

Trends in use and misuse of opioids in the Netherlands: a retrospective, multi-source database study

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Summary

Background The USA is currently facing a serious opioid misuse epidemic that started with increased prescribing of oxycodone and the inclusion of pain as a fifth vital sign, and eventually resulted in massive overdose mortality. In Europe, including the Netherlands, the medical use of opioids (mainly oxycodone) has also increased since 2009, but an increase in proxies for opioid misuse has not yet been described.

Methods For this retrospective, multi-source database study, data were requested from several national databases in the Netherlands to evaluate the following time trends: (1) number of people with opioid prescriptions, (2) number of hospital admissions related to opioid intoxication, (3) number of people treated for opioid use disorder, and (4) number of people who died from opioid poisoning. Data were presented as the number per 100 000 inhabitants, using population data over the years 2008–17 from Statistics Netherlands (Centraal Bureau voor de Statistiek). Data about the number of people with opioid prescriptions was obtained from the Drug Information Project (Genees- en hulpmiddelen Informatie Project) database hosted by the Dutch National Health Care Institute (Zorginstituut Nederland). Data about opioid-related hospital admissions between 2008 and 2017 were obtained from the Dutch National Hospital Care Basic Registration (Landelijke Basisregistratie Ziekenhuiszorg), a database managed by Dutch Hospital Data. Data about addiction treatment were obtained from the National Alcohol and Drugs Information System (Landelijk Alcohol en Drugs Informatie Systeem). Data on opioid mortality between 2008 and 2017 were obtained from the cause-of-death statistics database hosted by Statistics Netherlands. Each database covered almost the entire population of the Netherlands.

Findings Between 2008 and 2017, the overall number of prescription opioid users nearly doubled from 4109 per 100 000 inhabitants to 7489 per 100 000 inhabitants, mainly because the number of oxycodone users quadrupled from 574 to 2568 per 100 000 inhabitants. In the same period, the number of opioid-related hospital admissions tripled from 2.5 to 7.8 per 100 000 inhabitants, and between 2008 and 2015 the number of patients in addiction care for opioid use disorders other than heroin increased from 3.1 to 5.6 per 100 000 inhabitants. Opioid-related mortality was stable between 2008 and 2014 with 0.21 deaths per 100 000 inhabitants, but after 2014 it increased to 0.65 per 100 000 inhabitants in 2017.

Interpretation Prescription opioid use increased substantially between 2008 and 2017, and several proxies for misuse show a parallel increasing trend. Although the Netherlands is far from the opioid epidemic faced by the USA, safe opioid prescribing guidelines should be implemented to prevent further escalation and to keep opioid painkillers available for those in need.

Funding Radboud University Nijmegen Medical Centre.

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Introduction

Opioids are mostly used as analgesics in the management of moderate to severe pain.^{1–3} Effectiveness of opioids compared with other painkillers differs per type of pain. For instance, when opioids are used for the treatment of acute pain or chronic cancer pain most patients experience adequate pain reduction.³ However, there is little evidence for the effectiveness of opioids for chronic non-cancer pain.^{1,2} Opioids also have frequent side-effects such as constipation, hypoventilation, and negative effects on cognition and mental health.² Effects on mental health particularly include hallucinations and the addictive potential of opioids. Approximately 3–3% of patients

exposed to chronic opioid therapy become addicted.⁴ Furthermore, opioid use is associated with an increased risk of suicide.⁵ Weighing the beneficial analgesic effects of opioids against their potential harms is therefore crucial.

The importance of balanced opioid prescription practices is further emphasised by the opioid epidemics in the USA and Canada. Between 1999 and 2010 the sales of opioids in the USA quadrupled,⁶ mainly because of increased use of oxycodone and the inclusion of pain as a fifth vital sign.^{7,8} At the same time, opioid-related mortality increased from 3 per 100 000 in 2000 to 7 per 100 000 in 2010.⁹ From 2010 onward, the number of opioid prescriptions in the USA

Lancet Public Health 2019; 4: e498–505

Published Online
August 20, 2019
[http://dx.doi.org/10.1016/S2468-2667\(19\)30128-8](http://dx.doi.org/10.1016/S2468-2667(19)30128-8)

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Research in context**Evidence before this study**

The use of prescription opioids in Europe has increased substantially since 2009. In the USA, the rise in opioid prescriptions has had a major societal and medical impact, and has caused a marked increase in addiction and opioid-related deaths. It remains to be seen whether the observed increase in opioid prescriptions in Europe will have a similar effect. We searched PubMed and Google Scholar without language restrictions between October, 2008, and March, 2019, with the terms “opioid”, “use”, “misuse”, and “Europe” to identify relevant papers that describe recent trends in prescription opioid misuse in Europe. The most recent evaluation of opioid misuse in Europe was published in 2015, but this narrative review used data from only some European countries, with different data available for different countries. Integrated systematic evaluations of trends in multiple proxies for opioid misuse are scarce.

