



Opioid sales and opioid-related poisonings in Switzerland: A descriptive population-based time-series analysis

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Summary

Background To examine time trends and characteristics of calls related to opioid poisonings reported to the National Poison Centre and opioid sales in Switzerland.

Methods We used population-level data from the Swiss National Poisons Information Centre on reported opioid-related poisonings and data provided by the Swiss Pharmacists' Association (pharmaSuisse) based on IQVIA data to identify sold opioid packages. The rate of opioid-related poisoning calls and dispensed opioid packages per 100,000 Swiss inhabitants between 2000 and 2019 were plotted by year and annual trends were assessed. All analyses were stratified by individual opioid and potency (strong vs weak).

Findings There was a significant 177% increase in the rate of calls for opioid-related poisonings (1.4 to 3.9 per 100,000 inhabitants, $p < 0.001$) and a 91.3% increase in opioid sales (from 14,364.0 to 27,477.6 per 100,000 inhabitants, $p < 0.001$). The increase associated with strong opioids was higher when compared to weak opioids, in both poison centre calls and sales. In 2019, tramadol was the most frequently reported opioid in the poison centre data (35.7%, $n=133$) and sales (37.5%, $n=8,863,377$), followed by oxycodone calls (24.4%, $n=91$) and sales 23.4%, $n=552,751$). Poisoning calls and sales related to oxycodone increased substantially between 2009 and 2016, as did the rate of poison centre calls requiring medical care.

Interpretation Calls to the Swiss National poison centre and sales for opioid have increased substantially in Switzerland in the last two-decades. Increases were primarily driven by oxycodone and tramadol; however, sales have attenuated since 2016. Our findings mirror other European countries and stress the importance of surveillance and monitoring.

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Introduction

The use of prescription opioids is considered the standard of care in treating malignant and acute postoperative pain. However, despite only modest evidence of efficacy in treating chronic noncancer pain (CNCP),¹ opioids are increasingly prescribed for the management of CNCP in Europe.²⁻⁴ While opioids are associated with short-term pain relief in patients with chronic pain, evidence on the long-term effectiveness is mostly

Research in context

Evidence before this study

Opioid-related harm has become a significant health issue, mainly caused by the high availability and prescription of medical opioids. While great attention has been given to the opioid crisis in North America, several observational studies from European countries have identified a growing use of opioids and related fatalities over the last two decades. Despite high narcotic use, information on opioid use and opioid-related harms in Switzerland is lacking. We updated a search in PubMed on April 4th, 2022, using keywords “opioids” and “Switzerland” and did not identify any study assessing the trends in both the use and potential harm associated with opioids.

Added value of this study

This study found that calls to the National poison centre for opioid-related poisonings and opioid sales more than doubled between 2000 and 2019, and mirror increases observed in other European countries. The increasing trends were primarily driven by strong opioids, particularly a substantial rise in oxycodone poisonings and sales since 2011. In 2019, tramadol was the most frequently reported in poison centre calls (35.7%) and sold (37.5%) opioid, followed by oxycodone (24.4% and 23.4%, respectively). The number of calls to the National poison centre requiring medical care by a physician showed a 3-fold increase.

Implications of all the available evidence

Despite the known harms associated with strong opioids, Switzerland, like other European countries, have seen a startling increase in consumption and harms in the past decade. Notably, the rising use of oxycodone is cause for concern. Surveillance and monitoring of opioids are needed in Switzerland to prevent an opioid epidemic.

lacking.^{1,5} Furthermore, long-term treatment remains controversial due to concerns about adverse events, non-medical use or substance use disorders, and the risk of fatal and non-fatal overdose.^{5,6}

The importance of balanced and reduced opioid prescribing is emphasised by the opioid crisis in the United States (US), which saw prescription opioid sales quadruple between 1999 and 2010.⁷ The increase was primarily driven by the increased use of prescription oxycodone. Moreover, opioid-related deaths increased significantly between 1999 and 2019.^{7,8} The age-adjusted rate of opioid-related hospitalizations was a startling 26.6 per 100,000 persons in 2016.⁹ Similarly, in Canada, the prevalence of opioid-related harm has increased substantially between 1999 and 2015, with the rate of opioid-related harm reported at 16.4 per

100,000 persons in 2017.^{10,11} Additionally, recent studies have shown that rates of opioid-related hospitalizations and deaths have increased during the COVID-19 pandemic in Canada and the US.^{12,13}

While great attention has been given to the opioid crisis in North America, recent European countries have reported growing use of opioids and opioid-related fatalities over the last two decades,^{3,4,14–18} leading to concerns of an emerging opioid crisis.¹⁹ The 2019 report from the International Narcotics Control Board identified that many of the top ten nations with the highest levels of narcotic consumption were in Europe. The US, Germany, Austria, Canada, and Switzerland were the five nations with the highest global narcotic consumption. While previous studies have found that tramadol is the most frequently used opioid, a startling increase in the consumption of oxycodone has been observed in the Netherlands and Denmark since 2010.^{14,18} Given the known risks with high oxycodone consumption, as seen in the US and Canada, the increases observed in Europe should not be taken lightly.

Thus, it is pertinent that we closely monitor opioid consumption and harm trends in Europe. Despite being among the top five countries in legal narcotic consumption, information on prescription opioid use in Switzerland is scarce. We, therefore, aimed to examine time trends in opioid-related poisonings and sales in Switzerland.

