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Opioid-related deaths and previous care for drug use and pain relief in Sweden

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ABSTRACT

Aim: In 2006–2014, the rate of drug-related deaths, typically opioid poisonings, more than doubled in Sweden. Opioid prescriptions for pain control or opioid agonist therapy also increased. In this retrospective study, we compared death rates between individuals whose first recorded contact with prescribed opioids was for pain control and individuals that had received substance use disorder (SUD) treatment before their first recorded opioid prescription.

Methods: We included 2834 forensically examined individuals (ages 15–64 years) that died of poisoning in Sweden in 2006–2014. For each death we acquired data on previous opioid prescriptions and SUD treatments. We compared three study groups: pain control (n = 788); a SUD treatment group (n = 1629); and a group with no prescription for pain control or SUD treatment (n = 417).

Results: Overall fatal poisonings increased from 2.77 to 7.79 (per 100,000 individuals) from 2006 to 2014 (relative 181% increase). Fatal poisoning increased from 2006 to 2014 by 269% in the pain control group (0.64 to 2.36 per 100,000) and by 238% in the SUD treatment group (1.35 to 4.57 per 100,000). Heroin-related deaths remained constant; consequently, the increase was likely attributable to prescription opioids.

Conclusion: A rapid increase in deaths attributable mainly to prescription opioids for pain control, was reported previously in the United States. Our study indicated that increased access to prescription opioids might contribute to higher death rates also in Sweden among patients seeking pain control and individuals with an established SUD; however, deaths related to prescription opioids mainly occurred among those with SUDs.

1. Introduction

The rate of drug-related deaths increased from 3.6 to 8.1 per 100,000 individuals between 2006 and 2014 according to official Swedish mortality statistics (Official Statistics, 2015). More than two thirds of these deaths involved opioid overdoses (Simonsen et al., 2015). Over the same period, the European Monitoring Centre for Drugs and Drug Addiction reported a general increase in deaths involving prescription opioids, such as methadone, buprenorphine, fentanyl and oxycodone (European Monitoring Centre for Drugs and Drug Addiction, (EMCDDA, 2014). In the United States, an epidemic of opioid overdose deaths began with a first wave in the 1990s, which was related mainly to prescription opioids. A second wave occurred after 2010, which included heroin. Then a third wave occurred after 2013, which included illegally manufactured fentanyl (Seth et al., 2018a, b).

It has been suggested that increasingly intensive opioid marketing and more generous prescriptions for chronic pain have contributed to the increase in prescription opioid overdose-related deaths in the United States (Dart et al., 2015). The number of prescriptions dispensed appeared to correlate with the opioid death rate with regard to both geographic region and time (Rigg and Monnat, 2015; Manchikanti et al., 2012; King et al., 2014). However, in most cases, the deceased did not have opioid prescriptions; instead, the opioids were obtained from relatives or friends or the illicit drug market (Compton et al., 2015).

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In Sweden, the frequency of strong opioid prescriptions has increased (Rhodin, 2014). According to statistics from the National Board of Health and Welfare on pharmaceuticals (Socialstyrelsen, 2018a), strong opioid prescriptions for pain relief (morphine, fentanyl and oxycodone) have increased from 3.39 to 7.20 Daily Defined Doses (DDD) per 100,000 individuals from 2006 to 2014. In contrast, over the same period, prescriptions for the weaker opioid, tramadol decreased from 17.85 to 11,41 DDD per 100,000 individuals.

The use of opioids in opioid agonist therapy (OAT) for individuals with problematic drug use has also increased. Prescriptions for methadone and buprenorphine in OAT increased from 2.86 to 4.86 DDD/100,000 individuals from 2006 to 2011, due to the less rigorous regulations on OAT introduced in 2005 and the subsequent gradual increase in treatment facilities. Unfortunately, changes after 2011 are difficult to trace, because currently OAT drugs are more often dispensed directly by the caregiver to the patient, and those drugs are not covered by the National Board of Health and Welfare statistics on pharmaceuticals (Socialstyrelsen, 2015).

According to a recent Swedish study, 24% of 400 patients in OAT reported that they had given their methadone or buprenorphine dose to other people “in the last month” (Johnson and Richert, 2015). Similarly, a Finnish study found that 20% of patients in OAT gave away or sold their doses (Launonen et al., 2015).

