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Short-term mortality following tramadol poisonings in Denmark

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Abstract

Tramadol is a commonly used opioid with a potential of addiction and abuse. Using Danish nationwide registers, we aimed to (1) characterise opioid poisonings; (2) assess the 30-day mortality following morphine, oxycodone, and mixed poisonings compared to tramadol poisonings; and (3) assess the development in tramadol poisonings during a 12-year period.

Poisonings were identified from 2006 to 2017. A Cox proportional hazards regression model was used to estimate adjusted hazard ratios (aHRs) along with 95% confidence intervals (CIs) for 30-day mortality following morphine, oxycodone or mixed poisonings compared to tramadol poisonings.

We identified 7718 opioid poisonings among 6365 patients. The patients with a tramadol poisoning were younger and had less comorbidities than the patients with a morphine, oxycodone or mixed poisoning. Within 30 days, a total of 205 patients died. The 30-day mortality risk was higher following morphine (aHR 3.2, 95% CI 2.0–5.1), oxycodone (aHR 2.1, 95% CI 1.2–3.6) and mixed poisonings (aHR 1.6, 95% CI 1.0–2.7) compared to tramadol poisonings. The annual number of tramadol poisonings increased from 233 in 2006 to 501 in 2013 and declined to 348 in 2017.

In conclusion, despite a lower mortality risk compared to other opioid poisonings, physicians should consider the poisoning and abuse risks when prescribing tramadol.

KEYWORDS
epidemiology, intoxications, mortality, opioids, poisonings

1 | INTRODUCTION

Tramadol was marketed in Denmark in 1993 and was considered less addictive than traditional opioids.[1–4] The use of tramadol increased for many years and is now widespread in Denmark despite a decreasing use during the recent years.[5] The potential for addiction and misuse has been a debated topic which has led to tramadol being

regulated more closely from authorities in, for example, the United States and the United Kingdom.[6,7] In Denmark, from January 2018, tramadol has followed the same regulatory restrictions of prescribing as opioids with a known abuse potential (e.g. morphine and oxycodone).[8] These restrictions entail, among other, that tramadol can only be dispensed once per prescription and the use and prescription pattern is under surveillance by the authorities.[8]

Tramadol is a centrally acting opioid that, unlike traditional opioids, also inhibits the reuptake of noradrenalin and serotonin leading to various poisoning symptoms.[9] These include classic opioid symptoms such as nausea and vomiting, central nervous system depression, and respiratory depression.[10–13] Non-opioid symptoms include cardiac conduction disorders, seizures, serotonin syndrome, and cardiogenic shock.[10,11,13–15] Fatal cases of tramadol poisoning have been reported in several countries.[16–18] The use of opioids in the general Danish population has changed dramatically during the past decades.[5,19] The annual prevalence of tramadol, morphine, and oxycodone users increased from 2006 to 2017 and reached a total of 265 030, 97 765 and 69 470 users per year in 2017, respectively.[20]

Due to the widespread use of tramadol and potential of addiction, the risk of tramadol poisoning is presumed high but is sparsely investigated. In this study, we assessed the mortality following a morphine, oxycodone, or mixed poisoning compared to a tramadol poisoning. Additionally, we characterised cases of opioid poisoning and assessed the annual number of tramadol poisonings during a 12-year period.

2 | METHODS

The study was a retrospective cohort study covering patients registered with a tramadol, morphine, oxycodone, or mixed poisoning in Denmark from 1 January 2006 to 31 December 2017.

2.1 | Data sources

To identify poisonings, we collected data from the Danish Poison Information Centre database (DPIC), the Danish National Patient Registry (DNPR), and the Danish Register of Causes of Death (DRCD). In order to link the data sources, we used the unique identifier, the Civil Personal Register (CPR) number, which is assigned to all Danish residents at birth or immigration.

