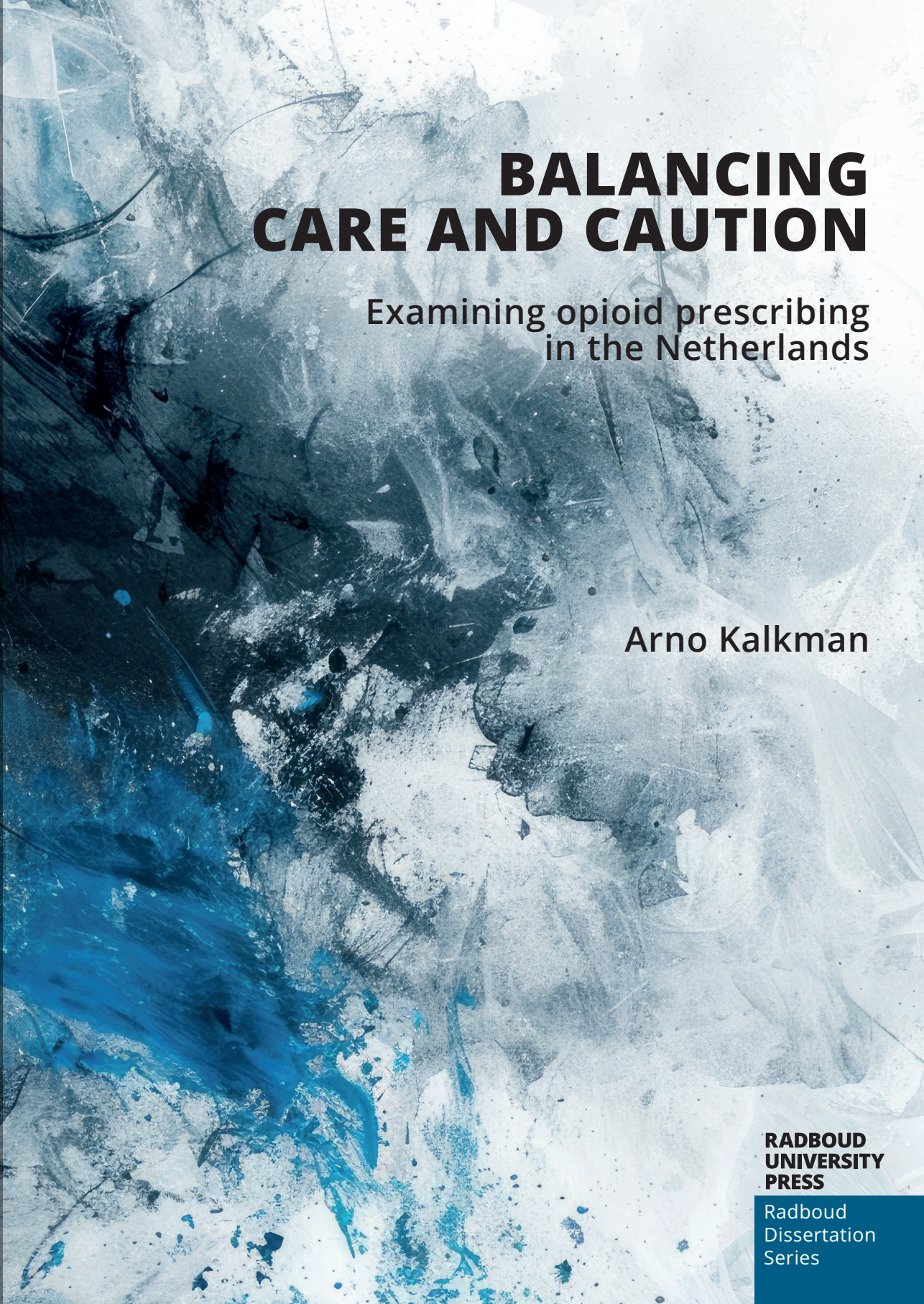

BALANCING CARE AND CAUTION

Examining opioid prescribing in the Netherlands

Arno Kalkman

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Balancing care and caution

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Arno Kalkman

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Examining opioid prescribing in the Netherlands

