

SHORT COMMUNICATION

Trends in utilization of tramadol and other opioids in Denmark 2017–2023: A nationwide drug utilization study

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None.

The use of tramadol and other opioids for pain management has been accompanied by a multitude of challenges and concerns worldwide. The use of tramadol saw a decline in Denmark during 2017–2019 accompanied by a slight increase in the use of morphine and oxycodone. Using the Danish National Prescription Registry and utilizing data until and including 2023, we aimed to provide updated data on the utilization patterns of tramadol and other opioids in Denmark. We found a 35% decline in the use of tramadol from 2017 to 2023 most likely due to media attention, regulatory actions, health campaigns and targeted education of physicians and patients by the Danish health authorities. This decline was accompanied by an increase in the number of new (+90%) and current users of morphine (+57%), which surpassed those of tramadol, oxycodone and other opioids in 2023.

KEYWORDS

Denmark, drug utilization, opioids, tramadol

1 | INTRODUCTION

The widespread use of tramadol and other opioids for pain management has been accompanied by a multitude of challenges and concerns worldwide. While these medications can offer effective relief for acute pain, their effect in chronic non-malignant pain is limited, and their misuse and abuse have become significant and pressing public health issues.¹ The use of tramadol in Denmark saw a decline from 2017 to 2019,² a trend potentially influenced by heightened media attention and regulatory risk minimization actions initiated by the Danish health authorities in 2017–2018 aimed at reducing tramadol prescribing and working for a more rational consumption of opioids in general. The consumption of tramadol and other opioids was for a number of years considerably higher than in the other Scandinavian countries prior to the actions initiated by the Danish health authorities.^{2,3} Concurrent with the declining use of tramadol, there was a slight increase in the prevalence of morphine and oxycodone driven by short-term and sporadic use.² The decline in tramadol prescribing in Denmark has been most evident

in general practice, while hospital physicians were increasingly responsible for the prescribing of morphine and oxycodone in the period from 2000 to 2021.⁴ There have been continued efforts by the Danish health Authorities to restrict the use of tramadol and facilitate rational use of opioids. As the prescribing pattern of tramadol and other opioids has changed dramatically over time, especially in recent years,^{2,3} and with new regulations and initiatives from the health authorities, we aim to provide updated data on the utilization patterns in Denmark utilizing data until and including 2023.

2 | METHODS

2.1 | Data sources

We used the Danish National Prescription Registry to identify all opioid prescriptions.⁵ The registry holds information on all drugs dispensed at Danish pharmacies since 1995. For every filled prescription,

it includes information on the personal identification number, the dispensed drug, the date of dispensing, the dispensed volume in WHO defined daily doses (DDD),⁶ the WHO anatomical therapeutic chemical (ATC) code⁶ and a prescriber identifier, which denotes the prescriber specialty.⁷

2.2 | Study population and study drugs

We identified all individuals living in Denmark ≥ 18 years filling at least one prescription of tramadol, morphine, oxycodone, codeine and other opioids from 1 January 2017 to 31 December 2023. We included opioids in oral solid dosage forms (i.e., tablets and capsules) and opioids for transdermal use and excluded opioids in the following dosage forms: intravenous formulations, gels, suppositories, oral suspensions and oral drops and nasal sprays (all of which are very rarely used in Denmark). All three codeine combination products available in Denmark were included, while we restricted to codeine tablets and disregarded oral codeine suspensions (used to treat cough). Opioids (ATC N02A and R05DA04) were grouped into the three most commonly used opioids: tramadol, morphine, oxycodone and codeine.² A group of 'other opioids' included the remaining opioids in ATC group N02A of which 85% were fentanyl and buprenorphine for transdermal use. Population counts were extracted from Statistics Denmark. Definitions of drugs using ATC codes can be found in Appendix S1.

2.3 | Analysis

We calculated the monthly incidence rate by using the monthly number of new opioid users in the numerator and the total person-time at risk on the first day in each quarter in the denominator. New users of opioids were defined as those having no dispensing of the same drug or drug class within the last 5 years. We calculated the quarterly prevalence proportion by using the number of current opioid users in the numerator and the total population count on the first day in each quarter in the denominator. Current use was defined as the filling of at least one prescription in the given quarter. In a supplementary analysis, we calculated the incidence rate and prevalence proportion stratified by the five Danish regions. We calculated the total monthly use of tramadol and other opioids in oral morphine equivalents (OMEQs) and DDDs per 1000 individuals. OMEQs were used to quantify the equipotent amount of opioids used, while the DDD is a standardized measurement unit often used to compare drug use between populations and countries.⁶ For OMEQs, we used and applied conversion factors published by Svendsen et al. and Jarlbaek.^{8,9} In a post hoc analysis, we split morphine into modified-release tablets and instant-release tablets and analysed those separately. Lastly, we calculated the annual proportion of new and subsequent (representing maintenance treatment) prescriptions of tramadol and other opioid that was prescribed by general practitioners and hospital physicians.