The DPIC was established in 2006 and offers a nationwide 24-h telephone advisory service for health-care professionals and the public on pharmacological and non-pharmacological toxicological issues. Inquiries to DPIC are handled by specialised nurses, and when required, a physician is consulted. All inquiries are registered in the DPIC database with information on, among others, drug, time of intake, symptoms, recommended treatment, co-exposure drugs, age, sex, and, for most inquiries, the CPR number is recorded. In addition, the database has a 'free text' section where the nurse (or physician) can describe the specific case and the provided advice. Information on suspected drugs is registered using the Anatomical Therapeutic Chemical (ATC) classification system which is a coding system classifying drugs according to the organ or system on which they work.[21]

Information on poisonings registered at hospitals was obtained from the DNPR.[22] The DNPR contains information on all admission and discharge diagnoses from Danish hospitals since 1977. From 1994 and onwards, diagnoses are classified according to the tenth revision of the International Classification of Diseases (ICD-10). Information on death and causes of death was obtained from the Danish Civil Registration System and the DRCD.[23,24]

2.2 | Cohort definitions

All patients registered in the DPIC database or in the DNPR with a tramadol, morphine and/or oxycodone poisoning from 1 January 2006 to 31 December 2017 or in the DRCD with a tramadol, morphine and/or oxycodone poisoning from 1 January 2006 to 31 December 2016 were included in the study. Due to annual and not continuous updates of the DRCD, data from 2017 were unavailable. We compared tramadol with these opioids as they are the most frequently used, have similar indications and drug formulations, and are well known among physicians.[5,25]

In the DPIC database, a case of poisoning was defined as the registration of a relevant ATC code (tramadol = N02AX02, morphine = N02AA01, or oxycodone = N02AA05) as the suspected cause of the poisoning. In addition, inquiries with a registration of tramadol, morphine, or oxycodone, or a related word in the 'free text' section were manually searched and included in the relevant exposure cohort. A list of words used in the search is provided in the supporting information. In the DNPR and the DRCD, a case of tramadol, morphine, or oxycodone poisoning was based on specific ICD-10 codes and a supplementary code of tramadol, morphine, or oxycodone (by ATC code). Codes are provided in the supporting information.

We included both mono (cases in which tramadol, morphine, or oxycodone were the only administered

substance) and mixed poisonings (cases with multiple administered substances in addition to tramadol and/or morphine, and/or oxycodone). For example, poisonings with both tramadol and paracetamol, or morphine and oxycodone, were classified as mixed poisonings.

In the DNPR, a hospitalisation can consist of one or more registrations. If the time span between two registrations was ≤6 hours, we considered the registrations to belong to the same hospitalisation. An inquiry to the DPIC and a hospitalisation were considered related to the same poisoning case if the inquiry to the DPIC was made between 24 h before the time of hospitalisation and until the time of discharge.

2.3 | Outcomes

The primary outcome was the 30-day mortality risk following a tramadol, morphine, oxycodone, or mixed poisoning. In addition, we characterised poisoning cases and calculated the annual number of cases of tramadol poisoning in Denmark from 2006 to 2017.

2.4 | Statistics

Descriptive statistics were used to present patient and case characteristics. The patients were categorised according to sex, age group (≤10, 11–30, 31–45, 46–65, 66–79 and ≥80), and comorbidities. Among the cases registered in the DPIC, we analysed the reason for the poisoning (intentional, unintentional, or abuse). If more than one reason was registered, the reasons were ordered so that abuse superseded intentional and unintentional, which were exclusive. For cases in the DNPR, we assessed the duration of hospitalisation (in days). Age, sex, and comorbidities were analysed at date of first contact to DPIC, date of admission, or date of death, whichever occurred first. For patients registered in the DNPR, we included comorbidities in the analyses based on a 10-year history. We used the Elixhauser comorbidity measure to calculate a comorbidity score based on ICD-10 codes.[26,27] ICD-10 codes are provided in the supporting information (Table S1).