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door

Gerard Arnoldus Kalkman
geboren op 8 oktober 1988
te Scheemda

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on the authority of the Rector Magnificus prof. dr. J.M. Sanders,
according to the decision of the Doctorate Board
to be defended in public on

Wednesday, October 9, 2024
at 10.30 am

by

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Chapter 1

General introduction

Opioids are a class of analgesics that have long been used in medical practice for managing moderate to severe pain. They are derived from the opium poppy plant (papaver somniferum) or created by chemical synthesis, and include compounds such as morphine, oxycodone, and fentanyl. In healthcare settings, they are used for pain relief during anaesthesia and after surgery, cancer treatment and palliative care, and various types of acute somatic pain. Although opioids can be highly effective in managing pain, their potential for abuse, dependence, and overdose makes them both a blessing and a curse.[1] Opioids can be classified into two categories: weak and strong opioids. Weak opioids, such as codeine and tramadol, have a lower potency and are used for mild pain. Strong opioids have a higher potency and a potential for stronger analgesic effects. They are used for severe pain and include morphine, fentanyl, and oxycodone. For acute pain, such as post-surgical pain or pain from traumatic injury, opioids are often prescribed for short-term use, until the pain subsides. This short-term use limits the potential for abuse. In cancer-related pain, especially in advanced stages, they are prescribed more liberally as the pain is often severe, and there is a limited risk for dependence during a life-limiting disease. Opioids are also a key component of palliative care for terminally ill patients, where they are unparalleled in providing comfort in the last stages of life. Their use is well-defined and accepted for these types of pain, as their benefits generally outweigh their risks. However, for chronic pain unrelated to cancer (e.g., lower back pain or arthritis pain), their place is less clear and controversial. Evidence for their long-term effectiveness in this type of pain is lacking, and their harmful effects are more likely to outweigh the potential benefits.[2]

Rising prescription opioid use in the Netherlands: a growing concern

Prescription opioid use in the Netherlands has increased strongly between 2008 and 2015, mainly caused by an increase in oxycodone use. Of all strong opioids used in 2015, oxycodone had the most users with approximately 350.000 users in the Netherlands.[3] This was double the number of users compared to 2012. This growth appears to be exponential, as there were only 100.000 users in 2008. Other commonly used opioids were fentanyl, morphine, and buprenorphine. In 2015, fentanyl had over 110.000 users and morphine nearly 100.000. This amounts to over half a million opioid users in the Netherlands in 2015.[3]

Several signals indicate that this increase could be a worrisome trend and a potential public health problem. For example, news reports in national media have linked

prescription opioid use to addiction and overdose. As seen in Figure 1, examples can be found in the Volkskrant[4], Algemeen Dagblad[5], and Metro[6]. These news reports highlight the rapid increase in oxycodone use in the Netherlands, stress their addictive potential, and express concerns that this could escalate into a public health crisis. These concerns are not without merit, as the escalating use of opioids in the Netherlands, coupled with reports of addiction and overdose, bears an striking resemblance to the early stages of a health crisis that has already had devastating consequences: the "opioid epidemic" in the United States. This epidemic started with a rapid rise in prescription opioid use, similar to what is currently observed in the Netherlands, and led to extremely high mortality rates and a strained health care system. A brief overview of the timeline of the US opioid epidemic offers insight into the potential trajectory of the Dutch situation when opioid usage keeps growing unchecked.

Figure 1. News reports from Dutch media mention increased prescription opioid use and its negative effects

The timeline of the US opioid epidemic

The evolution of the opioid epidemic in the United States can be divided into three waves, each characterised by mortality from different types of opioids. The first wave started around 2000 and was characterised by high addiction and overdose rates from prescription opioids, particularly oxycodone, driven by increased prescribing.[7] Pharmaceutical companies sought to expand the opioid market by promoting their use for a range of pain conditions, including chronic non-cancer pain. Marketing campaigns emphasised the benefits of opioids while downplaying the risks, falsely

claiming that addiction was rare when used for pain management.[8] Consequently, opioid prescribing increased significantly, which was initially perceived as an improvement in pain care.