2.4 | Others

All analyses were performed using Stata Release 18.0 (StataCorp, College Station, Texas, USA). Approval from an Ethics Committee is not required according to Danish law. The study was registered at the University of Southern Denmark's inventory (record no. 10.490).

3 | RESULTS

A total of 1 368 950 individuals filled at least one opioid prescription from 2017 to 2023. Figure 1 depicts the incidence rate, prevalence proportion and the total drug use of opioids measured in OMEQs from 2017 to 2023. The incidence rate of tramadol use decreased during the study period from 1.98/1000 person-months in January 2017 to 0.46/1000 person-months in December 2023. During the same period, the incidence rate of morphine use increased markedly (from 0.87 to 1.66/1000 person-months). The incidence rate of use of oxycodone, codeine and other opioids decreased during the study period (Figure 1 and Table S1).

The prevalence proportion followed the same pattern as the incidence rate. The prevalence of tramadol use decreased from 30 to 9.9/1000 individuals from January 2017 to December 2023. Meanwhile, the prevalence of morphine use increased from 8.7 to 14/1000 individuals. Total drug use measured in OMEQs/1000 individuals (Figure 1 and Table S1) and DDDs/1000 individuals (Figure 1S) decreased for all opioids from 2017 to 2023. Total drug use for morphine decreased from 9667 to 8850 OMEQs/1000 and for tramadol from 22 530 to 7961 OMEQs/1000 individuals. Total drug use halved for 'other opioids' from 10 033 to 5261 OMEQs/1000 individuals (Figure 1 and Table S1).

The post hoc analysis showed an increase in the incidence rate and prevalence proportion of use of both instant- and modified-release morphine dosage forms, a decrease in the total use of modified-release morphine and a stable and low use of instant-release morphine from 2017 to 2023 (Figure 2).

The incidence and prevalence of opioid use followed the same pattern in all regions (data not shown), although there were regional variations in the relative distribution of use of tramadol and morphine (Table S2).

The percentage of tramadol initiated and maintained by general practitioners and hospital physicians decreased from 2017 to 2023. Whereas tramadol accounted for 44% of all opioids initiated by general practitioners in 2017, this went down to 21% in 2023. Meanwhile, morphine accounted for a greater percentage of all opioids prescribed over time among general practitioners and hospital physicians both in regard to treatment initiation and treatment maintenance (Figure 3).

4 | DISCUSSION

This study presents current evidence on the real-world utilization patterns of tramadol and other opioids in Denmark. The 35% decline in