The index date was defined as the date of poisoning, which was either the date of inquiry to the DPIC or the date of hospitalisation with a poisoning, whichever came first. For the mortality analyses, we included the first poisoning case for each patient during the study period. No patients emigrated from the country within 30 days following the date of poisoning, and hence, no patients were censored. The patients with a registration of death in the DRCD during the study period but without a related registration in the DNPR or DPIC were excluded from the mortality analyses as no information on date of poisoning was available. The patients registered in DPIC without a CPR number were excluded from the mortality analyses as linkage to the remaining registers was unfeasible. The 30-day mortality risks for cases of tramadol, morphine, oxycodone, or mixed poisonings were presented using the Kaplan-Meier estimate. A Cox proportional hazards regression model was used to estimate the crude and adjusted hazard ratio (HR) for 30-day mortality following a morphine, oxycodone, or mixed poisoning compared to a tramadol poisoning. Results were presented with corresponding 95% confidence intervals (95% CI). In the first adjusted model, we included age (grouped) and sex. In the second adjusted model, we added the Elixhauser comorbidity score. The proportional hazards assumption was tested using the supremum test, and a HR was reported at 7 days if the assumption was violated for the 30-day mortality analysis. To account for non-linearity in the Cox proportional hazards regression model, the Elixhauser comorbidity score was included as a third degree polynomial.

When calculating the annual incidence of tramadol poisonings recorded in the DPIC, DNPR, or DRCD, the denominators were the total yearly number of poisonings in the DPIC, DNPR, or DRCD, respectively. The number of yearly poisonings was identified in the DNPR and the DRCD based on ICD-10 codes. In the DPIC database, the number of yearly poisonings was identified based on all inquiries. Hence, the denominators were not restricted to opioid poisonings but included any type of poisonings. The results were presented per 10 000 poisonings per year.

Due to national regulations on data protection, cases <5 were not presented. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

2.5 | Ethics

This study was approved by the Danish Data Protection Agency (BFH-2016-070). Anonymised, retrospective register studies do not require ethical approval or written informed consent according to the Danish Act on Processing of Personal Data. This study follows the Strengthening the Reporting of Observational Studies in Epidemiology statement.[28]

3 | RESULTS

From 1 January 2006 to 31 December 2017, we identified 7718 tramadol, morphine, oxycodone, or mixed

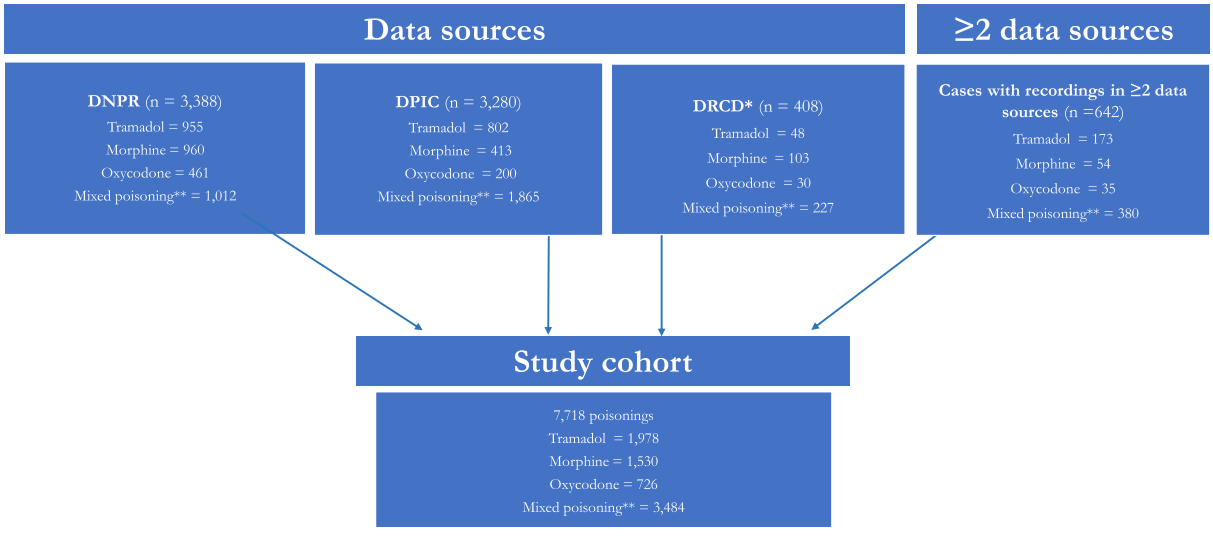
poisonings among 6365 patients (Figure 1). Among the inquiries to the DPIC, 589 did not include a CPR number and hence could not be identified in the DNPR and/or DRCD. Across the three data sources, mixed poisonings ($n = 3484$) were the most frequent followed by tramadol ($n = 1978$), morphine ($n = 1530$), and oxycodone ($n = 726$). In cases with a tramadol poisoning, 49% were mono poisonings. Corresponding percentages for cases of morphine or oxycodone poisoning were 58% and 54%, respectively. The distribution of cases across data sources is illustrated in the supporting information (Figure S1). The overlap of cases between data sources was largest for the DNPR and DPIC with 613 cases registered in both. A total of four cases were registered in all three data sources. In a post hoc analysis, we found that among the 3280 inquiries to the DPIC, 2214 resulted in a hospitalisation (defined as hospitalisations from 24 h before the inquiry to the DPIC) without a specific poisoning code in the DNPR.