As addiction and mortality rates from prescription opioids rose, policies were implemented to curb opioid prescribing. This led many addicted individuals to seek alternative options, creating an opportunity for illicit drug dealers to supply opioids such as heroin, marking the beginning of the second wave in 2007.[7] Research indicates that most people who began using heroin between had previously abused prescription opioids.[9]

The third wave emerged in 2015 with increased overdoses from synthetically manufactured opioids, mainly illicitly manufactured fentanyl (IMF). Fentanyl offered several advantages over heroin, including lower production costs, the need to smuggle smaller quantities due to its much higher potency, and a more stable supply chain. Drug suppliers began mixing heroin with fentanyl to increase profit and compensate for insufficient heroin supply.[10] However, due to its high potency, even small quantities of IMF can lead to overdoses, which makes dosing more dangerous and increases the risks for users. Opioid mortality in the US is still increasing, with more than 70.000 people dying from an opioid overdose in 2020.[8]

Assessing the causes and consequences of increasing prescription opioid use in the Netherlands

The rise in prescription opioid use in the Netherlands, combined with signals of addiction and overdose, set against the backdrop of the US opioid epidemic, can be seen as a potential public health problem and requires further investigation. However, in the Netherlands, the exact situation, remains uncertain. We must address several gaps in our understanding of this issue to guide future policies and interventions. According to Wight et al.[11], the process of designing effective public health interventions can be described in six steps: 1) defining and understanding the problem and its causes, 2) identifying modifiable causal or contextual factors, 3) deciding on the mechanisms of change, 4) clarifying how these will be delivered, 5) testing and adapting the intervention, and 6) collecting sufficient evidence of effectiveness to proceed to a rigorous evaluation. For example, it is unclear whether the rise results in a growing problem of misuse, addiction, and overdose. Therefore, potential interventions could span a broad spectrum, such as refining prescribing practices, early recognition and treatment of patients with an iatrogenic opioid

addiction, or determining that no intervention is needed. Therefore, a thorough understanding of the situation is essential to decide what type of intervention, if any, is required.

When viewed in this context, the first step in addressing a potential Dutch opioid epidemic would be a comprehensive analysis of trends in prescription opioid use and related harm. A comprehensive view on the opioid situation and evaluation of drivers both at the level of prescribers and consumers could direct measures to prevent an opioid epidemic as observed in the US.

Some data on prescription opioid use trends were available, but a thorough investigation which includes possible consequences such as misuse, addiction, and mortality in the Netherlands was lacking when we set out this project. Such an analysis is crucial for determining the severity and extent of the potential problem. Second, although existing literature discusses a rise in opioid use in Europe (including the Netherlands) and compares this with the United States, knowledge of the factors driving this increase in Europe is lacking. The focus tends to be on evaluating the vulnerability of Europe to an opioid epidemic rather than the forces that have led to increased opioid use or could prevent or mitigate an opioid epidemic. Consequently, there is a lack of understanding of why opioid use has increased in countries other than the United States.

When monitoring various aspects of opioid use and misuse, it is crucial to have comparable data and adequate definitions that can be consistently applied across countries. Consistent classification and quantification of opioids and different usage patterns is needed. This not only aids in understanding the scope of the problem but also enables meaningful comparisons between different regions or countries.

In the Netherlands, general practitioners prescribe most opioids. There is a need to gain more insight into the quality of opioid prescribing in primary care and whether this is appropriate. More specifically, we need to investigate there is practice variation with respect to chronic high dose prescribing. If this appears to be the case, this can provide target points for improvement.

Finally, it is important to identify patients susceptible to chronic opioid use. Existing literature shows a strong link between psychiatric disorders and illicit opioid use. In addition, pain and psychiatric disorders often occur together and can negatively influence each other. Therefore, patients with psychiatric disorders might be especially at risk of developing chronic opioid use, but longitudinal data investigating psychiatric

disorders as risk factors for chronic opioid use are lacking. In the context of the six steps in effective intervention development, this thesis covers the first two steps: defining and understanding the problem and its causes, and identifying causal or contextual factors.

Aims and outlines

Chapter 1 is the general introduction.

Chapter 2 presents an overview of trends in the use and misuse of prescription opioids in the Netherlands between 2008 and 2017. Data from several nationwide databases are used to evaluate trends in the number of people having opioid prescriptions, the number of opioid-related hospital admissions, the number of people treated for opioid use disorder, and opioid-related mortality.