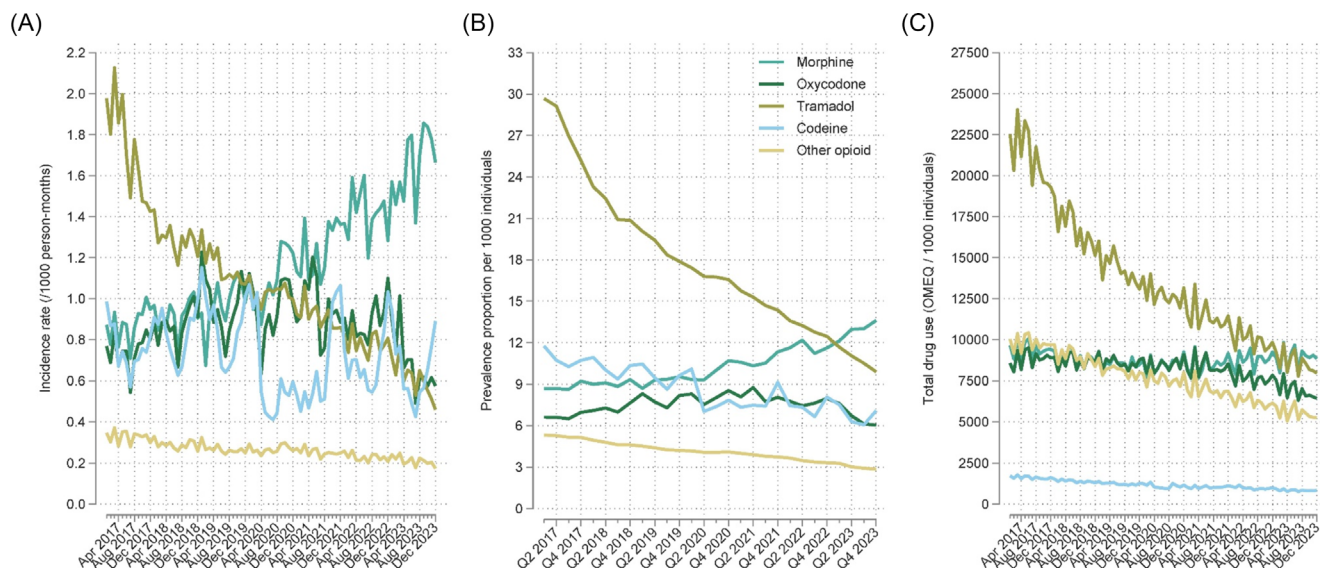


FIGURE 1 The monthly incidence rate (A), quarterly prevalence proportion (B) and the total drug use in oral morphine equivalents (OMEQs) (C) for use of morphine, oxycodone, tramadol, codeine and other opioids from 1 January 2017 to 31 December 2023. Please note different scales on y-axis.

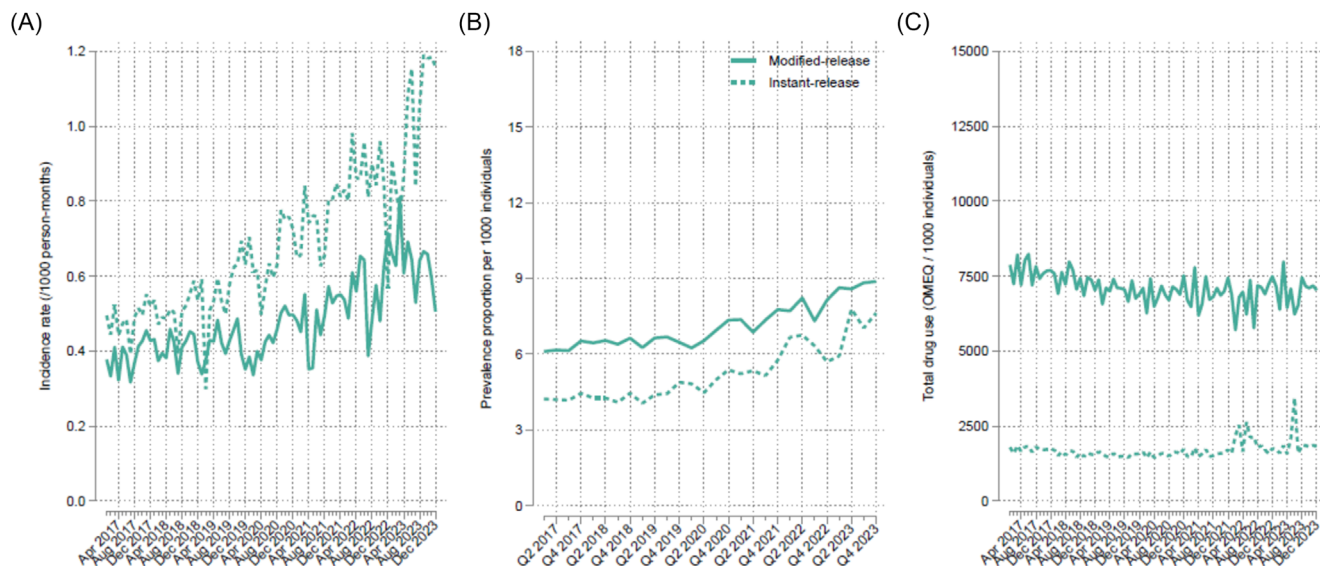


FIGURE 2 The monthly incidence rate (A), quarterly prevalence proportion (B) and the total drug use in oral morphine equivalents (OMEQs) (C) for use of morphine split into instant-release and extended-release dosage forms from 1 January 2017 to 31 December 2023. Please note different scales on y-axis.

total use of tramadol during 2017–2023 is most likely a combined consequence of media attention, regulatory actions, health campaigns and a strong collaboration between general practitioners, hospitals, non-governmental organizations and health authorities. Our findings underscore the effectiveness of a combined effort to facilitate rational use of opioids in Denmark.