The patient characteristics are shown in Table 1. Mean (SD) age in years was 48.6 years (21.5), and the proportion of males was 45%. Generally, the patients with a tramadol poisoning had less comorbidities compared to the patients with a morphine, oxycodone, or mixed poisoning (Table 1). The Elixhauser mean score (SD) among tramadol poisonings was 0.92 (3.5), which was lower than for morphine (2.8 [5.1]), oxycodone (2.6 [5.0]), and mixed poisonings (1.4 [4.1]), indicating a lower level of comorbidity. Particularly, the prevalence of cancer and drug abuse was lower among patients with a tramadol poisoning (Table 1). Case characteristics are displayed in Table 2. Among hospitalisations due to tramadol poisonings, the mean (SD) duration of hospitalisation was 1.5 (3.9) days, which was lower than for cases of morphine (2.8 [4.8]), oxycodone (2.7 [5.0]), and mixed poisoning (1.6 [3.1]). Among poisonings with a registered cause, drug abuse was registered for 11.5% of mixed poisonings, 11.7% of tramadol poisonings, 13.8% of morphine poisonings, and 21.0% of oxycodone poisonings (Table 2).

During the study period, 2059 (32.3%) patients died. Deaths only registered in the DRCD ($n = 408$) represented 48 tramadol, 103 morphine, 30 oxycodone, and 227 mixed poisonings. These cases were excluded from the mortality analyses as the index date was unknown. A total of 205 patients (3.2%) died within 30 days following the index date representing 22 tramadol, 92 morphine, 28 oxycodone, and 63 mixed poisonings.

The Kaplan-Meier plot is shown in Figure 2. The mortality (fully adjusted model) within 30 days was higher among morphine (HR 3.2, 95% CI 2.0–5.1), oxycodone (HR 2.1, 95% CI 1.2–3.6), and mixed poisonings (HR 1.6, 95% CI 1.0–2.7) compared to cases of tramadol poisoning. The adjusted analyses resulted in lower HRs compared to the unadjusted model. In all three models, the HRs were higher among morphine, oxycodone, and mixed poisonings compared to tramadol poisonings (Table 3).

Because the proportional hazards assumption was (marginally) violated for the 30-day mortality, the follow-up period was shortened to 7 days. Within this time period, the proportional hazards assumption was fulfilled. Unadjusted and adjusted HRs for the 7-day mortality are presented in supporting information Table S2.