The viewpoint in **Chapter 3** emphasises the need for shared definitions and measurements of opioid use and related harms in Europe. It discusses the importance of understanding the drivers of the increased prescription opioid use in Europe and its associated problems and proposes strategies to move forward.

Chapter 4 investigates the quality of opioid prescribing for non-cancer pain in Dutch primary care by examining variation in prescribing between general practices. The aim is to identify target points for quality improvement and reduce inappropriate care and unwarranted variation.

Chapter 5 prospectively investigates the relationship between psychiatric disorders and the subsequent risk of developing chronic high-dose opioid use in primary care patients newly receiving opioids.

The exchange of letters in **Chapter 6** revolves around the Stanford-Lancet Commission's publication on the North American Opioid Crisis and how their recommendations compare to European practice. The discussion highlights differing opinions on the quality of European healthcare, particularly pain management, and how this relates to preventing an opioid epidemic in Europe.

The general discussion in **Chapter 7** synthesises the findings of this thesis, highlighting key contributing factors, the quality of opioid prescribing, and psychiatric disorders as a risk factor for chronic use. It concludes with recommendations for future research and possible interventions in opioid management.

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Chapter 2

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

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Cornelis Kramers
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Wim van den Brink
Arnt Schellekens

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Abstract

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.

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.

Introduction

Opioids are mostly used as analgesics in the management of moderate to severe pain.[1, 2, 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 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 evaluation[12] 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 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 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).

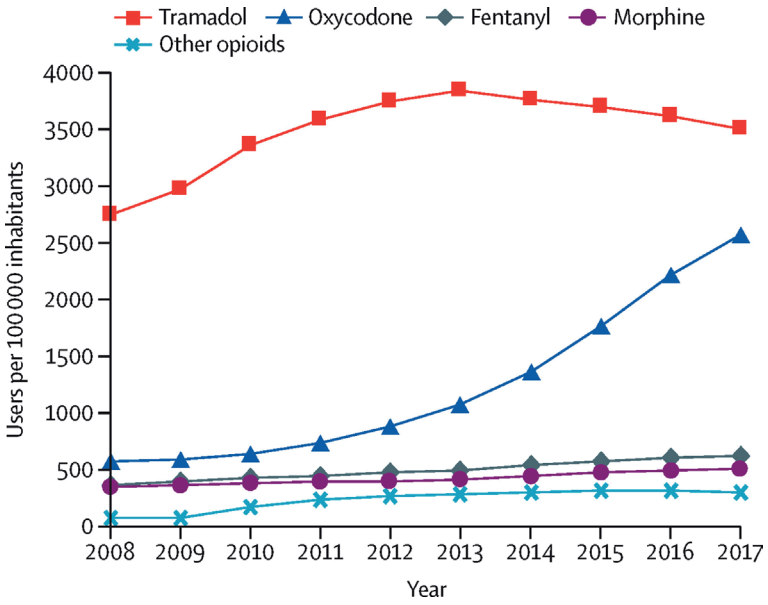

Figure 1. Users of prescription opioids in the Netherlands per 100 000 inhabitants

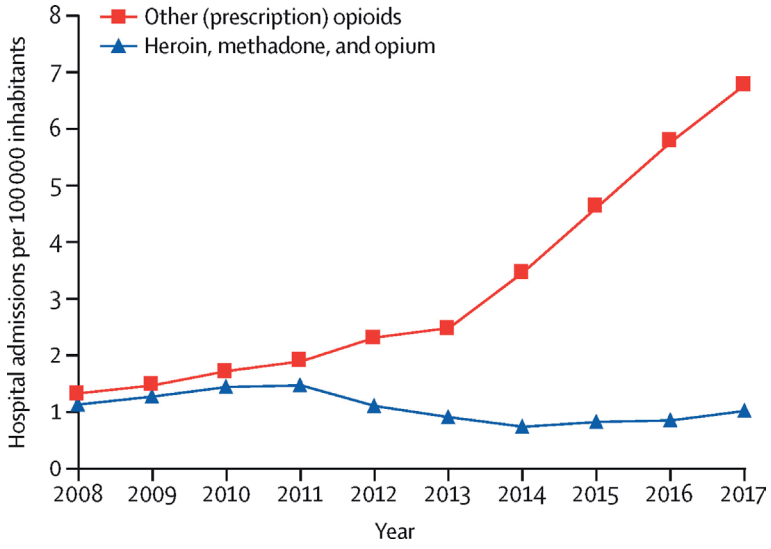

Figure 2. Number of hospital admissions in the Netherlands related to opioid intoxication