Added value of this study

To our knowledge, this is the first paper that uses a combination of national registries to explore prescription opioid use and several proxies for misuse, including addiction, hospitalisations, and mortality. Using this approach, we give an integrated overview of trends in use and multiple proxies for misuse of opioids in the Netherlands.

Implications of all the available evidence

Prescription opioid use and proxies for misuse in the Netherlands have increased between 2008 and 2017. Although opioid misuse in the Netherlands is still substantially lower than in the USA, our results warrant detailed monitoring of opioid misuse proxies in Europe. To prevent further escalation of opioid misuse and to keep opioid painkillers available for those in need, implementing safe, evidence-based opioid prescribing guidelines is of utmost importance.

gradually declined from roughly 80 prescriptions per 100 people per year to about 70 per 100 people per year in 2015.⁶ However, mortality caused by opioid overdose continued to increase to 15 per 100 000 in 2017. This is mainly explained by the shift from prescription opioid use to heroin use, and more recently to illicitly manufactured fentanyl.^{9,10} In total, an astonishing 399 233 Americans died from an opioid overdose between 1999 and 2017.¹⁰ Canada is facing a similar crisis with an overall increase in opioid-related deaths and a stark increase in fentanyl-related deaths in some provinces.¹¹

In Europe, including the Netherlands, the medical use of opioids has also substantially increased since 2009.¹² However, the situation in Europe may well differ from the USA.¹² For instance, although the number of opioid prescriptions in Europe continues to rise, no increase has been described in the number of opioid-related deaths and in the number of patients in addiction treatment for opioid use disorder. Between 2007 and 2016, deaths caused by opioid overdose in Europe were stable at about 1·2 deaths per 100 000 per year,¹³ a much lower number than the 15 deaths per 100 000 caused by opioid overdose in the USA in 2017.¹⁰

Given the tremendous impact of the opioid epidemic in the USA and Canada, it is of utmost importance to closely monitor trends in opioid use and misuse in Europe, in particular any signs of increased misuse of prescription opioids, since those could prelude large-scale opioid-related harm and mortality. However, recent epidemiological studies on opioid misuse in Europe are scarce. The most recent evaluation¹² was published in 2015; this narrative review used ad hoc data from some European countries with different data available for each country. Given this lack of systematic data, we set out to monitor trends in prescription opioid use and multiple proxies for opioid misuse in

the Netherlands over the past ten years (2008–17), using a combination of national databases and registrations.

Methods**Study design**

For this retrospective, multi-source database study, data were requested from several national databases in the Netherlands to evaluate the following time trends: (1) number of people with opioid prescriptions, (2) number of hospital admissions related to opioid intoxication, (3) number of people treated for opioid use disorder, and (4) number of people who died from opioid poisoning. All data were gathered in accordance with Dutch privacy laws and following the procedures required by the different databases. There were no exclusion criteria. As only aggregated data were available, individual patient data from the different databases could not be linked. Each database covered almost the entire population of the Netherlands. Data were presented in figures as the number per 100 000 inhabitants, using population data over the years 2008–17 from Statistics Netherlands (Centraal Bureau voor de Statistiek; CBS).¹⁴ Rates were calculated by dividing the absolute number by the number of inhabitants in the corresponding year and multiplying by 100 000.

Data about the number of opioid users was obtained from the Drug Information Project (Genees- en hulpmiddelen Informatie Project; GIP) database hosted by the Dutch National Health Care Institute (Zorginstituut Nederland).¹⁵ This database contains information about reimbursements of prescriptions filled by public pharmacies. The data are publicly accessible in aggregated form and cover about 96% of all Dutch inhabitants. The GIP database contains information on the number of unique users per Anatomical Therapeutic Chemical (ATC) code and year.

Currently the database covers the years 2003–17. Information on the duration of use or dose is unavailable in the publicly accessible dataset. The four most commonly used opioids (tramadol [ATC code N02AX02, N02AJ13, and N02AX52], oxycodone [N02AA05], morphine [N01AA01 and N02AA51], and fentanyl [N02AB03]) were shown separately. All other opioids were combined in the category of other opioids, including hydromorphone (N02AA03), nicomorphine (N02AA04), pethidine (N02AB02), dextromoramide (N02AC01), piritramide (N02AC03), pentazocine (N02AD01), buprenorphine (N02AE01), and tapentadol (N02AX06). Codeine was excluded because it is not exclusively used for pain treatment, and the codeine plus paracetamol combination tablet is no longer reimbursed since 2013. Patients who received opioid prescriptions with different ATC codes were counted separately for each ATC code.

