead of non-steroidal anti-inflammatory drugs (NSAIDs). Our study does not support the notion that increasing opioid utilisation was due to an aging population, instead indicating that utilisation of the selected opioids increased most for the age group 0–64 years. The tendency of age-related trends in dose or strength over time for tramadol and oxycodone will not be evident when examining utilisation trends independently. Our data do not allow speculation on opioid and NSAID utilisation trends.

A study in Australia, using the same analysis method as our study, without age stratification, from 2006 to 2015 [20] found that, for oxycodone, there was a pattern of proportionality of trends similar to our study. However, for tramadol, the utilisation trends were nearly proportional, unlike our finding. Hence, oxycodone was also used in a growing population in declining doses or strengths, whereas tramadol utilisation did not display a trend of increasing doses or strengths.

#### 4.8 Strengths and Limitations

The major strength of this study was our access to population-based nationwide aggregated wholesale data linked



**Fig. 2** Trends over time in prescription dispensing [18] according to **a** OMEQ/1000/day and **b** prevalence proportion according to users/1000/day of the most commonly used opioids stratified by age groups. **a** Prescription dispensing according to OMEQ/1000/day of tramadol (N02AX02) (circles), codeine and combination products (R05DA04, N02AJ06 and N02AJ07) (triangles), morphine (N02AA01) (inverted triangles), and oxycodone (N02AA05) (squares) for age groups 0–64 years, 65–79 years, and ≥ 80 years. Complete data for all investigated opioids are available in Table 4

in the Electronic Supplementary Material. **b** Prevalence proportion according to users/1000/day of tramadol (N02AX02) (circles), codeine (R05DA04) (triangles), codeine and paracetamol combination products (N02AJ06) (plus signs), codeine and acetylsalicylic acid combinations (N02AJ07) (crosses), morphine (N02AA01) (inverted triangles), and oxycodone (N02AA05) (squares) for age groups 0–64 years, 65–79 years, and ≥ 80 years. Metrics do not include over-the-counter sales of codeine and paracetamol combination products. OMEQ oral morphine equivalents

to individual characteristics. However, our study also has several limitations.

Any study on drug utilisation statistics without access to individual-level data will be unable to assess the quality

of opioid prescribing. Nor will it be possible to definitively identify irrational prescriber behaviour. This would require detailed knowledge of predisposing conditions and long-term follow-up with both quantitative and qualitative

methods. Hence, studies on drug utilisation statistics primarily allow some insight into medical culture and attitudes [29].

We converted DDDs to OMEQs in this study when displaying opioids of varying potency, as in Figs. 1 and 2. This allows for a better comparison of utilisation despite differences in clinical potency [13, 14]. There is limited consensus on equianalgesic ratios [38, 39], but OMEQs are likely best applied in epidemiological research, as it could be argued that there are no universal conversion factors, only a median population-based estimate. We consider OMEQs the best currently acknowledged approach to compare opioids of varying potency. The estimate of equianalgesic ratio derived from population studies should not be applied in clinical practice without significant caution given the variability in acquired tolerance, drug interactions, metabolism, body composition, and pain control [40], and that equianalgesic ratios cannot be considered bi-directional [39].

Furthermore, this study assumes proportional changes in prevalence of different severities of pain.

This assumption might be wrong and would require structured interviews and stringent quantification of pain on a large scale. A recent attempt to examine the prevalence of different severities of pain in the USA [41] found a nearly proportional increasing prevalence of all severities of pain. Hence, the assumption of proportional increases is likely to remain valid for our study.

Choosing to single out the four opioids with the highest number of users/1000/year in 2017 ensured the focus remained on utilisation patterns of the opioids most used by most prescribers; notably, though, we missed fentanyl. In the age group  $\geq 80$  years, fentanyl was dispensed in quantities surpassing those of morphine in DDD and OMEQs but only one-third of morphine when measured with users/1000/year (Tables 2 and 3 in the ESM), making it equally tempting to address in future guidelines regarding opioid treatment in old age.

Methadone (N07BC02) utilisation according to DDD/1000/day was significant, but we did not analyse this opioid in this study because it is largely used for treatment of opioid addiction. The exact proportion used for treatment of opioid addiction is unknown but considered to be the vast majority, and only about 50% can be linked to individual-level data, as the rest is distributed from clinics for substance abuse according to a recent report on Danish opioid utilisation [37]. This might have interfered with the results albeit probably only marginally, as methadone users outside addiction treatment comprise a clear minority (most often palliative patients) and would not have been included as any of the four opioids selected for analysis in Table 1.

Finally, we assumed consumption of opioids after collection of the prescription, which might bias the data towards a marginal overestimation of consumption.

## 5 Conclusion

Tramadol is the most utilised opioid in Denmark and was prescribed at increasing doses or strengths over the study period. This was most pronounced for the younger ( $< 80$  years) age groups. Oxycodone was prescribed at decreasing doses or strengths over time, but this was nearly unchanged for the age group  $\geq 80$  years. There is a need to address the pharmacological treatment of pain with regards to age, with tramadol and oxycodone being possible targets for regulatory efforts.

## Compliance with Ethical Standards

**Funding** No sources of funding were used to conduct this study or prepare this manuscript.

**Conflict of interest** Søren Kabell Nissen, Anton Pottegård, and Jesper Ryg have no conflicts of interest that are directly relevant to the content of this study.

**Ethical approval** This study was based on aggregate data, and no ethical approval was necessary.

**Data availability** All data generated or analysed during this study are included in the paper or its supplementary files.

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