Methods

Study design and data sources

We conducted a population-based case-time series study using cross-sectional data from two national databases in Switzerland over 20 years (2000–2019). The National Poisons Information Centre provided Swiss nationwide data on poisonings resulting from both drugs and other substances.²⁰ The National Poisons Information Centre offers free consultations around the clock (24/7) by medical professionals specially trained in clinical toxicology and pharmacology. In 2019, the Swiss National poison centre received 39,217 inquiries, with approximately one-third of the reported exposures being related to pharmaceuticals. The public or treating physicians can make calls to the poison centre. The data on reported poisonings are entered in real-time, and information on patient demographics (age, sex, region of Switzerland) and clinical characteristics (drug type, route of administration, other drugs or substances ingested, symptoms) are systematically collected and standardized by a trained clinical toxicologist. Additionally, in cases where patients are referred to medical care (i.e., in-patient hospitalization, ambulatory, or outpatient care), physician follow-up reports from the treating physician are requested to know the clinical course of

the poisoning. Thus, among a subset of cases where physician follow-up was received, further information on the severity of symptoms and a causality assessment is available.

Data on drug sales were derived from IQVIA and prepared by the Swiss Pharmacists' Association (pharmaSuisse). IQVIA collects information on all drug sales (prescription and over-the-counter [OTC] drugs) in Switzerland from wholesalers, doctor suppliers, and manufacturers to community pharmacies, drugstores, self-dispensing physicians, and hospitals. For our analysis, only drug sales to pharmacies and self-dispensing physicians were included as an indicator of community use. These data included the year, month, anatomical therapeutic chemical (ATC) code of the medication, the channel of dispensing (pharmacy or physician), and the total number of packages and units purchased, including the geographical region.

Study population

The study population consisted of all opioid-related poisoning calls to the National Poisons Information Centre and all opioid sales by community pharmacies and dispensing physicians between 1 January 2000 and 31 December 2019. Opioids were defined as opioid analgesics only (i.e., any medication with an ATC code starting with N02A). We did not identify calls related to opioids used to treat substance use disorders (e.g., methadone). All calls originating from outside Switzerland, with unknown canton, or with an unknown origin were excluded from the National Poisons Information Centre data. Also, we excluded calls that involved opioids other than with an ATC code starting with N02A.

From the pharmacy dispensing data, we identified all dispensed packages for analgesic opioids with an ATC code starting with N02A. Sales for opioids primarily used to treat substance use disorders (e.g., methadone with ATC code "N07BC02") were not included as these are not indicated for analgesic use. In Switzerland, opioids are not available OTC and are only available with a physician's prescription.

Outcomes of interest

The primary outcomes of interest were the annual rate of opioid-related poisoning calls to the Swiss National Poisons Information Centre and opioid packages sold per 100,000 inhabitants, overall and stratified according to opioid type and potency.

Statistical analysis

We tabulated the number of calls for opioid-related poisonings and sales by year. The annual data on the number of calls for opioid-related poisonings and sales were standardized to the national population from the Federal Office of Statistics (Bundesamt für Statistik [bfs.

admin.ch]) to calculate the rate of opioid poisoning calls or sales per 100,000 inhabitants. To calculate the relative change in number of poisonings we log-transformed the annual values. Trends in the annual rates were assessed using linear regression or basis splines (B-splines), depending on the presence of nonlinearities. Given the potential for serially correlated errors, we used the Newey-West standard errors, also known as heteroskedasticity and autocorrelation consistent (HAC) standard errors.

We further stratified calls and sales by opioid potency. Opioids were classified as weak or strong, following the approach described by Wertli et al.²¹ In short, weak opioids included all opioid formulations with a morphine conversion factor of 0.3 or less and included codeine, dextropropoxyphene, dihydrocodeine, meptazinol, opium, tilidine, and tramadol (Supplementary Table S1). Strong opioids were all opioids not defined as weak. When the active pharmaceutical ingredient was missing in the National Poisons Information Centre data, it was inferred from the product name and ATC code. Additionally, in poison centre calls with multiple opioids reported, poisonings were categorized as caused by strong opioids when at least one strong opioid was present. If only weak opioids were reported, the poisoning was classified as caused by weak opioids.

Finally, we stratified by individual opioids. From the poison centre, we plotted the rate of calls by year among the opioids with 100 poisonings or more between 2000 and 2019. From the sales data, opioids were classified based on ATC codes, and we selected the same opioids as those identified from the poison centre data (i.e., with >100 reports) for plotting.

In secondary analyses, we stratified the poison centre data by patient- (age and sex) and poisoning-related characteristics (intentionality and number of agents involved) when available. We calculated and plotted age- and sex-specific rates of opioid poisonings per 100,000 persons by year using the Federal Statistical Office data. We also identified and plotted the rate of National poison centre calls that required medical care (hospitalization or outpatient care), as identified from the additional files submitted by the treating physician.

We further examined the patient- and poisoning-related characteristics of opioid poisonings, stratified by opioid potency. As appropriate, we summarized patient demographics and poisoning-related characteristics from the National Poisons Centre as counts and proportions or means and standard deviations (SDs). Significant differences between categorical variables were tested using a Chi-square test, while t-tests were used for continuous variables.

All statistical analyses were performed using R Statistical Software (version 4.0.4; R Foundation for Statistical Computing, Vienna, Austria).

Ethical approval

The Swiss Cantonal Ethics Commission approved the use of the National Poisons Information Centre data (KEK No.: 2015-0627). A waiver of informed consent was provided related to the practicability of clinical toxicological studies and the use of de-identified data. No ethical approval was required to use IQVIA data on opioid sales since no patient information is included. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Role of the funding source

The research did not receive external funding.

Results

From 2000 to 2019, the National Poisons Information Centre was contacted for 4,566 poisonings related to opioid analgesics. Following exclusions (Figure 1), 4,273 eligible calls were identified, of which 2,398 (56.1%) were for weak opioids and 1,875 (43.9%) were for strong opioids.