Data about opioid intoxication-related hospital admissions between 2008 and 2017 were obtained from the Dutch National Hospital Care Basic Registration (Landelijke Basisregistratie Ziekenhuiszorg), a database managed by Dutch Hospital Data.¹⁶ This database contains medical, administrative, and financial information on hospital admissions and covers all Dutch hospitals. The reasons for hospital admissions are coded according to the ninth or tenth revision of the WHO International Classification of Diseases (ICD-9 or ICD-10). ICD-9 was used until 2013 and ICD-10 was used from 2011 onward. Between 2011 and 2013 hospitals coded admissions using either ICD-9 or ICD-10. ICD-9 codes 965.00 (opium), 965.01 (heroin), 965.02 (methadone), and 965.09 (other opioids), and ICD-10 codes T40.0 (opium), T40.1 (heroin), T40.2 (other opioids), T40.3 (methadone), and T40.4 (other synthetic opioids) were used to identify hospital admissions related to opioid poisoning. Opium (965.00 and T40.0), heroin (965.01 and T40.1), and methadone (965.02 and T40.3) were grouped into one category. All other opioids (965.09, T40.2 and T40.3) were combined in the category of other (prescription). The ICD-9 and ICD-10 codes for opium include preparations of opium tincture, opium powder, laudanum, and papaveretum. We grouped opium with heroin and methadone because none of the opium preparations are available as a prescription drug in the Netherlands.

Data about addiction treatment were obtained from the National Alcohol and Drugs Information System (Landelijk Alcohol en Drugs Informatie Systeem; LADIS). LADIS contains information about all regular addiction care provided in the Netherlands, to monitor changes in health-care consumption.¹⁷ LADIS data were available until 2015. We extracted data on opioid-related addiction care between 2007 and 2015. LADIS categorises opioid-related addiction care into the following ten categories: heroin, methadone, methadone substitution, buprenorphine, morphine, fentanyl, oxycodone, tramadol, miscellaneous, and unknown opioids. We regrouped these categories, because of differences in registration between different

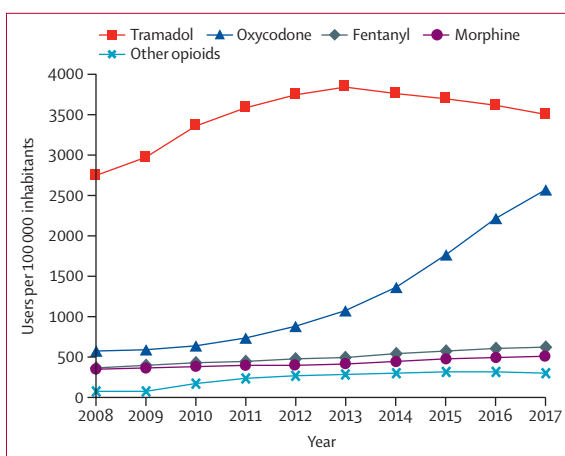


Figure 1: Users of prescription opioids in the Netherlands per 100 000 inhabitants

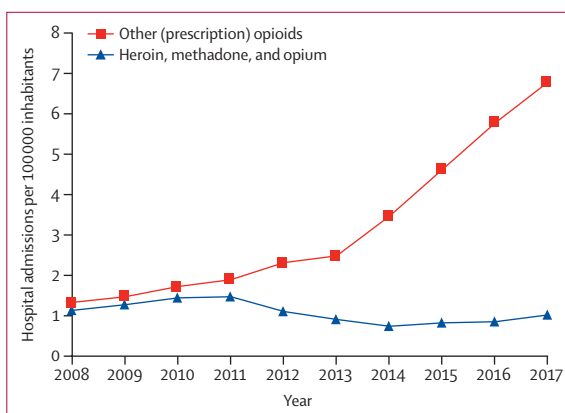


Figure 2: Number of hospital admissions in the Netherlands related to opioid intoxication

addiction care centres. For instance, some centres register methadone treatment under substitution, whereas other centres register it as methadone. Similarly, prescription opioid use disorders are sometimes categorised under miscellaneous (this category might include patients receiving different prescription opioids) and sometimes under a specific substance like morphine or oxycodone. Therefore, we used three categories of patients with opioid use disorder in addiction care: patients with opioid use disorder receiving substitution treatment (including methadone, methadone substitution, and buprenorphine), patients with (prescription) opioid use disorder (including morphine, fentanyl, oxycodone, tramadol, and miscellaneous opioids, and excluding heroin), and patients with heroin use disorder.