In Sweden, there has been an increase in opioid poisonings involving drugs prescribed for pain control (primarily morphine, fentanyl, oxycodone, and tramadol, but also methadone and buprenorphine) (Wikner et al., 2014; Ludvigsson et al., 2009) and drugs prescribed for OAT (primarily methadone and buprenorphine). In the present study, we investigated whether the increase in fatal poisonings in Sweden was attributable mainly to opioid prescriptions for pain control, as reported in the United States prior to 2010 (Seth et al., 2018b), or to opioid poisonings among individuals with an established substance use disorder (SUD) as suggested by a recent report published by the National Board of Health and Welfare (Socialstyrelsen, 2015). To that end, we compared differences in death rates between individuals whose first recorded contact with prescribed opioids was for pain control but who had no previous record of SUD treatment, and individuals with a documented SUD diagnosis that had received SUD treatment before their first recorded opioid prescription. We also explored whether these two groups differed in sex, age, presence of drugs at death, previous prescriptions of opioids and treatments for dependence. In addition, we included a comparison group of individuals with no opioid prescription for pain control and no documented SUD treatment.

Sweden has comprehensive registries on causes of death, filled prescriptions, and health care treatments. These databases can be linked at the individual level with the unique personal identification number (PID), which is given to all Swedish residents (Ludvigsson et al., 2009). Therefore, opioid-related deaths could be linked to previous purchases of opioid drugs prescribed for pain and to previous SUD treatment episodes.

An increase in deaths among individuals with filled opioid prescriptions for pain control but no previous history of SUD treatment, might be interpreted as a similar situation to that seen, for example, in the United States at the beginning of the opioid epidemic. In other words, pain treatment might have introduced this group of individuals to opioids. Alternatively, an increase in deaths among individuals with a history of SUD treatments or with filled prescriptions for opioid agonist drugs might indicate that individuals with an established SUD had more access to prescription drugs during the study period than they had previously. Finally, an increase in deaths among individuals with no history of opioid prescriptions for pain and no previous SUD treatment might suggest that a mechanism other than increasing the number of opioid prescriptions contributed to the increasing number of fatal opioid poisonings.

2. Methods

2.1. Material

2.1.1. Forensic data: Toxreg

In Sweden, forensic investigations, including toxicological analyses, are routinely carried out when individuals < 65 years of age die of unnatural causes. The annual number of forensic investigations has been relatively constant, and approximately 5000 investigations have been conducted annually since 1994. Forensic investigations have been conducted in more than 90% of all unnatural deaths among individuals < 65 years of age (Fugelstad et al., 2017). The frequency of forensic examinations is lower in older age groups.

The primary aim of the Toxreg database is to capture drug-related deaths. The database includes all deaths in Sweden since 1994, for individuals aged 15–64 years that exhibited the presence of illegal drugs (including heroin) or pharmaceutical drugs in their system, based on forensic toxicological analyses. The pharmaceutical drugs investigated included morphine, methadone, fentanyl, buprenorphine, oxycodone or tramadol. All individuals with one or more drugs in their systems were recorded in the registry, regardless of whether the death was certified as drug-related or not, Individuals older than 64 years were not included, because only a small proportion of older individuals undergo forensic examination.

In the Toxreg database each death was counted only once, regardless of the number of drugs present in the system at the examination. When several drugs were found, the death was listed under the drug considered to be primarily responsible for the death (the “main drug”). The order of priority was based on that used by the Nordic Forensic Chemists in periodical reports on fatal poisoning among substance users in the Nordic countries, but it was adapted to the Swedish situation (Simonsen et al., 2015; Fugelstad et al., 2017). The order of priority for opioids was: 1) heroin, 2) morphine, 3) methadone, 4) fentanyl, 5) buprenorphine, 6) oxycodone and 7) tramadol. To distinguish heroin from morphine, heroin was identified by the presence of 6-acetylmorphine or a small amount of codeine. In some cases, isolated morphine might be related to heroin intake, but in most cases the death was related to prescription morphine. During the study period, most cases of fentanyl poisoning were related to prescribed fentanyl, mainly transdermal pain patches. After 2014, highly toxic fentanyl analogues administered with a nasal spray were involved in a large number of fatal intoxications (Guerrieri et al., 2017).