*Study period for DRCD: January 1, 2006 to December 31, 2016, **Mixed poisonings are defined as cases with multiple administered substances in addition to tramadol, and/or morphine, and/or oxycodone
DNPR: the Danish National Patient Registry, DPIC: the Danish Poison Information Center, DRCD: the Danish Register of Causes of Death

FIGURE 1 Description of the study cohort (1 January 2006 to 31 December 2017)

TABLE 1 Patient characteristics

Drug n = unique patients	All (n = 6365)	Tramadol (n = 1554)	Morphine (n = 1313)	Oxycodone (n = 610)	Mixed (n = 2888)
Sex (male)	45.0%	41.5%	51.0%	44.1%	44.4%
Missing	0.1%	0.1%	-	-	0.2%
Mean (SD) age (years)	48.6 (21.5)	45.2 (22.4)	55.6 (21.9)	53.5 (23.5)	46.2 (19.3)
Age groups					
≤10	3.8%	6.4%	3.7%	5.7%	2.1%
11–30	17.7%	20.3%	10.7%	12.6%	20.5%
31–45	23.5%	24.9%	16.8%	16.6%	27.2%
46–65	31.6%	29.5%	31.2%	29.8%	33.3%
66–79	13.9%	9.4%	21.1%	21.3%	11.0%
≥80	9.5%	9.5%	15.5%	13.9%	5.7%
Missing	0.1%	0.1%	-	-	0.2%
Comorbidities[a]					
Congestive heart failure	4.9%	3.5%	7.3%	9.0%	3.8%
Cardiac arrhythmias	8.9%	6.9%	13.3%	11.6%	7.3%
Valvular disease	2.3%	2.1%	3.1%	4.8%	1.6%
Pulmonary circulation disorders	2.2%	1.3%	3.2%	3.1%	1.9%
Peripheral vascular disorders	5.0%	3.9%	8.6%	7.5%	3.4%
Hypertension, uncomplicated	17.1%	14.3%	24.0%	24.3%	14.0%
Hypertension, complicated	1.7%	1.0%	2.2%	3.1%	1.5%
Paralysis	13.5%	11.1%	15.8%	19.3%	12.4%
Other neurological disorders	8.9%	7.2%	11.0%	7.4%	9.1%
Chronic pulmonary disease	14.2%	11.0%	18.1%	19.0%	13.2%
Diabetes, uncomplicated	8.8%	5.8%	13.9%	13.1%	7.1%
Diabetes, complicated	4.8%	2.3%	8.5%	9.2%	3.6%
Hypothyroidism	2.4%	2.6%	2.8%	3.3%	1.9%
Renal failure	2.8%	1.3%	4.4%	5.3%	2.3%
Liver disease	6.1%	3.6%	9.4%	4.3%	6.3%
Peptic ulcer disease excluding bleeding	2.8%	2.2%	3.0%	3.0%	3.1%
AIDS/HIV	0.3%	0.1%	0.6%	0.1%	0.4%
Lymphoma	0.9%	0.7%	1.4%	1.0%	0.7%
Metastatic cancer	1.7%	0.7%	4.2%	2.6%	1.0%
Solid tumour without metastasis	7.7%	4.3%	13.3%	13.3%	5.8%
RA/collagen vascular diseases	4.0%	3.8%	5.2%	4.6%	3.5%
Coagulopathy	1.2%	0.8%	0.8%	2.0%	1.4%
Obesity	8.6%	8.9%	7.5%	9.5%	8.8%
Weight loss	1.9%	1.6%	2.4%	3.0%	1.6%
Fluid and electrolyte disorders	9.9%	5.5%	16.3%	14.9%	8.3%
Blood loss anaemia	0.5%	0.4%	1.1%	0.7%	0.2%
Deficiency anaemia	2.5%	2.1%	3.4%	4.1%	1.9%
Alcohol abuse	29.5%	25.6%	27.8%	22.3%	34.0%
Drug abuse	21.6%	16.5%	28.3%	21.6%	21.2%

(Continues)

TABLE 1 (Continued)

Drug n = unique patients	All (n = 6365)	Tramadol (n = 1554)	Morphine (n = 1313)	Oxycodone (n = 610)	Mixed (n = 2888)
Psychoses	9.5%	8.2%	9.8%	7.2%	10.5%
Depression	36.8%	34.5%	29.8%	30.8%	42.5%
Elixhauser score (mean, SD)	1.7 (4.4)	0.92 (3.5)	2.8 (5.1)	2.6 (5.0)	1.4 (4.1)

RA, Rheumatoid Arthritis; AIDS/HIV, Acquired Immune Deficiency Syndrome/Human Immunodeficiency Virus.
[a]Only applicable for cases identified in the Danish National Patient Registry (n = 4024).
Results are presented as percent or mean (SD).