Data on opioid mortality between 2008 and 2017 were obtained from the cause-of-death statistics database hosted by the CBS. This database contains information on deaths of all Dutch inhabitants. After a death occurs, a physician or pathologist is required to fill out a cause-of-death form for statistical purposes. The form is then

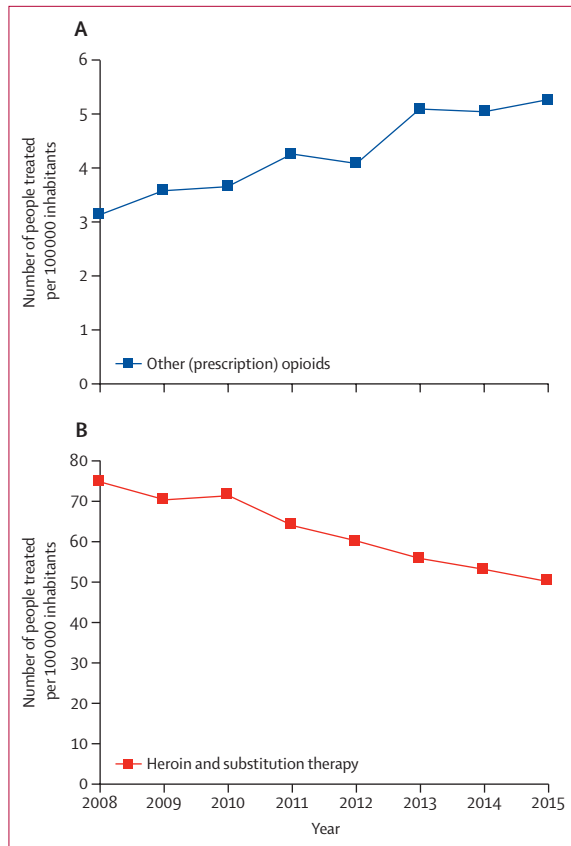


Figure 3: Number of people in the Netherlands in addiction care
(A) Patients treated for addiction to (prescription) opioids.
(B) Patients treated for heroin addiction, and patients receiving opioid substitution therapy such as methadone.

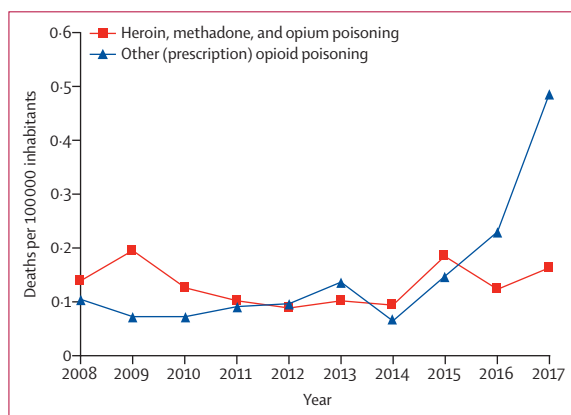


Figure 4: Mortality caused by opioid poisoning in the Netherlands per 100 000 inhabitants

processed by CBS according to ICD-10 guidelines. In 2013, CBS switched from a manual to a semi-automatic coding process of cause-of-death form. This limits comparability of data before and after 2013. Deaths caused by opioid poisoning are identified using ICD-10 codes T40.0 (opium), T40.1 (heroin), T40.2 (other opioids, including morphine and oxycodone), T40.3 (methadone),

and T40.4 (other synthetic opioids, including fentanyl). Opium (T40.0), heroin (T40.1), and methadone (T40.3) were grouped into a single category. Other opioids (T40.2) and other synthetic opioids (T40.4) were grouped as other (prescription) opioids. Opium was grouped with heroin and methadone, similar to our hospitalisation data.

Role of the funding source

The study sponsor had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit for publication. GAK and AS had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The population of the Netherlands increased from 16.4 million in 2007 to 17.1 million in 2017. Between 2008 and 2017, opioid use increased substantially from 4109 per 100 000 inhabitants in 2008 to 7489 per 100 000 inhabitants in 2017 (figure 1). Tramadol, oxycodone, morphine, and fentanyl are shown separately. Hydromorphone, nicomorphine, pethidine, dextromoramide, piritramide, pentazocine, buprenorphine, and tapentadol are combined in a single category. In this 10-year period the number of oxycodone users almost quadrupled from 574 to 2568 per 100 000 inhabitants. Use of fentanyl, morphine, and other opioids also increased, but not to the extent of oxycodone. The number of tramadol users first increased from 2736 users per 100 000 inhabitants in 2008 to 3830 per 100 000 inhabitants in 2013 and then gradually declined to 3494 per 100 000 inhabitants in 2017.

Hospital admissions related to opioid intoxication increased from 2.5 per 100 000 inhabitants in 2008 to 7.8 per 100 000 inhabitants in 2017. This was mainly due to an increase in intoxications in the category of other (prescription) opioids (figure 2). Intoxications involving opium, heroin, and methadone remained stable, while intoxications involving other opioids increased from 1.3 per 100 000 inhabitants in 2008 to 6.8 per 100 000 inhabitants in 2017.