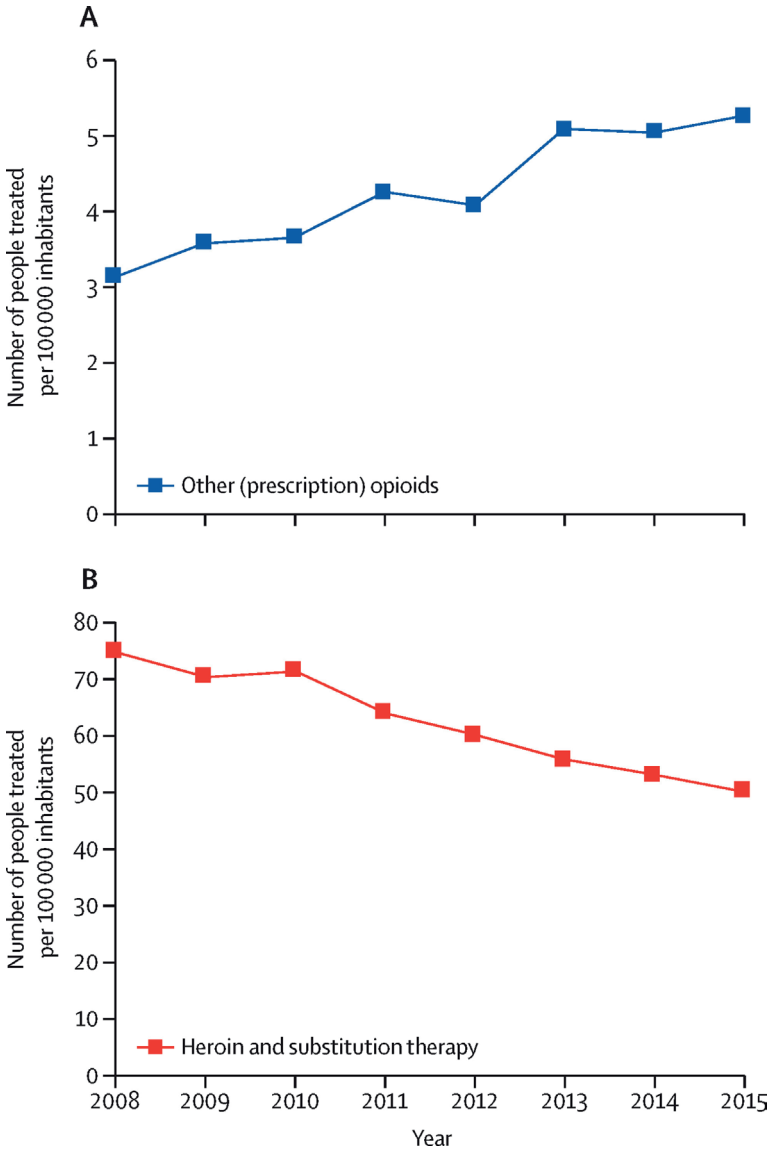

Figure 3. Number of people in the Netherlands in addiction care

(**A**) Patients treated for addiction to (prescription) opioids. (**B**) Patients treated for heroin addiction, and patients receiving opioid substitution therapy such as methadone.