Overall, there was a significant 177% ($p < 0.001$) increase in the rate of calls for opioid-related poisonings in Switzerland between 2000 and 2019, from 1.4 to 3.89 per 100,000 inhabitants (Figure 2). The linear regression model with adjusted standard errors predicted an average yearly increase in the rate of poisonings per 100,000 inhabitants of 0.13 (95% CI: 0.11 – 0.16, $p < 0.001$). From 2000 to 2019, the rate of poisonings due to strong and weak opioids increased by 331% and 99%, respectively. The linear regression identified a higher rate of increase in poisoning calls with strong opioids (0.10 per 100,000; 95% CI: 0.09 – 0.12, $p < 0.001$) than with weak opioids (0.03 per 100,000; 95% CI: 0.01 – 0.04). Supplementary Table S2 provides the regression coefficients, and Supplementary Table S3 provides the total number and rate of annual poisoning calls.

The rate of dispensed opioid packages is provided in Figure 3. We identified 39,099,472 dispensed packages for opioids from the IQVIA data, consisting of 21,681,376 (58.9%) weak opioids and 15,139,048 (41.1%) strong opioids. Overall, the number of opioid sales increased 128.5% between 2000 and 2019,

corresponding to a 91.3% increase when standardized to the population, from 14,364.0 to 27,477.6 per 100,000 inhabitants. The increase in sales was steady from 2002 until 2016. However, the rate of sales has slowly declined since 2016. Differences were found when stratified by potency. Between 2000 and 2019, the total number of strong opioid packages increased by 669.6% and weak opioid packages by 25.2%. The fitted B-splines showed a significant difference in the rate of increase of opioid sales over time, overall and by potency. Supplementary Table S4 provides the annual number and rate of opioid sales, overall and by potency, while Supplementary Table S5 provides the B-spline regression coefficients.

The rate of annually reported poisoning calls by individual opioids is illustrated in Figure 4. Due to non-linearities B-splines were fitted, and the regression coefficients are provided in Supplementary Table S6. Overall, tramadol was the most frequently reported opioid in the poisoning calls (43.9%, $n=2,036$), followed by oxycodone (16.9%, $n=782$), morphine (15.5%, $n=718$), codeine (10.6%, $n=493$), buprenorphine (5.1%, $n=236$), and fentanyl (2.3%, $n=107$). The number and rate of annual poisoning calls is provided in Supplementary Table S7. Calls for oxycodone-related poisonings had the largest proportion increase, from <5 calls in 2003 to 91 in 2019 (2,933% increase). Of note, there was a 571% increase in oxycodone-related calls between 2009 and 2017 (from 17 to 114 calls). However, since 2017 the calls declined slightly (from 114 to 91, 20.2% decrease). Fentanyl was reported less often but increased considerably between 2000 and 2016 (from <5 to 17 calls, a 750% increase). Like oxycodone, tramadol calls between 2009 and 2017 increased (from 5 to 17 calls, a 240% increase). However, after 2017, the number of fentanyl poisonings decreased again to 10 calls in 2019 (41.2% decrease). In 2019, 60.1% of calls were for tramadol (35.7%) or oxycodone (24.4%).

The sales data identified similar patterns when stratified by individual opioids (Figure 5). The fitted B-Splines showed significant differences between opioids on the rate of increase over time (Supplement Table S7). While fentanyl was not among the top 5 most frequent opioids reported in poisoning calls, it was the third most frequently sold opioid in Switzerland overall (12.4%, $n=4,558,560$). Only tramadol (47.5%, $n=17,494,599$) and oxycodone (12.9%, $n=4,742,419$)

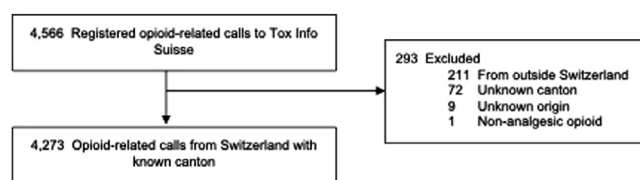


Figure 1. Flowchart of opioid-related poisoning calls to the National Poison Centre in Switzerland between January 1, 2000, and December 31, 2019.