The total number of patients treated for opioid addiction decreased from 80 per 100 000 inhabitants in 2008 to 55 per 100 000 inhabitants in 2015. More than 80% of opioid addiction treatments are for heroin addiction and the number of treatments gradually decreased from 75 per 100 000 in 2007 to 50 per 100 000 in 2015. By contrast, the number of people being treated for addiction to other (prescription) opioids increased from 3.1 per 100 000 inhabitants in 2007 to 5.6 per 100 000 inhabitants in 2015 (figure 3).

Total mortality from opioid poisoning was stable between 2008 and 2014 with an average of 0.21 deaths per 100 000 (35 people). After 2014 total mortality increased to 0.65 per 100 000 (111 people) in 2017. This increase was mainly driven by an increase in poisoning from other (prescription) opioids (figure 4). Poisoning from other

(prescription) opioids was stable between 2008 and 2014 at an average of 0·091 per 100 000 (15 people). After 2014, mortality from other (prescription) opioids increased to 0·49 per 100 000 (83 people) in 2017. By contrast, mortality from heroin, methadone, and opium poisoning remained stable between 2008 and 2017 at an average of 0·13 per 100 000 (22 people).

Discussion

Exploring trends in opioid use and proxies for opioid misuse in multiple databases in the Netherlands between 2008 and 2017 showed that (1) the number of prescription opioid users nearly doubled, (2) the number of hospitalisations caused by an opioid intoxication tripled, (3) addiction care for opioids other than heroin and substitution therapy nearly doubled, and (4) opioid-related mortality also doubled. The relative increase in opioid-related hospitalisations was greater than other proxies for misuse, and greater than the relative increase in opioid prescriptions. These findings clearly show an increase in opioid prescriptions being paralleled by an increase in multiple proxies for opioid misuse. Compared with the USA however, the use and misuse of prescription opioids and opioid-related mortality are still very low.

In line with the Netherlands, other European countries have seen similar increases in the number of opioid prescriptions. For instance, in Scotland the dispensing of oxycodone, fentanyl, and morphine increased five-fold between 1995 and 2010.¹⁸ Additionally, a serious increase in deaths caused by opioid-related overdose in Scotland has been observed, with 15 opioid-related overdose deaths per 100 000 in 2017.¹⁹ In the UK, the number of opioid prescriptions quadrupled between 2000 and 2010, with most prescriptions being for non-cancer pain.²⁰ However, in England and Wales the number of deaths related to opioid overdose increased between 1993 and 2017, from 0·84 to 3·5 per 100 000 inhabitants.²¹ Because registration of the cause of death in England and Wales can be delayed by months or even years, this number is most likely an underestimation. Importantly, such a delay in availability of monitoring data hampers adequate and timely policy responses. In Germany the use of strong extended-release opioids increased four-fold between 2000 and 2010.²² France had a doubling of strong opioid use between 2004 and 2017. However, it should be noted that the number of deaths caused by opioid overdose in the EU has been stable at least until 2016, at a relatively low rate of approximately 1·2 deaths per 100 000 inhabitants.¹³

Several factors might have contributed to the rise in prescription opioid use in the Netherlands—for example, an ageing population with more pain and more contraindications for other analgesics such as non-steroidal anti-inflammatory drugs. However, this can only explain a rather small amount of the observed increase, since the proportion of people older than 70 years rose from 10·3% in 2008 to 12·6% in 2017.¹⁴

Furthermore, the increase in opioid use was seen in all age categories, not only in older patients.²³

Since 2013, the paracetamol-codeine combination tablet is no longer reimbursed in the Netherlands. This might also have contributed to the rise of other opioids, particularly because the number of users of this combination has been fairly high in the past, with around 2500 users per 100 000 per year before 2013. Another important factor might be the increased attention to pain treatment in Dutch hospitals. In 2009 a national hospital patient safety programme was started, aiming to recognise and treat pain early.²⁴ This programme called for frequent measurement of pain scores and (mainly pharmacological) treatment of moderate to severe pain (numeric pain rating scale ≥ 4). Additionally, the percentage of patients with low pain scores (numeric pain rating scale < 6) was used as an important quality indicator in the benchmarking between hospitals. The increased focus on pain management combined with increasingly short hospital stays has likely resulted in more patients being discharged with opioid prescriptions.²⁴

Key drivers of the opioid epidemic in the USA were the false beliefs that opioids are safe when used for chronic non-cancer pain and that development of addiction is rare; the large-scale public advertisement of opioid painkillers, increasing the pressure on doctors to prescribe them; and the existence of opioid pharmacies (so-called pill mills).^{25–27} US marketing of oxycodone by the pharmaceutical company Purdue is thought to have contributed substantially to the opioid epidemic,²⁸ leading to trials and convictions of representatives of this firm. However, in the Netherlands public marketing by pharmaceutical companies is not allowed and so-called pill mills do not exist. Together with the warning example of the enormous opioid epidemic in the USA, which emphasises the addictive potential of prescription opioids, these factors might so far have prevented a similar opioid epidemic from happening in the Netherlands and Europe.¹²

Still, the number of addiction treatments for opioids other than heroin and methadone in the Netherlands nearly doubled from 2008 to 2015, paralleling the increase in prescription opioid users. A similar trend was observed in the USA, where an increase in opioid addiction treatments from 1999 to 2008 paralleled an increase in opioid sales.²⁹ The number of opioid-related hospitalisations and mortality in the Netherlands increased from 2014 onward, mainly driven by other (prescription) opioids. Although not an a priori hypothesis, there seems to be a delay between the rise in opioid prescriptions and opioid-related mortality, in contrast with the USA where these developments occurred simultaneously.