In addition to information on the main drug Toxreg also contained data on other identified drugs, including pharmaceuticals and alcohol. The most common other drugs in Toxreg were benzodiazepines, pregabalin and alcohol. Toxreg also contained the individuals PIDs (Ludvigsson et al., 2009). All toxicological analyses were performed at one national laboratory, the Division for Forensic Toxicology in Linköping. This central analysis ensures uniform measurement and records.

2.1.2. Official mortality data: the cause of death register

Swedish official mortality statistics are derived from death certificates, issued by physicians. Under Swedish law, death certificates are mandatory for all deaths in Sweden. Death certificates are sent to the National Board of Health and Welfare, where professional coders assign codes to all conditions mentioned on the certificates. In addition, they assign the underlying cause of death, according to the International Classification of Diseases Tenth revision (ICD-10). The Cause of Death Register is maintained by the National Board of Health and Welfare, and it has had a nationwide coverage since 1952. Due to compulsory registration the attrition is < 1%. For each death, the registry states the individual’s PID, place of residence, and both the underlying and contributing causes of death (Brooke et al., 2017).

2.1.3. Filled prescriptions for opioids: the pharmaceutical statistic

Official pharmaceutical statistics, published by the National Board of Health and Welfare, are based on the reports of all individual purchases of prescribed drugs in Sweden, since 2005. In addition to the patient's PID, the reports contain the Anatomical Therapeutic Chemical Classification System (ATC) code for the substance purchased, the amount dispensed, the dates of the prescription and dispensation, and the type of clinic where the prescription was issued (Socialstyrelsen, 2018a).

2.1.4. Hospital or out-patient treatment for drug abuse: the national patient register

The National Patient Register has maintained records of all inpatient episodes in Sweden since 1964. Its coverage has been nationwide since 1987. It has also maintained records of all outpatient hospital visits since 2001, including day surgery and psychiatric care, at both private and public hospitals. It does not contain records of visits to local surgeries. The registry records the patient's PID and main and secondary diagnoses for each episode or visit (Socialstyrelsen, 2018b). The registry is maintained by the National Board of Health and Welfare and reporting is compulsory.

2.1.5. Population database

All population figures were retrieved from the Statistics Sweden's database. This database maintains the official population statistics reported each year (Statistics Sweden, 2019).

2.2. The study groups

We extracted Toxreg data on all deaths that occurred from 2006 to 2014 of individuals aged 15–64 years that exhibited heroin or a pharmaceutical opioid in their system (n = 4274). We linked the PIDs of these individuals to the Cause of Death Register, and we selected all those classified as poisoning (ICD-10X40-44, X60-64, and Y10-14) for the underlying cause of death (n = 2834). We retrieved information for each individual from the Cause of Death Register, the pharmaceutical statistics database, and the National Patient Register. No PID was available for 40 Toxreg cases, most likely because the deceased was not a Swedish resident.

We then divided the study population into three main groups based on whether the first record was an opioid prescription for pain or whether it indicated SUD. We regarded these as the potential starting point for harmful opioid use:

The first group included 788 individuals with an opioid prescription for pain control (Pain group). The first prescription was issued before any outpatient or inpatient care for SUD, (if any occurred). We included prescriptions for morphine, buprenorphine (prescribed for pain relief according to the ATC code), fentanyl, oxycodone, and tramadol. We also included prescriptions for methadone, when prescribed as tablets.

The second group included 1629 individuals with an outpatient or inpatient diagnosis indicating a SUD (SUD Tr group). In this group, the first treatment episode preceded any opioid prescriptions. To identify SUD cases we used a list of SUD-related ICD-10 codes compiled by the National Board of Health and Welfare (Official Statistics, 2015); these included: F11-F16, F18-F19, O35.5, P04.4, T40, T43.6, Z50.3, and Z71 (See Box 1). We also included a small number of individuals that did not have a SUD diagnosis in the National Patient Register, but had prescriptions for liquid methadone, the preparation generally used in OAT, or buprenorphine, which is also prescribed for OAT.

The third group included 417 individuals with no registry record of opioid prescription for pain relief or no record of SUD treatment (No records group).

2.3. Statistical analysis

We used the chi-squared test to compare the three study groups (Pain, SUD Tr, and No records) regarding the presence of opioids, benzodiazepines, and alcohol at death. We also compared groups in terms of sex, age at death, previous treatment for alcohol problems, prescriptions of opioids for pain relief during the year prior to death and treatment for drug problems during the year prior to death.