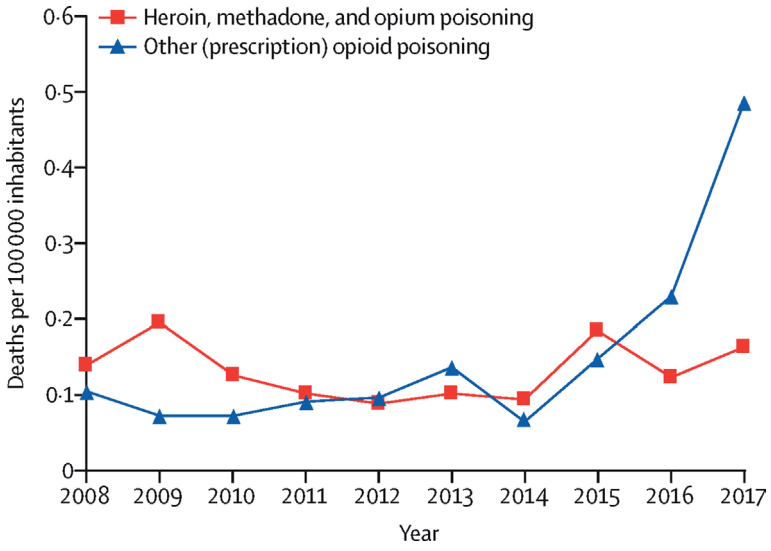

Figure 4. Mortality caused by opioid poisoning in the Netherlands per 100 000 inhabitants

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, 26, 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 (Figure 2, Figure 3, Figure 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, 33, 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.

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Chapter 3

Monitoring Opioids in Europe: The Need for Shared Definitions and Measuring Drivers of Opioid Use and Related Harms

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Abstract

The past 20 years, the USA is facing a serious opioid crisis initiated by an increase in prescription opioid use. Europe has also seen an increase in prescription opioid use, but the extent of related harm is still largely unknown. Given the impact of the US opioid epidemic, it is important to closely monitor signs of emerging opioid-related problems to guarantee early warnings and timely actions. Shared and meaningful definitions for opioid use and related harms, and relevant information about specific drivers for opioid use and related problems are needed for an adequate policy response. In this commentary, we discuss these definitions, the need to know more about the specific drivers for increased opioid use, its related harm, and proposals for strategies to move forward. Policy recommendations include making a distinction between licit and illicit opioids when monitoring and reporting on opioid-related harm, and using oral morphine equivalents to quantify prescription opioid use in a clinically relevant and comparable manner. A major topic of further research is exploring unique and universal drivers of prescription opioid (mis)use across Europe, in particular the role of opioid diversion.

Introduction

For the past 20 years, the USA has been facing a serious opioid crisis. The number of opioid-related deaths increased from 3.0 per 100,000 in 2000 [1] to 14.9 per 100,000 in 2017 and levelled off to 14.6 per 100,000 in 2018 [2]. Between 1999 and 2018, a total of 446,032 deaths involved opioids [2]. The opioid epidemic was initially driven by an increase in medical (prescription) opioid use, as a result of, amongst other things, the inclusion of pain as the fifth vital sign and the incorrect belief that opioid addiction is rare in prescription opioid users [3]. While the opioid crisis in the USA started with increased prescription opioid use and abuse, many prescription opioid users later switched to heroin because of the lower cost and higher availability [4]. This change was subsequently paralleled by an increase in heroin overdose deaths around 2010. Since 2013/14, fentanyl has become the main cause of opioid-related overdose deaths in North America, most likely due to adulteration of heroin with illicitly manufactured fentanyl (IMF) [5].

Europe has also seen a steady increase in prescription opioid use over the past 10 years, mainly due to increased tramadol, fentanyl, and oxycodone prescribing [6]. Several reports have raised concerns about this increase in prescription opioid use and the potentially associated opioid-related harms, including opioid-related deaths [7-9]. However, the level of prescription opioid use [10] and opioid-related deaths in most European countries is still (much) lower than in the USA. For example, opioid-related mortality in the EU was 1.3 per 100,000 population in 2017 (US: 14.9 per 100,000) [11]. Although opioid-related harm appears limited in the EU as a whole, there are some EU (constituent) countries (e.g., Estonia and Scotland) that reported an opioid-related mortality rate similar to the USA [6]. A recent investigation into prescription opioid use and related harms in 19 European countries found that only Scotland was facing an opioid epidemic comparable in severity to the USA, with an opioid-related mortality of 22.7 per 100,000 in 2018 [11]. However, the authors noted that comparison of opioid-related harm (e.g., hospital admissions, treatment demand, and mortality) between countries was limited by differences in definitions. In a recent systematic review published in European Addiction Research, van Amsterdam et al. [12] investigated the drivers for the high opioid-related death rate in Scotland and compared them to England/Wales. Important drivers contributing to the opioid-related mortality in Scotland were: (1) a high number of drug users, (2) steep ageing of drug users, (3) polydrug use (e.g., benzodiazepines and gabapentinoids), and (4) low-treatment coverage for opioid addiction. In addition, they noted that restricting opioid prescribing would be an important step in reducing opioid-related mortality in Scotland.