The observed trends in opioid painkiller prescribing and proxies for misuse in the Netherlands warrant implementation of safe opioid prescribing guidelines to prevent further escalation of a potential threat to public health. For instance, doctors should prescribe the smallest quantity of opioids required to sufficiently treat

acute pain and only for a limited period, because chronic use often begins with treatment of acute pain. Furthermore, chronic opioid therapy should only be initiated when realistic goals for pain management, functioning, and quality of life have been established. Opioid therapy should be discontinued when these goals are not met or when the harms outweigh the benefits. Moreover, non-pharmacological and non-opioid pain therapy should always be considered in addition to or instead of opioid therapy.² To tackle the rise in opioid use, close collaboration between hospital prescribers (eg, surgeons and anaesthesiologists), addiction specialists, psychiatrists, general practitioners, and pharmacists is needed. Additionally, prescribers should take risk factors for opioid misuse into account when first prescribing opioids, so patients at risk can be monitored and guided more closely.³⁰ Guidelines with respect to duration of opioid prescriptions should be readily available and implemented, and general practitioners should not renew prescriptions for patients on opioids without careful consideration. Early identification of patients who increase or extend their opioid prescriptions is especially important, so that they can be referred for consultation with addiction specialists or psychiatrists in individual cases. The Dutch Ministry of Health has recently declared that the increase in opioid use in the Netherlands is a public health priority and is exploring how to reverse the observed trends. The increase in opioid use has been subject to media attention, leading to more vigilance on opioid misuse among prescribers and patients alike. Additionally, the general practitioners guideline for management of chronic non-cancer pain has been adapted and has become more conservative concerning indications for prescription of opioids.

A major strength of our study is the use of national databases that cover almost the entire population of the Netherlands, and the use of several proxies for misuse. However, we should also consider several limitations. First, our prescription data provide no information on the duration, dose, prescriber and reason for opioid use. Such information is of great value for more detailed analyses of observed trends. Moreover, such information would allow us to calculate morphine equivalents, facilitating more precise monitoring of opioid use. Similarly, information on specific opioids involved in opioid-related mortality and demand for addiction treatment could show which opioids might be most harmful. However, most countries and the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) do not differentiate between different prescription opioids (eg, oxycodone and fentanyl) and classical opioids (eg, heroin) in their data monitoring systems. This is highly relevant, as our data show that the total treatment demand for opioids in the Netherlands decreased over the past years (in line with EMCDDA data), masking an increase in treatment demand for prescription opioids. Although we were

able to separate trends in heroin and heroin substitution therapy (methadone) from trends in prescription opioids, we were not able to identify which prescription opioids were involved in mortality and demand for addiction treatment (figures 2–4). Moreover, since methadone is also used for treatment of pain, our inability to distinguish prescription opioids might have led to an underestimation of opioid misuse indicators.

Second, codeine was excluded because reliable data on codeine use for pain was not available. Codeine can be used in high doses as an analgesic or in lower doses as a cough suppressant. The GIP database does not distinguish between these two uses for codeine-only formulations. A possible option to examine codeine use for pain would be to only examine combination formulations that are exclusively used for pain. However, this would underestimate codeine use for pain since codeine-only formulations are not taken into account. Furthermore, the paracetamol-codeine combination tablet is no longer reimbursed in the Netherlands since 2013, so its use for pain is unlikely to have increased. Thus, the impact of the exclusion of codeine from our study is likely to be low, because use of codeine combination tablets for pain was stable before 2013, and the Dutch general practitioners guideline for management of chronic non-cancer pain recommends the use of tramadol instead of codeine when pain is insufficiently treated with paracetamol or non-steroidal anti-inflammatory drugs. The increase in proxies for misuse is unlikely to be caused by misuse of prescription codeine; a detailed study of patient-level prescription data, including dose and indication, would be required to obtain complete information on codeine use, to investigate the effect of the change in reimbursement status.