Two-sided p-value < 0.05 was considered as significant. We calculated death rates for each study group over the study period (2006–2014), for all deaths that were certified as being due to poisoning and with opioids present in the system at death according to Toxreg. We calculated the death rates per 100,000 Swedish residents aged 15–64 years. We calculated the relative change in death rates from 2006 (reference value) to 20014 as follows: (2014 death rate – 2006 death rate)/2006 death rate*100%. The relative changes are reported as percentages. Furthermore, we analyzed the trends in mortality rates, including the relative change from 2006 to 2014, using ordinary least square regression analysis with 95% two-tailed confidence intervals. We evaluated correlations between the annual number of strong opioidprescriptions, the drugs used in OAT, and the death rates per 100,000 individuals due to the same drugs. We also calculated the annual rates of fatal poisoning per 100,000 individuals aged 15–64 years according to the main drug listed in the Toxreg database. All analyses were performed with IBM SPSS Statistics for Windows, Version 24.0 Armonk NY: IBM CorpV 24.

3. Results

We retrieved data for 2834 individuals from Toxreg that died from poisoning between 2006 and 2014, and opioids were found in the forensic examination. The average age at death was 38 years (SD ± 12.1), and 24% of the deceased were women. A total of 1932 (68%) individuals had been treated for SUD at some point and 1717 (61%) had at least one filled prescription for opioids. More than one opioid was found in 482 individuals (17%). Here, our analyses included only the main drug identified in the forensic examination, unless mentioned otherwise.

We compared the three study groups regarding age, sex, main drug, presence of opioids other than the main drug, benzodiazepines, and alcohol > 0.2 mg/ml (Table 1). In addition, we compared groups according to their previous treatments, including any alcohol treatments, opioid prescriptions for pain relief during the year prior to death and SUD treatments during the year prior to death. The Pain group had a higher proportion of women than the other two groups, as well as more deaths in the age group of 45–64 years and more findings of tramadol and oxycodone than the other two groups. The SUD Tr group included more deaths related to heroin, methadone, and buprenorphine than the other groups. Forensic evidence of alcohol use was found at equivalent frequencies in the three groups, but findings of benzodiazepines were more common in the SUD Tr group. Roughly half of the individuals in the SUD Tr group and a third of the individuals in the Pain group had previously received care for alcohol problems. The No records group had a lower average age and more frequent morphine findings than the two other groups. In the year prior to death, 31% of the Pain group had prescriptions for strong opioids, and nearly two thirds of the SUD Tr group had SUD treatments.

We also examined the number of cases with polyopioid detection and presence of benzodiazepines, pregabalin and alcohol according to the main drug identified at death (Table 2). Deceased with morphine as the main drug at death had the highest proportion of polyopioid detection. The proportion of cases with presence of benzodiazepines was equally high regardless of the main drug at death. Pregabalin was most common in deaths with buprenorphine as main drug.

We evaluated the annual rates of deaths from opioid poisoning according to the main drug detected at death (Table 3). Overall, the annual rates increased from 2.77 to 7,79 per 100,000 individuals from 2006 to 2014. Methadone was the most common main drug, and fatal methadone poisonings increased substantially between 2006 and 2011.

Box 1
ICD-10 codes (introduced 1997), which indicated drug abuse.

F11-F16 Mental and behavioral disorders due to use of opioids, cannabinoids, sedatives or hypnotics, cocaine, other stimulants including caffeine, or hallucinogens
F18-F19 Mental and behavioral disorders due to the use of volatile solvents or multiple drugs, or other psychoactive substances
O35.5 Maternal care for (suspected) damage to fetus by drugs
P04.4 Fetus and newborns affected by maternal use of addictive drugs
T40 Poisoning by narcotics and psychodysleptics [hallucinogens]
T43.6 Poisoning by psychostimulants with abuse potential
Z50.3 Drug rehabilitation
Z71.5 Drug abuse counseling and surveillance.