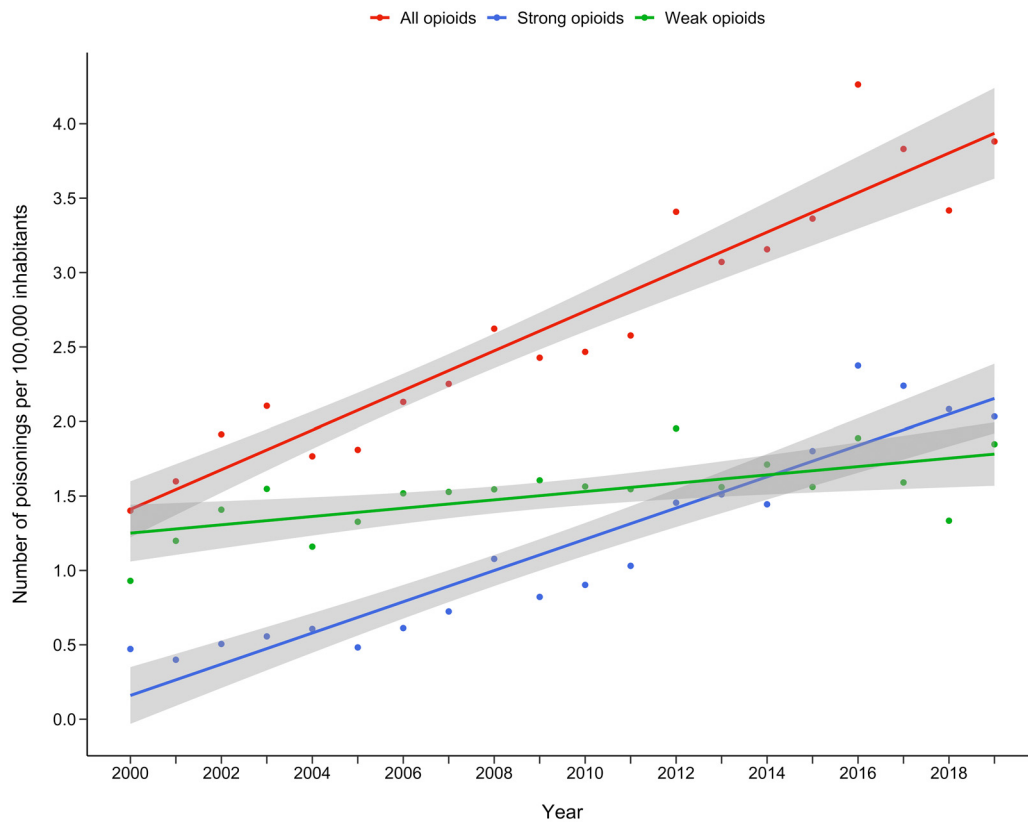


Figure 2. Rate of opioid-related poisoning calls to the Swiss National Poison Centre per 100,000 inhabitants from 2000 to 2019 stratified by opioid potency. Grey shading indicates 95% confidence intervals, calculated using linear regression adjusted for standard errors.

had higher sales. By 2019, the proportion of sales for oxycodone and fentanyl increased to 23.4% and 14.0%, respectively, while tramadol decreased to 37.5%. Tramadol dispensing peaked in 2011, with 12,507 packages dispensed per 100,000 inhabitants; however, an 18% decline was observed after 2011.

In the secondary analyses, trends in opioid-related poisonings found a steeper rise in adults compared to children (Supplementary Figure S1) but no differences in the level of increase and distribution between males and females (Supplementary Figure S2). Similarly, there was no pronounced change over time in the distribution of the circumstance of poisoning between intentional and unintentional (Supplementary Figure S3), nor for the number of substances reported (Supplementary Figure S4). Among the 1,546 poison centre calls requiring medical care, we found that the rate increased from 0.6 to 1.1 per 100,000 during the observation period, and the increase was primarily driven by strong opioids, which increased from 0.2 to 0.6 per 100,000 (Supplementary Figure S5). Similar to all calls, the number of calls with clinical care saw a 225.6% increase from 2000 to 2016 (from 43 to 140); however, there was an attenuation in the rate from 2016 to 2019 (from 140

to 96). The number and rate of annual poisoning calls with clinical care are provided in Supplementary Table S10, and the fitted B-Spline coefficients are provided in Supplementary Table S11.

The demographic characteristics of the calls to the National poison centre are provided in Table 1. Overall, the sex distribution was almost 60% female and 40% male, and the mean age was 35.9 years (SD 22.1 years). Most opioid poisonings were intentional (60.5%), and nearly three-fourths of intentional poisonings were suicidal attempts. When stratified by opioid potency, differences were observed in almost all characteristics. While women represented the majority in both groups, the proportion of men was significantly higher in the strong opioid poisonings compared to the weak (42.6% vs. 34.6%, $p < 0.001$). The mean age of strong opioid calls was significantly higher than the mean age of weak opioid calls (42.0 ± 23.3 years vs. 31.3 ± 20.1 years, $p < 0.001$). Regional differences were also observed, with the proportion of calls from German-speaking regions representing 81.3% of calls for strong opioids, compared to 69.4% for weak opioids. When looking at the circumstances of the poisoning, significant group-level differences ($p < 0.001$) were identified. Suicidal

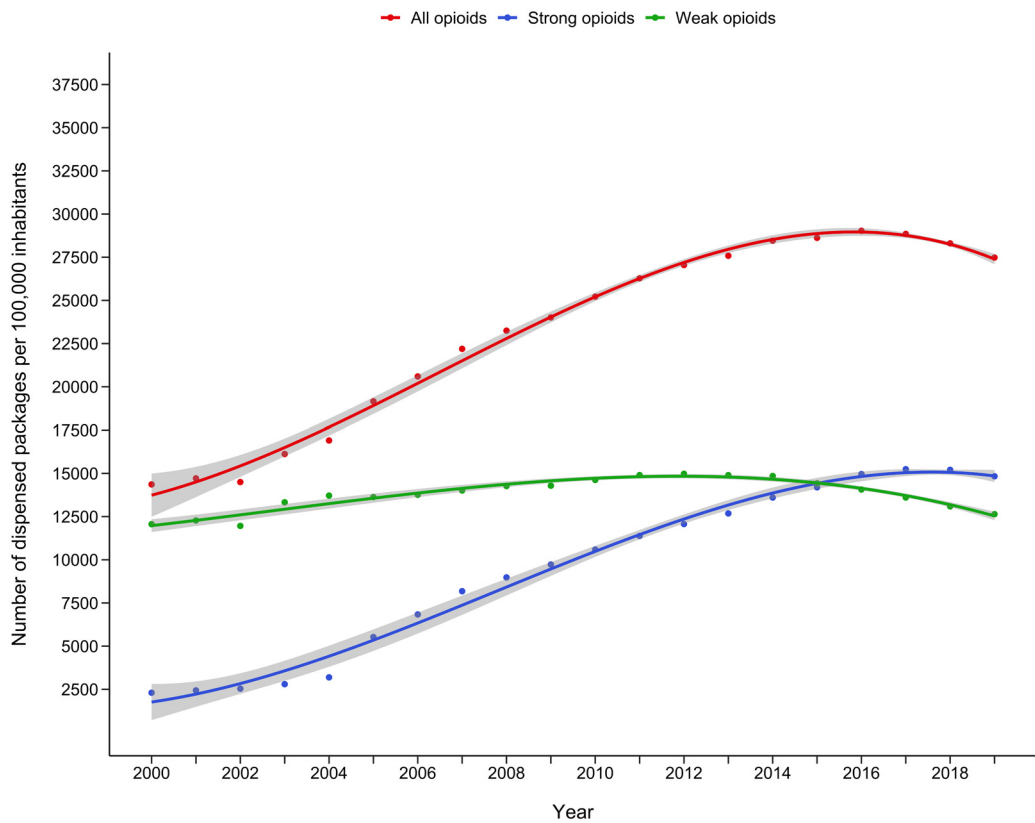


Figure 3. Rate of sold opioid packages per 100,000 inhabitants from 2000 to 2019 stratified by opioid potency. Grey shading indicates the 95% confidence intervals from the basis-spline regression model.