The main strength of the study is the use of complete and nationwide data⁵ on opioid prescriptions filled by all adults in Denmark with no risk of selection or recall bias. The study also has

some limitations. First, the study was based on filled prescriptions, which are only proxies of drug use. However, filled prescriptions are considered superior to data from questionnaires or medical records, and the rate of primary nonadherence for tramadol and codeine has been found to be low.¹⁰ Second, we had no data on in-hospital use of opioids, although we were able to capture opioids prescribed by hospital physicians and dispensed at community pharmacies. Third, we did not look at the use of non-opioid analgesics such as gabapentinoids, which may have increased as a response to the changing

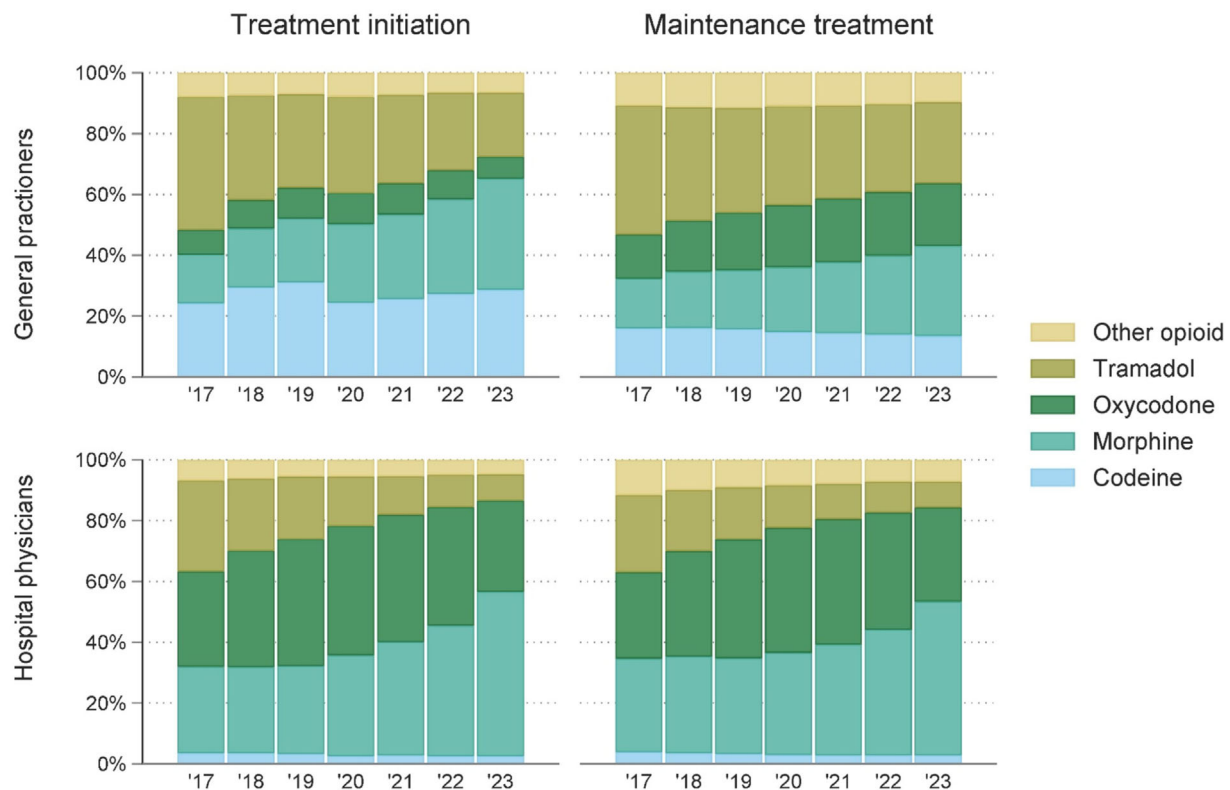


FIGURE 3 Proportion of first (treatment initiation) and subsequent (maintenance treatment) prescriptions for tramadol and other opioids prescribed by general practitioners and hospital physicians 2017 to 2023.

utilization patterns of opioids. However, a previous study did show increases in the use of gabapentinoids from 2014 to 2019,² and a recent study showed that these trends continued until 2023 (Pottgård et al., under review.). Finally, we have no data on the illicit sales and use of opioids, which is closely monitored by the Danish Health Authorities.^{11–13}