Fig. 1 shows the death rates over time for the three study groups. Both the Pain and SUD Tr groups showed significant increases in death rates from 2006 to 2014; in contrast, the corresponding rates in the No records groups remained relatively stable over time. The death rates in the Pain group increased from 0.64 to 2.36 per 100,000 individuals from 2006 to 2014, which corresponded to a relative increase by 268.7% (ß = 0.21, 95% CI 016-0.25). In the SUD Tr group, the death rate increased from 1.35 to 4.57 per 100,000 individuals between 2006 and 2014, which corresponded to a relative increase by 238.5% (ß = 0.32, 95% CI 0.24-0.41).

The amount of strong opioids (morphine, fentanyl or oxycodone) dispensed annually to individuals aged 15–64 years in Sweden increased from 4.24 to 7.49 DDD per 100,000 individuals between 2006 and 2014 (Table 4). During the same period, the number of deaths from poisoning with the presence of these drugs among individuals aged 15–64 years increased from 6.3 to 24.6 per 100,000 individuals. We found a strong correlation between the trends in dispensed strong opioids and in deaths from poisoning ($r = 0.98$, $p < 0.001$). In addition, between 2006 and 2011, the sales of methadone and buprenorphine, which are mainly used in OAT, increased from 4.56 to 7.23 DDD per 100,000 individuals aged 15–64 years. During that same period the incidence of deaths from methadone and buprenorphine poisoning increased from 0.41 to 3.1 per 100,000 individuals in the same age groups. ($r = 0.83$, $p < 0.01$). After 2011 an increasing amount of agonist drugs (estimated at 25% of the total sales), was dispensed directly by the care-giver, and therefore, they were not recorded in the registry (Socialstyrelsen, 2015).

4. Discussion

Our results indicate that the increase in opioid-related deaths in Sweden could be explained both by an increase in the frequency of opioid prescriptions for pain control and an increase in the use of prescribed opioids among individuals with an established SUD. Experiences reported in the United States indicated that a substantial number of patients that first experienced opioids with a prescription for pain relief later become dependent on the drug (King et al., 2014).

In our study most individuals had a history of SUD (i.e., the SUD Tr

Table 1
Descriptive characteristics of forensically examined cases of fatal poisonings in 2006–2014 due to the presence of opioids (n = 2834) that occurred in Sweden in 2006–2014.

		Total cohort (n = 2834)		Pain group (n = 788)		SUD Tr group (n = 1629)		No records group (n = 417)		p-value*	p-value**
		n	%	n	%	n	%	n	%		
Sex	Male	2150	75.9	512	65.0	1307	80.2	331	79.4	< 0.001	< 0.001
	Female	684	24.1	276	35.0	322	19.8	86	20.6	< 0.001	< 0.001
Age, y	15–29	858	30.3	177	22.5	495	30.4	186	44.6	< 0.001	< 0.001
	30–44	1071	37.8	275	34.9	681	41.8	115	27.6	< 0.001	< 0.01
	45–64	905	31.9	336	42.6	453	27.8	116	27.8	< 0.001	< 0.001
Main drug at death	Heroin	572	20.2	54	6.9	453	27.8	65	15.6	< 0.001	< 0.001
	Morphine	376	13.3	118	15.0	179	11.0	79	18.9	< 0.001	< 0.001
	Methadone	607	21.4	126	16.0	407	25.0	74	17.7	< 0.001	< 0.001
	Fentanyl	192	6.8	56	7.1	105	6.4	31	7.4	0.70	0.37
	Buprenor-phine	384	13.5	67	8.5	253	15.5	64	15.3	< 0.001	< 0.001
	Oxycodone	224	7.9	114	14.5	85	5.2	25	6.0	< 0.001	< 0.001
	Tramadol	479	16.9	253	32.1	147	9.0	79	18.9	< 0.001	< 0.001
Polyopioid detection***		482	17.0	126	16.0	318	19.5	38	9.1	< 0.001	< 0.05
Benzodiazepines		1727	60.9	467	59.3	1051	64.5	209	50.1	< 0.01	0.052
Pregabalin		427	15.1	125	15.9	268	16.5	34	8.2	< 0.001	0.12
Alcohol > 0.2‰		674	23.8	194	24.6	363	22.3	117	28.1	0.08	0.18
Previous treatment for alcohol problems		1081	38.1	241	30.6	1629	46.8	77	18.5	< 0.001	< 0.001
Prescriptions of strong opioids during the year prior to death		430	15.2	248	31.5	182	11.2	0	0	–	< 0.001
Treatment for drug problems during the year prior to death		1262	44.5	231	29.3	1031	63.3	0	0	–	< 0.001