Given the impact of the opioid epidemic in the USA and Scotland, and the increased use of prescription opioids in Europe, it is important to closely monitor the situation in Europe for signs of emerging opioid-related problems and respond adequately and timely to such signals. To implement a balanced policy response at a national or regional level, the availability of reliable epidemiological data on opioid use and opioid-related harm is key. This commentary elaborates on several issues that should be considered when analysing the current opioid situation in Europe.

Although the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) is regularly reporting about the opioid situation in the EU, these reports suffer from serious limitations due to the inconsistent use of definitions per reporting country and a lack of information on potential drivers per country [13]. In addition, the EMCDDA is mostly concerned with harm related to illegal opioids, whereas data on harm specifically related to prescription opioids is lacking. We argue that improved reporting requires: (1) clear and shared definitions of different patterns of opioid use and opioid-related harm, and (2) better knowledge of the multiple drivers of prescription and illicit opioid use, and related harms in each country or regions within countries (e.g., Scotland vs. England [14]).

Definitions

The use of shared definitions is vital when reporting and comparing results on opioid use and related harms between countries and changes over time. Here, we discuss definition issues for: (1a) types of opioids (prescription vs. illicit opioids), (1b) quantification of opioid doses, (1c) patterns of opioid use (Table 1), and (1d) opioid-related mortality.

Prescription and Illicit Opioids

The distinction between prescription opioids and illicit opioids is often not as clear as one would hope, despite seemingly clear definitions. Prescription opioids are manufactured legally by pharmaceutical companies and are mostly obtained through bona fide medical prescriptions. In contrast, illicit opioids are manufactured and distributed by illicit means and are generally used for non-medical (e.g., recreational use, addiction) purposes. However, prescription opioids can be used legally as prescribed, legally not-as-prescribed (e.g., too frequent, too long, too much, other route of administration), but also diverted to the illegal market and then used illicitly.

A clear distinction between prescription and illicit opioids is not always possible. For example, fentanyl is currently manufactured by both legal and illegal producers, however toxicological screenings cannot distinguish between them, or define the source. Changes in mortality rates based purely on toxicological data can thus

be difficult to interpret. This in turn has consequences for the interpretation of epidemiological data and for (data driven) policy responses.

Table 1. Overview of definitions for different types of opioids, units for quantifying dose, and use patterns relevant for research

Definition	Description
Types of opioids	
Prescription opioid	Opioid manufactured legally by pharmaceutical companies and mostly obtained through legal medical prescriptions.
Illicit opioid	Opioid manufactured and distributed by illicit means and generally used for non-medical (e.g. recreational) purposes.
Dosage	
Defined daily dose (DDD)	"The assumed average maintenance dose per day for a drug used for its main indication in adults", as defined by the World Health Organisation (WHO)
Oral Morphine Equivalent (OME)	The dose of an opioid expressed as the equianalgesic dose of oral morphine.
Use patterns	
Chronic high-dose use	Continuous opioid use for more than 3 months with a dose greater than 90 OME.
Misuse	"Opioid use contrary to the directed or prescribed pattern of use, regardless of the presence or absence of harm or adverse effects", defined by ACTTION.
Abuse	"Intentional use of the opioid for a non-medical purpose, such as euphoria or altering one's state of consciousness", defined by ACTTION.
Addiction	"Pattern of continued use with experience of, or demonstrated potential for, harm", defined by ACTTION. This definition captured a broader group than DSM-5 opioid use disorder and ICD-11 dependence.

Quantification of Opioid Consumption and Dosages

Opioid doses can be quantified in several different ways, most commonly in Defined Daily Doses (DDDs) or oral morphine equivalents (OME) [15-17]. Most national prescription databases report opioid consumption in DDDs, a unit recommended by the World Health Organization for drug consumption studies. DDD is defined as "*the assumed average maintenance dose per day for a drug used for its main indication in adults*" [16]. DDDs are, however, of limited value in quantifying and comparing different opioid doses because they do not fully reflect the relative potency of each individual opioid [15]. This limits the comparison of opioid use between countries where different types of opioids are used.