We document a persistent and substantial decline in the incidence, prevalence and total use of tramadol alongside a continuous and substantial increase in the incidence and prevalence of morphine use during the 6-year period following the first regulatory actions and media attention. Accordingly, the proportion of tramadol prescribed by both general practitioners and hospital physicians continued to decrease thus extending the trends observed in Denmark from 2000 to 2021.⁴ Our findings of a continued decline in tramadol use over the period most likely reflect the effect of combined and continued efforts by the Danish health authorities to facilitate rational use of opioids and a strong collaboration with general practitioners, hospitals and non-governmental organizations. As examples, the Danish Health Authority published a pain guideline in 2019 targeting prescribers in both the primary and secondary health care sector,¹⁴ a patient folder was developed to educate patients using drugs with abuse potential,¹⁵ the AVLIV campaign was launched in 2020 targeting patients living with chronic pain,¹⁶ in April 2022 tramadol was added to the list of euphoric substances by the Danish Health Authority, and lastly, from January 2018 and onwards, tramadol has followed the same regulatory restrictions of prescribing

as opioids with a known abuse potential such as morphine and oxycodone.²

By the end of 2023, the incidence and prevalence of morphine use surpassed those of tramadol, oxycodone and other opioids aligning with guidelines recommending morphine as the first-choice treatment for acute and cancer-related pain when treatment with opioids is indicated.¹⁴ Accordingly, morphine accounted for a greater proportion of prescriptions over time, both among general practitioners and hospital physicians. Our findings show that there was an increased use of both instant- and modified-release morphine dosage forms. As it is recommended to prescribe modified-release morphine due to improved pain coverage, fewer breakthrough pain episodes, and less euphoric effect compared to instant-release morphine, this development should be monitored closely. However, the total use of morphine did not increase from 2017 to 2023 thus indicating that the increase in the incidence and prevalence of morphine use is due to more short-term use or use of lower doses as also demonstrated previously.² In addition, a report from the Danish Health Data Authority found that the proportion of users who use opioids in higher doses or for a longer duration than what is recommended by the Danish Health Authority has declined from 2016 to 2021.¹⁷

Comparison of our results with other studies is challenged by differences in measurements of opioid consumption, ambulatory vs. primary care setting¹⁸ and data coverage. In addition, most studies lack utilization data for the most recent years, which is where Denmark

has seen the most dramatic changes in the utilization of opioids. Furthermore, utilization patterns of opioids depend on national regulations and initiatives as shown previously.² However, a study from Slovenia 2010–2019¹⁹ based on health insurance claims data including all outpatient opioid prescriptions found a decline in the number of tramadol prescriptions per 1000 inhabitants, a decline in DDD per 1000 inhabitants, and an increase in the number of DDDs per prescription. Meanwhile, the authors found a decline in the number of morphine prescriptions per 1000 inhabitants, a decline in DDD per 1000 inhabitants and a decrease in the number of DDDs per prescriptions.¹⁹ The latter reflects less intensive prescribing of morphine¹⁹ in accordance with our results showing increases in the incidence and prevalence of morphine use but a decrease in the total amount of dispensed morphine.

In conclusion, we find a persistent decline in the use of tramadol most likely as a combined consequence of media attention, regulatory risk minimization measures and continued efforts by the Danish Health Authorities to facilitate the rational use of opioids in Denmark. The decline in tramadol use was accompanied by increases in the number of new and current users of instant- and modified-release morphine, which should be monitored closely in future studies due to the high abuse potential of instant-release morphine. Our results can assist in future prioritization of interventions to further facilitate rational use of opioids in Denmark and emphasizes the already successful regulations and initiatives to reduce the use of tramadol.

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CONFLICT OF INTEREST STATEMENT

JS, MTE, AMSS and SF report no conflict of interest. LR reports participation in research projects funded by Novo Nordisk with funds paid to the institution where she was employed (no personal fees) and with no relation to the work reported in this paper. AP reports participation in research projects funded by Alcon, Almirall, Astellas, Astra-Zeneca, Boehringer-Ingelheim, Novo Nordisk, Servier and LEO Pharma (all regulator-mandated phase IV-studies), and an unrestricted research grant from Novo Nordisk, all with funds paid to the institution where he was employed (no personal fees) and with no relation to the work reported in this paper.

DATA AVAILABILITY STATEMENT

Due to Danish legislation, individual-level data are not available. Deidentified data can be made available for authorized researchers after application to Forskerservice at the Danish Health Data Authority. MTE had full access to data. Coding scripts are available upon request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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