Note: Data on sex, age at death, main drug at death, polyopioid detection, forensic detection of benzodiazepines, pregabalin and alcohol > 0.2‰ were retrieved from Toxreg. Information on previous treatment for alcohol problems and SUD treatment during the year prior to death was retrieved from the National Patient Register. Information on prescriptions of strong opioids during the year prior to death was collected from The Pharmaceutical Statistics.
[a]Pain group: cases with initial prescriptions of opioids for pain relief.
[b]SUD Tr group: cases with an initial treatment for substance use disorder.
[c]No records group: cases with neither treatment nor prescriptions.
* For trend across three study groups (Chi2-analysis).
** For comparison between pain group and SUD Tr group (Chi2-analysis).
*** One or more opioids detected in addition to the main drug at death.

Table 2
Distributions of forensically detected polyopioids (i.e. finding of opioids other than the main drug) benzodiazepines, pregabalin and/or more than 0.2 mg/ml alcohol according to main drug at death.

Main drug at death	Total N	Polyopioid detection		Benzodiazepines		Pregabalin		Alcohol > 0.2 mg/ml	
		N	%	N	%	N	%	N	%
Heroin	572	131	22.9	309	54.0	48	8.4	160	28.0
Morphine	376	133	35.4	235	62.5	45	12.0	81	21.5
Methadone	607	123	20.3	391	64.4	113	18.6	93	15.3
Fentanyl	192	31	16.1	119	62.0	36	18.8	39	20.3
Buprenorphine	384	34	8.9	260	67.7	95	24.7	105	27.3
Oxycodone	224	30	13.4	156	69.6	37	16.5	64	28.6
Tramadol	479	0	0.0	257	53.7	53	11.1	132	27.6
Total cohort	2834	482	17.0	1727	60.9	427	15.1	674	23.8

Note: Information on main drug at death, polyopioid detection, forensic detection of benzodiazepines, pregabalin and alcohol > 0.2 mg/ml was retrieved from Toxreg.

Table 3
Annual rates of due to opioid poisoning in Sweden in 2006–2014 (n = 2834), according to the main drug present at death.

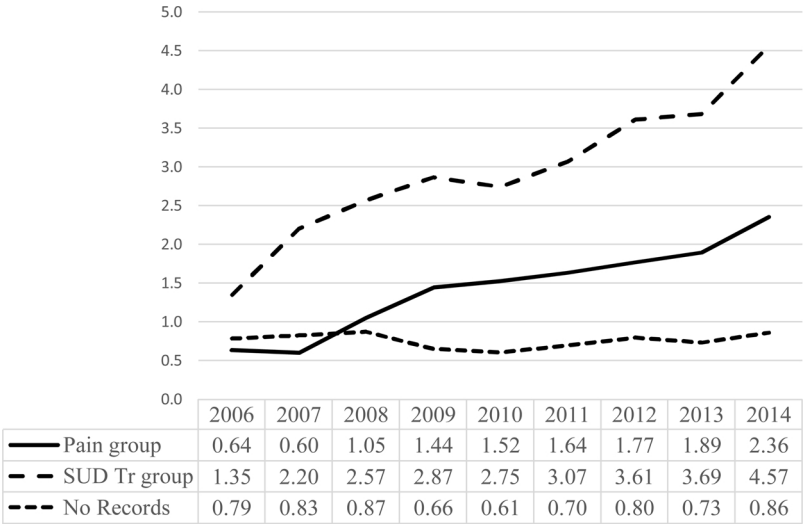
Main drug	2006	2007	2008	2009	2010	2011	2012	2013	2014
Heroin	0.90	1.48	1.07	1.07	0.79	0.79	0.82	1.01	1.48
Morphine	0.45	0.35	0.58	0.59	0.67	0.88	0.92	0.83	0.89
Methadone	0.17	0.61	0.84	1.05	1.18	1.13	1.70	1.57	1.69
Fentanyl	0.08	0.13	0.16	0.25	0.26	0.44	0.52	0.49	0.80
Buprenorphine	0.23	0.23	0.53	0.48	0.74	0.83	0.93	0.95	1.37
Oxycodone	0.08	0.23	0.30	0.38	0.21	0.38	0.57	0.72	0.80
Tramadol	0.85	0.60	1.02	1.16	1.03	0.97	0.72	0.75	0.76
Total	2.77	3.63	4.50	4.97	4.87	5.41	6.18	6.32	7.79