attempts were more often reported in weak opioids (47.8% vs. 36.4%), while accidental poisonings were slightly more prevalent among strong opioids (33.1% vs. 31.2%). Slightly more than one-third (36.2%, n=1,546) of the calls required hospital admission or medical care from a physician, with a similar proportion observed for both weak (35.9%) and strong (36.5%) opioids. Of those with physician follow-up, the majority (94.8%, n=) had a certain or probable causality assessment, 40.2% had moderate or severe symptoms, and 1.1% had a fatal outcome.

Discussion

In this Nationwide study, we identified that calls to the National poison centre for opioid-related poisonings and opioid sales in Switzerland increased substantially between 2000 and 2019, which was primarily driven by strong opioids, in particular oxycodone. Tramadol, a weak opioid, was the most reported opioid during the observation, representing 43.9% of overall calls and 47.5% of sales. However, strong opioids, such as oxycodone, showed the largest increases in both calls and sales, and by 2019 oxycodone and fentanyl represented the second (23.4%) and third (14.0%) highest sales. We

further observed the increase in calls to the National Poisons Information Centre was mirrored by a 2-fold increase in the number of cases requiring medical care, suggesting that the increases were not an artifact of opioid awareness. Thus, while the relative use of opioids in Switzerland has not reached the epidemic proportions observed in the US, these findings show that the use of strong opioids is on the rise in Switzerland.

We observed a substantial 177% (from 1.4 to 3.9 per 100,000 inhabitants) increase in total opioid-related calls to the National Poison Centre. While we used poison centre data, which may underestimate harm, our results are similar to other European countries. In France, hospital admissions related to prescription opioids showed a 167% increase from 2000 to 2017 (from 1.5 to 4.0 per 100,000 inhabitants).¹⁵ Similarly, in the Netherlands, the number of opioid-related hospital admissions for opioid-related harm tripled between 2008 and 2017, from 2.5 to 7.8 per 100,000 inhabitants.¹⁴ Additionally, self-reported data from the Netherlands found that hospitalizations due to opioid-related poisonings increased from 8.6 per 100,000 inhabitants in 2013 to 12.9 in 2017.²²

While the relative increase in opioid poisonings was higher than in opioid sales, which is comparable to

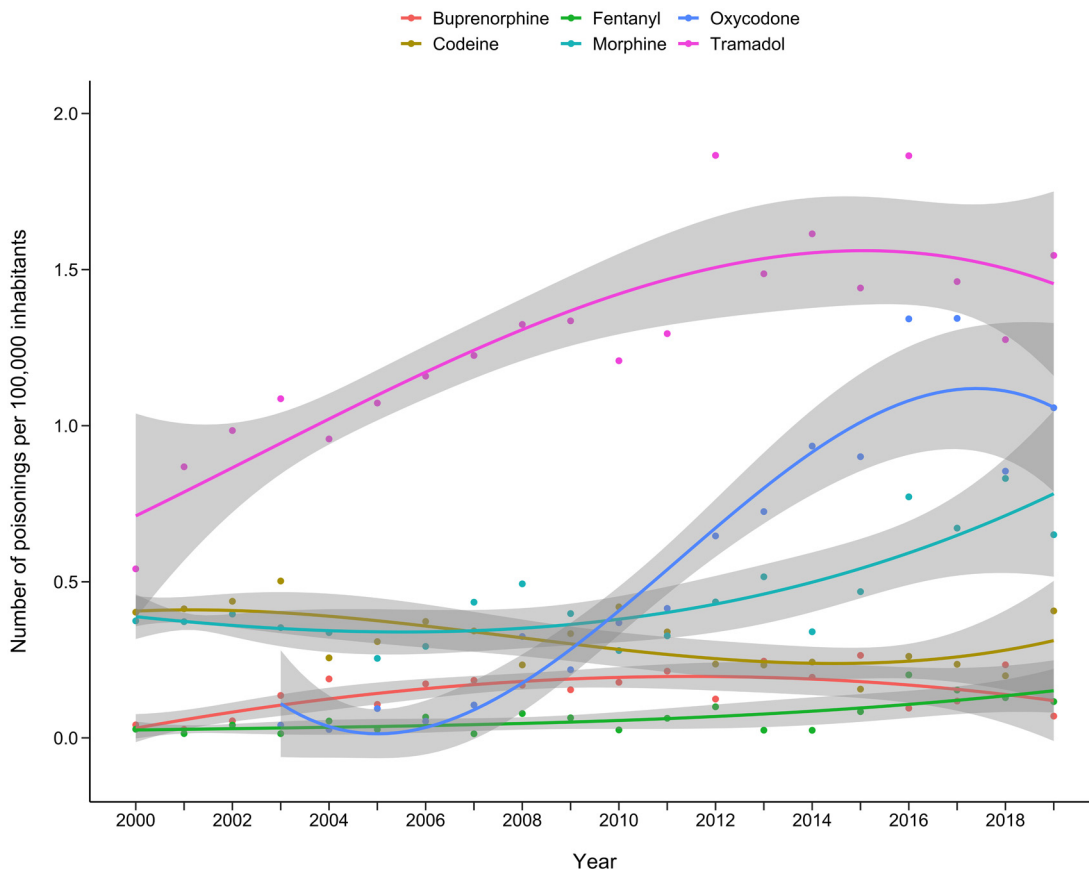


Figure 4. Rate of opioid-related poisoning calls to the Swiss National Poison Centre per 100,000 inhabitants from 2000 to 2019 for individual opioids with counts >100. Grey shading indicates the 95% confidence intervals from the basis-spline regression model.