Third, our data from addiction care do not contain information about the start of the opioid addiction. Therefore, we cannot say for certain that the increase in addiction to other opioids started with a prescription to a medical opioid. Our ability to see trends in addiction care is also limited to data before 2015. Additionally, treatment of opioid addictions in the Netherlands is mainly focused on illicit opioids such as heroin, so patients experiencing a problem with prescription opioids might seek treatment outside of regular addiction care—for instance at a general practitioner or in hospitals. This could result in an underestimation of the prevalence of opioid addiction in our data. Fourth, in recent years post-mortem toxicological screening has become more common, which could be causing an increase in opioid-related deaths being registered in the cause-of-death statistics database.³¹ Fifth, although our findings are in line with previous studies^{32–34} showing a clear link between the number of opioid prescriptions and opioid-related complications, the independence of datasets and observational nature of the data does not allow us to infer any causal relationships. Sixth, in the prescription data the number of users is provided per ATC code. This

means that people receiving more than one opioid might count double in the datasets, leading to an overestimation of the number of opioid users, but this does not affect the indices of misuse. Finally, we have no data on the way in which prescription opioids are misused. This is relevant from a public health perspective, since people who inject drugs are at greater risk of infection with blood-borne diseases. New infections with HIV and hepatitis B or C are currently very rare among people who inject drugs in the Netherlands.³¹ To consolidate this low number of new blood-borne infections, preventing further expansion of opioid misuse and transition to intravenous use is key. Taken together, our findings show that numbers of prescription opioid users and of several proxies for opioid misuse have increased in the Netherlands, but they have not reached the epidemic levels faced by the USA. Our findings stress the relevance of close monitoring and development of evidence-based guidelines. A similar retrospective, multi-source database approach can also shed light on opioid use and misuse in other European countries.

Contributors

AS conceived and designed the study. GAK and AS analysed and collected the data. GAK drafted the manuscript and all authors provided critical revisions and approved the final submitted version.

Declaration of interests

WvdB reports personal fees from Takeda, Mundipharma, Indivior, and Opiant Pharmaceuticals. All other authors declare no competing interests.

Data sharing

The underlying data for this study can be requested from the corresponding author, GAK.

Acknowledgments

This research was supported by a 2018 Junior Researcher Grant of the Radboud University Nijmegen Medical Centre.