TABLE 2 Case characteristics

Drug n = unique patients	All (n = 7718)	Tramadol (n = 1978)	Morphine (n = 1530)	Oxycodone (n = 726)	Mixed (n = 3484)
Duration of hospitalisation (days) (n = 4024)[a]	2.0 (4.1)	1.5 (3.9)	2.8 (4.8)	2.7 (5.0)	1.6 (3.1)
Cause (n = 3903)[b]					
Intentional	1,180 (30.2%)	254 (31.7%)	83 (20.1%)	44 (22.0%)	799 (42.8%)
Unintentional	682 (17.5%)	227 (28.3%)	117 (28.3%)	64 (32.0%)	274 (14.7%)
Abuse	406 (10.4%)	94 (11.7%)	57 (13.8%)	41 (21.0%)	214 (11.5%)

Results are presented as n (%) or mean (SD).
[a]Only applicable for cases identified in the Danish National Patient Registry.
[b]Only applicable for cases identified in the Danish Poison Information Center. The numbers do not add up to 100% due to missing data.

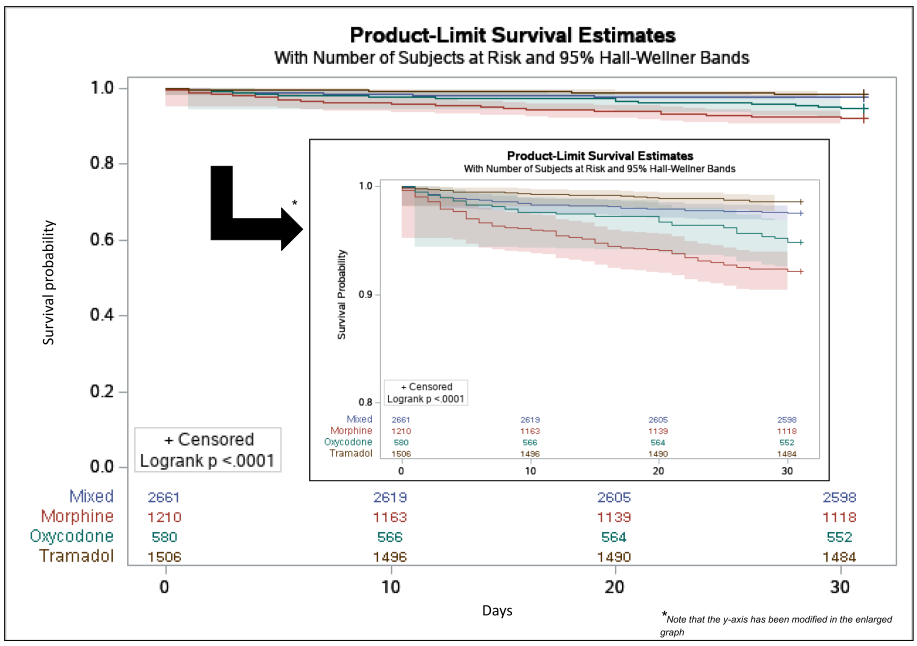


FIGURE 2 Thirty-day mortality risk for tramadol, morphine, oxycodone, and mixed poisonings

Within 7 days, the mortality (adjusted and unadjusted HRs) was higher among morphine, oxycodone, and mixed poisonings compared to cases of tramadol poisoning (Table S2).