reports from the Netherlands,¹⁴ opioid sales increased substantially in the last decade, from 14,364.0 to 27,477.6 per 100,000 inhabitants (a 91% increase). We identified that the general increase in opioid sales was primarily driven by a significant increase in strong opioids with no increase seen in the sales of weak opioids. Similar to other European countries,^{14–18,23} tramadol, a weak opioid, was the most frequently sold opioid (47.5%) and was also associated with the highest number of opioid-related calls to the National poison centre (43.9%). While the sales declined modestly since 2013 and the number of tramadol-related poison centre calls plateaued in 2016, tramadol remained the dominant opioid in our data, accounting for 37.5% of sales and 35.7% of calls in 2019. A similar trend was also seen in Denmark, the Netherlands, and the UK.^{14,17,23} Tramadol is a centrally acting synthetic weak opioid, which has often been considered to have a limited potential for non-medical use or substance use disorder, despite previous evidence demonstrating the contrary.²⁴ Thus, tramadol may be preferentially prescribed as a safe alternative when other analgesics, such as non-steroidal anti-inflammatories, are contraindicated.

However, the safety of tramadol, particularly the risk for serotonin syndrome, seizures, and cardiovascular events remains a concern. A recent population-based cohort study from the UK, with over one million tramadol or codeine users, identified that tramadol was associated with a significantly higher risk of mortality, cardiovascular events, and bone fractures, when compared to codeine.²⁵ Thus, the viewpoint that tramadol is a safe option should be revisited.

The marketed increase in the use of strong potency opioids, such as oxycodone, is in line with a previous Swiss study.²¹ Wertli et al. found a 117% increase in morphine equivalent dose for strong opioids between 2005 and 2013 in Switzerland.²¹ Of note in our study is the increase in oxycodone sales between 2009 and 2016, despite widespread awareness of the potential harms identified in the US. This increase is also similar to the trends observed in other European countries. In the Netherlands, the number of prescription opioids doubled between 2008 and 2017 from (4,109 to 7,489 per 100,000), which was driven by a quadrupling in oxycodone use (from 574 to 2,568 per 100,000).¹⁴ While the Dutch study identified the number of opioid users,

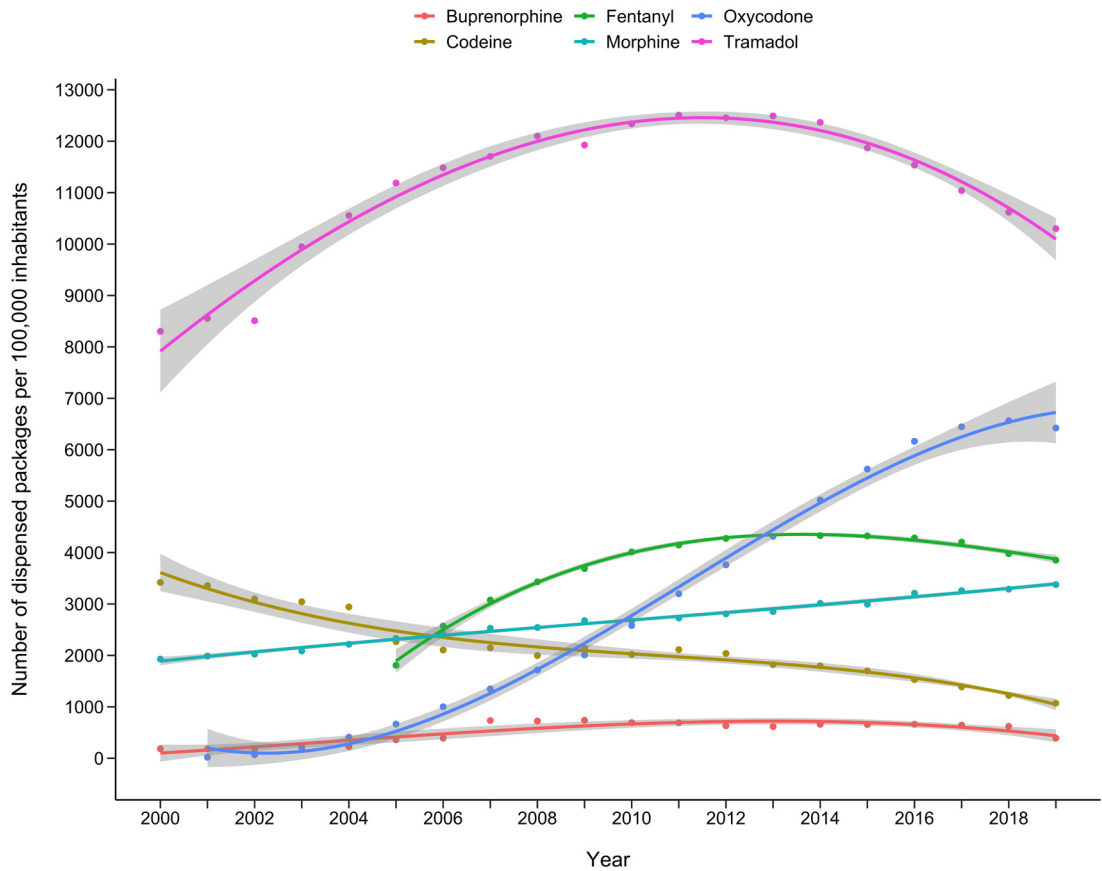


Figure 5. Rate of sold opioid packages per 100,000 inhabitants from 2000 to 2019 for the six most frequently sold opioids. Grey shading indicates the 95% confidence intervals from the basis-spline regression model.

we found similar increases in the national sales data. Indeed, from 2007 to 2017, the same period as the Dutch study, the sales of oxycodone showed an almost 4-fold increase.