References

- Busse JW, Wang L, Kamaleldin M, et al. Opioids for chronic noncancer pain: a systematic review and meta-analysis. *JAMA* 2018; **320**: 2448–60.
- Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. *JAMA* 2016; **315**: 1624–45.
- Wiffen PJ, Wee B, Derry S, Bell RF, Moore RA. Opioids for cancer pain—an overview of Cochrane reviews. *Cochrane Database Syst Rev* 2017; **7**: CD012592.
- Fishbain DA, Cole B, Lewis J, Rosomoff HL, Rosomoff RS. What percentage of chronic nonmalignant pain patients exposed to chronic opioid analgesic therapy develop abuse/addiction and/or aberrant drug-related behaviors? A structured evidence-based review. *Pain Med* 2008; **9**: 444–59.
- Bohnert ASB, Ilgen MA. Understanding links among opioid use, overdose, and suicide. *N Engl J Med* 2019; **380**: 71–79.
- Guy GP Jr, Zhang K, Bohm MK, et al. Vital signs: changes in opioid prescribing in the United States, 2006–2015. *MMWR Morb Mortal Wkly Rep* 2017; **66**: 697–704.
- Manchikanti L, Fellows B, Ailinani H, Pampati V. Therapeutic use, abuse, and nonmedical use of opioids: a ten-year perspective. *Pain Physician* 2010; **13**: 401–35.
- Kolodny A, Courtwright DT, Hwang CS, et al. The prescription opioid and heroin crisis: a public health approach to an epidemic of addiction. *Annu Rev Public Health* 2015; **36**: 559–74.
- Rudd RA, Aleshire N, Zibbell JE, Gladden RM. Increases in drug and opioid overdose deaths — United States, 2000–2014. *MMWR Morb Mortal Wkly Rep* 2016; **64**: 1378–82.
- Scholl L, Seth P, Kariisa M, Wilson N, Baldwin G. Drug and opioid-involved overdose deaths — United States, 2013–2017. *MMWR Morb Mortal Wkly Rep* 2018; **67**: 1419–27.
- Fischer B, Vojtila L, Rehm J. The ‘fentanyl epidemic’ in Canada – some cautionary observations focusing on opioid-related mortality. *Prev Med* 2018; **107**: 109–13.
- van Amsterdam J, van den Brink W. The misuse of prescription opioids: a threat for Europe? *Curr Drug Abuse Rev* 2015; **8**: 3–14.
- European Monitoring Centre for Drugs and Drug Addiction. European drug report 2018: trends and developments. Luxembourg: Publications Office of the European Union, 2018.
- CBS StatLine. Population; key figures. Oct 30, 2018. <https://opendata.cbs.nl/statline/#/CBS/en/dataset/37296eng/table?ts=1564055397579> (accessed Feb 1, 2019).
- Genees- en hulpmiddelen Informatie Project. GI Peilingen: ontwikkelingen genees- en hulpmiddelengebruik 2012–2016, raming 2017–2021. Zorginstituut Nederland. March, 2018. <https://www.zorgkennis.net/downloads/kennisbank/ZK-kennisbank-Zorginstituut-Nederland-GI-Peilingen-5343.pdf> (accessed Jan 8, 2019).
- Dutch Hospital Data. Landelijke Basisregistratie Ziekenhuiszorg (LBZ). <https://www.dhd.nl/producten-diensten/LBZ/Paginas/Dataverzameling-LBZ.aspx> (accessed Dec 6, 2018).
- Wisselink DJ, Kuijpers WGT, Mol A. Kerncijfers verslavingszorg 2015. Houten: Stichting Informatievoorziening Zorg, 2016.
- Ruscitto A, Smith BH, Guthrie B. Changes in opioid and other analgesic use 1995–2010: repeated cross-sectional analysis of dispensed prescribing for a large geographical population in Scotland. *Eur J Pain* 2015; **19**: 59–66.
- National Records of Scotland. Drug-related deaths in Scotland in 2017. July 3, 2018. <https://www.nrscotland.gov.uk/statistics-and-data/statistics/statistics-by-theme/vital-events/deaths/drug-related-deaths-in-scotland/2017> (accessed March 4, 2019).
- Zin CS, Chen LC, Knaggs RD. Changes in trends and pattern of strong opioid prescribing in primary care. *Eur J Pain* 2014; **18**: 1343–51.
- Office for National Statistics. Deaths related to drug poisoning in England and Wales: 2017 registrations. August 6, 2018. <https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsrelatedtodrugpoisoninginenglandandwales/2017registrations> (accessed June 13, 2019).
- Schubert I, Ihle P, Sabatowski R. Increase in opiate prescription in Germany between 2000 and 2010: a study based on insurance data. *Dtsch Arztebl Int* 2013; **110**: 45–51.
- Schepens MHJ, Leusink M, de Vries SE, et al. Toename in extramuraal opioidegebruik in Nederland. *Ned Tijdschr Geneesk* 2019; **163**: pii D3854.
- Veiligheidsmanagementsysteem (VMS). VMS veiligheidsprogramma: vroege herkenning en behandeling van pijn. November, 2009. https://www.vmszorg.nl/wp-content/uploads/2017/11/web_2009.0109_praktijkguids_pijn.pdf (accessed Jan 28, 2019).
- Beauchamp GA, Winstanley EL, Ryan SA, Lyons MS. Moving beyond misuse and diversion: the urgent need to consider the role of iatrogenic addiction in the current opioid epidemic. *Am J Public Health* 2014; **104**: 2023–29.
- Van Zee A. The promotion and marketing of oxycontin: commercial triumph, public health tragedy. *Am J Public Health* 2009; **99**: 221–27.
- Sauber-Schatz EK, Mack KA, Diekmann ST, Paulozzi LJ. Associations between pain clinic density and distributions of opioid pain relievers, drug-related deaths, hospitalizations, emergency department visits, and neonatal abstinence syndrome in Florida. *Drug Alcohol Depend* 2013; **133**: 161–66.
- Nguyen TD, Bradford WD, Simon KI. Pharmaceutical payments to physicians may increase prescribing for opioids. *Addiction* 2019; **114**: 1051–59.
- Centers for Disease Control and Prevention (CDC). Vital signs: overdoses of prescription opioid pain relievers—United States, 1999–2008. *MMWR Morb Mortal Wkly Rep* 2011; **60**: 1487–92.
- van Rijswijk SM, van Beek MHCT, Schoof GM, Schene AH, Steegers M, Schellekens AF. Iatrogenic opioid use disorder, chronic pain and psychiatric comorbidity: a systematic review. *Gen Hosp Psychiatry* 2019; **59**: 37–50.

- 31 van Laar MW, van Gestel B, Cruts AAN, et al. Nationale Drug Monitor: jaarbericht 2018. Trimbos-instituut/Wetenschappelijk Onderzoek- en Documentatiecentrum, Ministerie van Justitie en Veiligheid. <https://www.trimbos.nl/docs/8081bdca-2ff7-4b5d-98df-a961a3888fa8.pdf> (accessed April 15, 2019).
- 32 Bohnert ASB, Valenstein M, Bair MJ, et al. Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA* 2011; **305**: 1315–21.
- 33 Dhalla IA, Mamdani MM, Sivilotti MLA, Kopp A, Qureshi O, Juurlink DN. Prescribing of opioid analgesics and related mortality before and after the introduction of long-acting oxycodone. *CMAJ* 2009; **181**: 891–96.
- 34 Chenaf C, Kabore JL, Delorme J, et al. Prescription opioid analgesic use in France: trends and impact on morbidity-mortality. *Eur J Pain* 2019; **23**: 124–34.