Note: The annual rates were calculated as follows: Numerator: The annual number of deaths from opioid poisoning among the deceased aged 15–64 years (retrieved from Toxreg); denominator: the number of Swedish residents, aged 15–64 years, in each corresponding year according to the official statistics in the Statistics Sweden database was used for denominator. Annual rates are reported per 100,000 individuals in the population.

group) and were probably not introduced to strong opioids through pain treatment. However, in approximately one-quarter of opioid-related deaths, the first contact with prescribed opioids was for pain control, with no previous record of SUD treatment. The number of heroin-related deaths varied during the period without any clear trend over time. There were significant differences between the Pain and SUD Tr groups in terms of sex, age, and substances present at death, but these groups showed similar use of alcohol and benzodiazepines. In the Pain group, 65% of individuals had no prescription during the year before death, and within the same period 30% had been treated for a SUD. This finding was consistent with previous studies from the United States, which showed that few deaths from opioid poisoning were associated with a prescription of strong opioids at the time of death (Compton et al., 2015). Furthermore, approximately 15% of the decedents had no record of either a prescription for pain relief or SUD treatment (i.e., No records group); of these, 45% were under 30 years old at the time of death and they might not have developed a SUD.

Strong opioids have become more easily available in Sweden since 2006, for two reasons. First, broader treatment practices have led to more prescriptions for strong opioids and thus, over the period strong opioids were more frequently prescribed for chronic pain (Rhodin, 2014). Second, more treatment programs were initiated following the new OAT regulations introduced in 2005. More patients were admitted to OAT, which included treatment with methadone and buprenorphine. Previously, OAT had been restricted to a small number of highly motivated patients and drug diversion had been negligible according to a review of the largest OAT project in 1988–2000 (Fugelstad et al., 2007). The new and less restrictive national regulations and the gradual expansion of OAT resulted in far more individuals with access to methadone treatment.

It seems plausible that an increase in opioid treatment for either pain or OAT could contribute to more opioid-related deaths, since strong opioids are both highly addictive and highly toxic (Bohnert et al., 2011). Indeed, this higher availability could expose more individuals to the risk of developing an opioid use disorder and subsequently to the risk of opioid poisonings (Darke et al., 2007), similar to what occurred in the United States (Volkow et al., 2018). There is strong evidence that OAT reduces the mortality among opioid users



	2006	2007	2008	2009	2010	2011	2012	2013	2014
Pain group	0.64	0.60	1.05	1.44	1.52	1.64	1.77	1.89	2.36
SUD Tr group	1.35	2.20	2.57	2.87	2.75	3.07	3.61	3.69	4.57
No Records	0.79	0.83	0.87	0.66	0.61	0.70	0.80	0.73	0.86

Fig. 1. Rates of fatal poisonings with presence of opioids per 100,000 Swedish individuals, aged 15–64 years. Pain group: cases with initial prescriptions of opioids for pain relief; SUD Tr group: cases with an initial treatment for substance use disorder; SUD Tr group: cases with an initial treatment for substance use disorder; No records group: cases with no SUD treatment or prescriptions. *Note*: The annual death rate was calculated as follows: Numerator: the number of deaths from opioid poisoning (retrieved from Toxreg); denominator: the number of Swedish inhabitants (retrieved from Statistics Sweden database).

Table 4
The rates of annually dispensed Daily Defined Doses (DDD) of opioids and annual rates of fatal poisonings per 100,000 Swedish individuals, aged 15–64 years.

	2006	2007	2008	2009	2010	2011	2012	2013	2014
Dispensed amount of morphine, fentanyl or oxycodone, DDD/100,000 population	4.24	4.48	4.97	5.30	5.63	5.94	6.25	6.87	7.49
Fatal poisonings with presence of morphine, fentanyl or oxycodone as main drug /100,000 population	0.62	0.72	1.04	1.22	1.13	1.68	2.0	2.01	2.46
Dispensed amount of methadone or buprenorphine, DDD/100,000 population	4.56	5.40	6.35	7.00	7.50	7.94	7.54	7.43	7.23
Fatal poisonings with presence of methadone or buprenorphine as main drug /100,000 population	0.41	0.85	1.38	1.53	1.93	1.98	2.65	2.55	3.10

Note: Data on dispensed DDD of opioids per 100,000 Swedish individuals were retrieved from the Prescription Register. The annual death rate was calculated as follows: Numerator: the number of deaths from opioid poisoning among deceased individuals aged 15–64 years (retrieved from Toxreg); denominator: the number Swedish of inhabitants aged 15–64 years in each corresponding year (retrieved from Statistics Sweden database.