Since 2016, sales have plateaued. While the guidelines surrounding pain management have not changed in Switzerland, other European countries updated their guidance on appropriate opioid use between 2015 and 2017. Thus, this may have influenced Swiss prescribing practices. The decline in oxycodone sales is important. In North America, the delisting of high-potency opioids, such as oxycodone, saw a shift towards fentanyl and clandestinely manufactured opioids used on the illicit market.^{13,26} In particular, substantial increases in overdoses involving illicit fentanyl or heroine have been observed.^{13,26} In our analysis, only prescription sales were included, and therefore illicit drug utilization was not directly assessed. It is possible that illicit use may be captured in the poison centre data, however, we must acknowledge that use and harms associated with highly potent illicit opioids may be underrepresented. For example, heroin or fentanyl overdoses often result in fatal cases whereby a patient has been found with a fatal

overdose, or died prior to arriving at the hospital, and these are likely not reported to the poison centre. Thus, given the challenges with fentanyl observed in the US and Canada, it is essential that policies in Switzerland aiming to decrease opioid consumption are mindful of the consequences of delisting opioids without an exit strategy.

Strengths and limitations

To date, this is the first analysis of poisoning and sales data examining the use and potential harm of opioids in the Swiss population. The main strength of our study is the use of databases with national coverage over a 20-year period. The National sales were derived from IQVIA (www.iqvia.com), which collects similar data from 77 countries, is widely used in drug utilization studies. Moreover, poison centre data is collected in a comparable manner to other national poison centres (e.g., the National Poison Data System in the US or the National Poison Information Service in the UK), as it provides a comprehensive and nationwide free service regarding suspected poisoning events to substances or

	Overall (N = 4273)	Weak opioids (N = 2398)	Strong opioids (N = 1875)	P value*	
Sex – no. (%)					
Male	1,628 (38.1)	829 (34.6)	799 (42.6)	< 0.001	
Female	2,541 (59.5)	1,504 (62.7)	1,037 (55.3)		
Unknown	104 (2.4)	65 (2.7)	39 (2.1)		
Age – no. (%)					
Mean (SD) - years	35.9 (22.1)	31.3 (20.1)	42.0 (23.3)	< 0.001	
< 16	595 (13.9)	411 (17.1)	184 (9.8)	< 0.001	
16 - 24	431 (10.1)	316 (13.2)	115 (6.1)		
25 - 44	1,051 (24.6)	608 (25.4)	443 (23.6)		
45 - 65	719 (16.8)	344 (14.3)	375 (20.0)		
> 65	320 (7.5)	105 (4.4)	215 (11.5)		
Missing	1,157 (27.1)	614 (25.6)	543 (29.0)		
Age category – no. (%)					
Children	622 (14.6)	427 (17.8)	195 (10.4)	< 0.001	
Adults	3,649 (85.4)	1,971 (82.2)	1,678 (89.5)		
Unknown	<5	..	<5		
Region – no. (%)					
German part	3,187 (74.6)	1,663 (69.4)	1,524 (81.3)	< 0.001	
French part	959 (22.4)	660 (27.5)	299 (15.9)		
Italian part	127 (3.0)	75 (3.1)	52 (2.8)		
Circumstance of poisoning – no. (%)					
Intentional	2,585 (60.5)	1,510 (62.9)	1,075 (57.3)	< 0.001	
Suicidal	1,828 (42.8)	1,146 (47.8)	682 (36.4)		
Other [†]	757 (17.7)	364 (15.2)	393 (21.0)		
Unintentional	1,605 (37.6)	855 (35.7)	750 (40.0)		
Accidental	1,368 (32.0)	747 (31.2)	621 (33.1)		
Adverse event	182 (4.3)	100 (4.2)	82 (4.4)		
iatrogenic	55 (1.3)	8 (0.3)	47 (2.5)		
Unknown	83 (1.9)	33 (1.4)	50 (2.7)		
Number of agents involved – no. (%)					
Single	2,325 (54.4)	1,304 (54.4)	1,021 (54.5)		0.96
Multiple	1,948 (45.6)	1,094 (46.6)	854 (45.5)		
Caller – no. (%)					
Emergency service	175 (4.1)	76 (3.2)	99 (5.3)	< 0.001	
Home	25 (0.6)	5 (0.2)	20 (1.1)		
Hospital doctor	2,446 (57.2)	1,358 (56.6)	1,088 (58.0)		
Other doctor	252 (5.9)	148 (6.2)	104 (5.5)		
Pharmacist	88 (2.1)	57 (2.4)	31 (1.7)		
Public	1,129 (26.4)	683 (28.5)	446 (23.8)		
Various organizations	158 (3.7)	71 (3.0)	87 (4.6)		
Medical care required [‡]	1,546 (36.2)	861 (35.9)	685 (36.5)		0.67
Causality (certain or probable) [§]	1,465 (94.8)	815 (94.7)	650 (94.9)		0.18
Symptoms (severe or moderate) [§]	622 (40.2)	295 (34.3)	327 (47.7)		< 0.001
Fatal	17 (1.1)	6 (1.0)	11 (1.6)	0.15	

Table 1: Characteristics of opioid-related poisoning calls reported to the national poison centre in Switzerland between January 1, 2000, and December 31, 2019, stratified by opioid potency.