In the DPIC, the annual number of tramadol poisonings per 10 000 poisonings increased from 2006 to 2013 and levelled off at around 125/10 000 poisonings up until 2017 (Figure S2). During the study period, the total annual number increased from 24 to 293 (Table S3). From 2006 to 2013, the annual number of tramadol poisonings in the DNPR per 10 000 poisonings was stable around 50/10 000 poisonings but showed a decreasing trend from 2014 to 2017 (Figure S3). The corresponding annual number decreased from 197 to 55 during the study period

TABLE 3 Hazard ratio of 30-day mortality following tramadol, morphine, oxycodone or mixed poisoning

	HR (95% CI)	*p* value
Unadjusted		
• Tramadol	1 (reference)	-
• Morphine	5.5 (3.5–8.8)	<0.0001
• Oxycodone	3.6 (2.1–6.2)	<0.0001
• Mixed poisoning	1.7 (1.0–2.7)	0.03
Adjusted for age and sex		
• Tramadol	1 (reference)	-
• Morphine	3.5 (2.2–5.6)	<0.0001
• Oxycodone	2.4 (1.4–4.2)	0.002
• Mixed poisoning	1.8 (1.1–2.9)	0.02
Adjusted for age, sex and comorbidities		
• Tramadol	1 (reference)	-
• Morphine	3.2 (2.0–5.1)	<0.0001
• Oxycodone	2.1 (1.2–3.6)	0.01
• Mixed poisoning	1.6 (1.0–2.7)	0.04

HR, Hazard Ratio; CI, Confidence Interval.

(Table S3). In the DRCD, the annual number of tramadol deaths per 10 000 poisoning-related deaths fluctuated around 200/10 000 from 2006 to 2016, representing 7–20 deaths per year (Figure S4 and Table S3). The total numbers of annual poisonings in the DPIC, DNPR, and DRCD from 2006 to 2017 are presented in Table S4.

4 | DISCUSSION

In this study, we identified a lower 30-day mortality risk following a tramadol poisoning compared to morphine, oxycodone, and mixed poisonings.

Previous studies analysing tramadol poisonings primarily included case reports and cohorts identified from local or national poisoning centres.[11,14,17,29–33] Tramadol poisoning cases are often described among young males, who ingested large doses of tramadol. In line with our results, tramadol is often ingested as part of a mixed poisoning.[17,29,32] It has been described that fatal cases due to mono tramadol poisonings are rare.[32] More often lethal poisonings occur when tramadol is ingested in combination with other drugs.[32] Our results corroborate this as we found a higher 30-day mortality risk following a mixed poisoning compared to a tramadol poisoning. A study described opioid-related poisonings from the Paris poison centre between 2008 and 2017.[33] Tramadol was the most frequently reported opioid, but morphine was the most lethal (27% of deaths) followed by tramadol (24% of deaths).[33] We identified a higher number of morphine poisonings than tramadol poisonings that might be due to identification of cases from several data sources. The presented mortality risks are based on cases of poisoning and might not represent the risk among users of the specific opioids, which should be kept in mind when interpreting the results.

The comparison of mortality risks between morphine, oxycodone, tramadol, and mixed poisonings is prone to confounding due to unmeasured or unknown differences among the groups. We hypothesise that differences in, for example, socioeconomic status, ingested dose, treatment indication, and standard medication might be part of the explanation. The analysed poisonings include a variety of cases from mild to severe poisonings. If morphine and oxycodone poisonings more often reflect an intoxication with high doses, and hence increased risk, it may explain the observed increased mortality risk. Unfortunately, information on plasma drug concentrations and ingested dose was not available in our study and hence could not be adjusted for in the analyses. We found that the duration of hospitalisations due to tramadol poisonings was shorter than other opioid-related poisonings. This further indicates that the tramadol poisonings represented less severe cases.

Tramadol poisoning cases were younger and had less comorbidities than morphine, oxycodone, and mixed poisonings, which is in line with a previous study.[5] This was reflected in the Elixhauser score, which is a commonly used comorbidity classification systems, with tramadol cases having a lower score.