(Sordo et al., 2017). However, diverted methadone may contribute to a considerable number of opioid-related deaths (Fugelstad et al., 2010; Bernard et al., 2013; Heinemann et al., 2000). Individuals that use drugs might erroneously believe that diverted methadone and other similar drugs obtained from the healthcare system are less dangerous than street drugs.

There is a close relationship in time between the increasing number of prescriptions for strong opioids and the increase in deaths due to poisonings with the same opioids. Initially, the increase was associated mainly with methadone and buprenorphine, but deaths related to other prescription opioids also increased, particularly after 2010. In contrast, tramadol prescriptions and tramadol-related deaths decreased over the same period. Therefore, we assumed that wider availability of opioids (due to pain relief or OAT prescriptions) has contributed to the increase in drug-related mortality in Sweden.

The high proportion of individuals with benzodiazepines present in the system was notable but is consistent with what findings in other Nordic studies (Hakkinen et al., 2012; Jones et al., 2012). It is highly probable that benzodiazepines have also contributed to an increased number of fatal intoxications.

4.1. Limitations and strengths

The main strength of our study was the high coverage in the registries. The Toxreg database which was based on forensic examinations included > 90% of deaths due to violence and poisoning in Sweden among individuals aged < 65 years. Moreover, the cases are routinely screened for alcohol, pharmaceutical drugs, and most illicit drugs. In addition, the Prescription database had highly reliable information because it was linked to the administrative system used by pharmacies. The study also had some limitations. For example, prescription data were available only after July 2005, when the Prescription database was first established. As a result, individuals with opioid prescriptions prior to 2005 might have been erroneously assigned to the SUD Tr or No records group. This error would have resulted in overestimation in these two groups. Furthermore, as mentioned above, the Prescription database did not include information on medications administered in hospitals or used in hospital ambulatory care (for example intravenously) (Wettermark et al., 2007), or in clinical settings (e.g. some OAT units dispense methadone and buprenorphine directly to patients). Therefore, these doses were not included in the Prescription database. Consequently, the Prescriptions database probably underestimated the actual usage of opioids. In addition, the Patient Register had incomplete data on out-patient care for a few years after the introduction of out-patient data, in 2001. Therefore, a small number of cases might have been misclassified during that time period.

Other limitations should also be considered. First, we did not include individuals > 64 years of age, because in Sweden, much fewer forensic examinations are performed in this age group. Second, the number of deaths due to poisoning (ICD-10 × 40–44, X60-64, and Y10-14) was probably underestimated, because some poisonings might have been classified as being caused by a mental or behavioral disorder due to drugs (ICD-10 F11-F14, F16 and F19). Third, the main drug priority ranking was based on relative toxicity in average. Therefore, in a small number of cases the death could have been actually caused by a drug with a lower rank, rather than the drug assigned as the main drug. Fourth, drugs other than opioids, such as benzodiazepines, alcohol and pregabalin might have contributed to the fatal outcome. Finally, in the course of the study, all register data were available only for the period up to the end of 2014. As a result, we could not explore the trends in opioid-related mortality in Sweden after 2014.

4.2. Conclusions

Our findings indicated that most deaths in Sweden related to prescription opioids occur among individuals with an established SUD. However, we also found an increasing rate of opioid-related deaths among patients that had been prescribed opioids for pain relief. Therefore, we conclude that easier access to prescription opioids might have contributed to the higher death rate among both individuals with established SUDs and among individuals that used opioids for pain control.

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Nothing declared.

Contributors

AF originated the study concept and drafted the manuscript. LJ selected and analyzed the mortality statistics involved. IT provided forensic input. GÅ and AS planned and performed the statistical analysis. All authors contributed to the analysis, reviewed drafts of the manuscript and approved the final version.

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