N, total population; no., number of poisonings; SD, standard deviation. Percentages may not total 100 because of rounding.

* Associations between categorical variables and opioid potency were analysed using a Chi-square test; for comparison of the mean age, a two-sample T-test was used.

[†] The group “intentional, other” consists of all poisonings labelled as abuse, criminal intent, or other intentional circumstances.

[‡] Identified from the subset of calls with additional follow-up information submitted by the treating physician.

[§] Information available only among those with additional physician follow-up information. Proportions are therefore, only given using the number with hospitalization or physician care as the denominator. Note: counts with less than 5 occurrences are suppressed for data privacy.

toxins. Previous studies have found poison centre data are highly similar to emergency department visits for poisonings.²⁷

Nevertheless, there are inherent limitations. First, calls to the National Poisons Information Centre are voluntary, thus, opioid-related hospital admissions without poison centre consultation are not included. While poison centre data for opioid-related harm have been found to correlate well with emergency department visits, we expect that we may have missed some hospitalizations and underestimated harm. Indeed, fatal overdoses in the community (e.g., without hospitalization) will be missed in our data if the poison centre was not contacted for consultation. Additionally, since opioid overdoses are typically not complicated, with a known and available antidote, physicians are unlikely to contact the National poison centre for support. Thus, we will have missed cases arriving in ambulatory care where an initial consultation was not made with the poison centre. Moreover, we could only assess harm as identified in the poison centre calls. This does not capture all hospitalizations or deaths, nor does it capture the rate of dependency, which would be of interest given the utilization of strong opioids. Thus, we expect we have underestimated, and provide a conservative estimate, of the cumulative harm.

Second, while we standardized the number of calls to the national poison centre for the growing population size, we did not correct for the increase in overall calls to the poison centre during the study period. While there was a 26.8% increase in calls from 2000 to 2019,²⁰ the increase in the number of opioid-related poisonings was around 8.5 times higher (namely 231%), and therefore cannot be solely explained by the increase in calls. However, we are mindful that the increasing number of calls to the national poison centre may have been influenced by increased awareness of the potential for opioid related harm following the media attention to the opioid epidemic in the US. Although, we note that the proportion of calls resulting in hospitalizations also increased, indicating increasing opioid-related harm.

Third, our sales and poison centre data provided only the number of packages sold or calls, and therefore we cannot determine the number of patients or investigate patient-specific characteristics. As a result, we were unable to identify or exclude patients receiving opioids for cancer-related pain management. However, a previous Swiss study found that opioids were primarily used outside the context of cancer-related treatment.² Moreover, from the sales data we did not have information on the strength and package size of the sold opioid packages and therefore could not evaluate changes in the available morphine equivalent doses. Additionally, we could not distinguish between normal release oral morphine products and slow release oral morphine (SROM), which was approved as an opioid agonist treatment in 2013, in our database. Thus, we are unable to

examine if the modest increase in morphine use was an indicator of elevated morphine use or increasing rates of opioid treatment with SROMs. Nevertheless, our results provide insight into the general trend observed in opioid sales in Switzerland over the last two decades. To our knowledge, there were no major changes in package size or strength for opioids in Switzerland between 2000 and 2019, but some new opioids (e.g., SROMs) were licensed in the study time frame. Finally, our data only reflect the situation up to the end of 2019. Several reports from the US and Canada have indicated resurgences in opioid overdoses and deaths since the onset of the COVID-19 pandemic,^{12,28} and this should be monitored in Switzerland.

Taken together, our results suggest that numbers of opioid poisonings and opioid sales have increased substantially in Switzerland over the last decade. While the rate of opioid-related harm in Switzerland (3.9 per 100,000 inhabitants) is similar to other European countries, it remains significantly lower than the rates observed in the US (26.6 per 100,000 in 2016) or Canada (16.4 per 100,000 in 2017).^{9,11} However, with a 5.3% annual relative increase in opioid poisonings overall, and 10.2% annual relative increase in strong opioid poisonings, Switzerland is observing a startling rise in opioid harm. Thus, there is a need for increased monitoring and development of evidence-based prescribing practices. In the United Kingdom, calls for stronger opioid stewardship have led to the Medicines and Healthcare Products Regulatory Agency (MHRA) working group to recommend stronger warnings on prescription opioids and the National Institutes for Health and Care Excellence (NICE) has removed opioids (along with other pain medications) from the recommended treatments of chronic pain in adults.^{29,30} Similar strategies should be considered in Switzerland and other European countries.

Contributors

Study Conception: A.M.B., S.W.; Data Acquisition: S.W.; Data Analysis: M.H., A.M.-D.I.T.; Data Integrity and Validity: M.H., A.M.-D.I.T.; Data Interpretation: M.H., A.M.-D.I.T., S.W., A.M.B.; Manuscript Preparation: M.H., A.M.-D.I.T., and A.M.B.; Critical Revisions: M.H., A.M.-D.I.T., S.W., and A.M.B. All authors have read and agreed to the published version of the manuscript.

Data sharing statement

The data were obtained from a third party and are not publicly available. However, the data analyzed in this study may be made available upon a reasonable request to the corresponding author and following approval from the data providers (i.e., the Tox Info Swiss and IQVIA). The programming code for this project is available upon reasonable request to the corresponding author.

Declaration of interests

S.W. is a member of the Human Medicines Expert Committee (HMEC) board of Swissmedic. The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of any authority or working parties. The professorship of A.M. B. was partly endowed by the Swiss Pharmacists' Association (pharmaSuisse) and the ETH Foundation, but funds are not provided for research and the current project was not funded. M.H. and A.M.-D.I.T. have no conflict of interest to declare regarding this research.

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Supplementary materials

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