Our analyses included both children, adolescents, adults, and elderly. The underlying cause of a poisoning likely differs between the age groups as children accidentally ingest inappropriate drugs which is also more likely among elderly suffering from, for example, cognitive impairment. Both children and elderly can have a reduced kidney and liver function which affects the reaction to the poisoning.

During the study period, we identified an increase in the number of tramadol inquiries to the DPIC which could be cause for concern. However, the use of tramadol in the general population increased simultaneously, and knowledge on the publicly available service became widespread.[19] To estimate the burden on the health care sector, the number of hospitalisations was assessed and we did not identify a substantial increase. It is possible that our results were affected by the introduction of new electronic health record systems at public hospitals in three Danish regions (in 2010, 2016, and 2017, respectively), leading to decreased registrations during this period. In addition, we did not identify an increase in tramadol deaths which has been described in, for example, the United Kingdom, Northern Ireland, and Finland.[34–36]

Tramadol has been considered a drug with limited potential for abuse and addiction.[1,2,37] We found that the annual number of tramadol poisonings ranged from 233 to 501 during the study period, and with regard to inquiries to the DPIC, the annual number increased. Further, approximately 10% of tramadol poisoning cases in the DPIC were reported to be due to abuse which underlines that tramadol has a potential for abuse. Physicians should be aware of this risk when prescribing tramadol. The use of opioids in the general Danish population has changed dramatically during the past years with a decrease in tramadol use and an increase in morphine and especially oxycodone use.[25] A continued focus on opioid poisonings is deemed relevant, especially given the identified increased mortality risk among morphine and oxycodone poisonings.

In our study, as well as in other register-based studies, we rely on data from registers and databases. The validity of the data depends on many aspects including coding practices. There is a risk of selection bias as our study only identified and described cases actually registered in the databases. We identified a small overlap between the data sources, but in the post hoc analysis, we found that a large proportion of poisonings in the DPIC were hospitalised. However, they were not initially identified as they were not coded with a specific poisoning code. The poisonings identified in the three data sources potentially differed, but these differences were handled in the adjusted analysis. However, the risk of residual confounding should be kept in mind when interpreting the results.

This study had some limitations that need to be taken into consideration when interpretating the results. Firstly, we used the term poisoning to describe identified cases. However, some cases might not represent actual poisonings. It is possible that some cases, especially inquiries to the DPIC, represent presumed poisonings, for example, accidents and incorrect dosing. Hence, there is a risk of misclassification. However, we do not assume the misclassification to be differential across the groups. Secondly, as we assume that not all poisoning cases are registered in the DPIC, the DNPR, or the DRCD, our study cohort does not represent all cases of tramadol, morphine, oxycodone, or mixed poisoning in Denmark. However, in Denmark, there is just one national poison information centre making it reasonable to presume that most cases are registered. Lack of correct registration will result in a falsely low prevalence of poisonings across all three data sources. Data in the DPIC and the DRCD have not been validated, and using administrative registers entails a risk of misclassification. However, we do not assume any misclassification to be differential between patients with a tramadol, morphine, oxycodone, or mixed poisoning. Still, these limitations should be kept in mind when interpreting the results. Lastly, in our mortality analysis, the underlying cause of death is unknown. Hence, it is possible that the patients experiencing a poisoning die following a different cause of death. However, we do not assume that this is different across the poisoning groups. Strengths of the study include identification of cases from several data sources. This was considered necessary based on an assumption of missing registration of poisoning cases which was supported by the small overlap between the data sources. In addition, all data sources are nationwide, and the DNPR and the DRCD include all somatic hospital contacts and deaths during the study period. Further, the long study period provided a large study cohort. Lastly, for the mortality analyses, we were able to follow up all patients due to no cases of censoring.

5 | CONCLUSION

The patients with a tramadol poisoning have a lower short-term mortality compared to the patients with morphine, oxycodone, or mixed poisoning. Despite the lower risk associated with tramadol poisonings, these cases are prevalent, and physicians prescribing tramadol should be aware of the poisoning and abuse risk.

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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