A more useful unit for comparing opioid doses is OME, which is calculated by converting the opioid dose to an equianalgesic dose of oral morphine. This makes a more clinically relevant comparison of doses for different opioids possible. The choice between DDD and OME can significantly impact study results. For example, in a study by Svendsen et al. [15], opioid use was either higher in Sweden or in Denmark, depending on the use of either DDD or OME as the unit of analysis. A limitation of OME is, however, that the conversion ratios for different opioids are not universally agreed upon and not all are supported by high-quality evidence. In addition, conversion ratios for individual patients can vary depending on, e.g., genetics and tolerance. Fortunately, Nielsen et al. [18] developed a comprehensive list that gives a single OME conversion ratio for the different pharmaceutical formulations and routes of administration of most opioids. This list was based on different international resources and can be used to calculate OME doses in a consistent way.

Patterns of Opioid Use

A lack of clear definitions for the different patterns of (prescription) opioid use and the diagnosis and registration of opioid-related harm results in large variations in outcome estimates in different studies. Epidemiological variation due to different definitions for patterns of (prescription) opioid use and opioid-related harm hinders valid evaluations and adequate (data-based) policy responses. Below we discuss these different definitions for patterns in (prescription) opioid use and opioid-related harm and propose ways to move forward.

Firstly, quantitative trends in opioid use are often examined using healthcare registration data, based on predefined patterns of opioid use. Results from such studies are often difficult to interpret and comparisons with other studies are problematic if the definitions used to classify patterns of opioid use are different. For example, a systematic review by Jivraj et al. [19] on persistent postoperative opioid use found 29 different definitions for persistent opioid use in 39 studies. When these different definitions were applied to a single set of healthcare registration data, estimates for persistent postoperative opioid use in opioid-naive patients undergoing surgery varied more than 100-fold from 0.01% to 14.0% [19]. A review by Karmali et al. [17] also found a high variation in estimates of chronic opioid use, ranging from 1.3% to 25%.

A consensus definition for chronic opioid use and a uniform way to identify patients with chronic opioid use in registration data does not yet exist. However, several recommendations can be made based on the reviews by Jivraj et al. [19] and Karmali et al. [17]. Most importantly, chronic opioid use should be defined as continuous

opioid use over a specific period of time. To identify this in a data set, preferably both the date and duration of prescriptions should be used. Most studies use 3 months as a cut-off value for chronic use, which is in line with clinical guidelines.

In addition to duration, opioid dose and route of administration are important factors to consider. Patients receiving high dosages are at greater risk of opioid-related harms such as addiction, overdose, and motor vehicle injuries [20, 21]. Consensus on the definition of high-dose opioid use is currently lacking. However, the CDC Guideline for Prescribing Opioids for Chronic Pain recommends avoiding opioid dosages over 90 OME. Route of administration is also highly relevant because routes have a different onset of action. Opioids with a fast onset of action (e.g., injections or nasal sprays) have a higher addictive potential [22].

Secondly, studies focussing on problematic prescription opioid use should distinguish between misuse, abuse, and addiction. Definitions for these types of problematic use often differ per study and sometimes overlap [23]. In order to standardize these definitions, Smith et al. [23] formulated mutually exclusive definitions for prescription drug misuse, abuse and addiction based on a literature review and consensus amongst the multidisciplinary Analgesic Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION) working group [23, 24]. They defined misuse as "Opioid use contrary to the directed or prescribed pattern of use, regardless of the presence or absence of harm or adverse effects." This means that misuse includes higher and/or more frequent doses than intended by the prescriber, use of an opioid for pain reduction that was prescribed to another person, or use for a different medical indication than intended by the prescriber (e.g., for insomnia instead of pain). Misuse explicitly excludes non-medical use, which is categorized as either abuse or addiction. Abuse is defined as "Intentional use of the opioid for a non-medical purpose, such as euphoria or altering one's state of consciousness." Thus, abuse includes recreational opioid use, as well as opioid use to alleviate negative affect, independent of harm or adverse effects and is therefore different from the DSM-5 or ICD-11 diagnosis of opioid use disorder or addiction. This category also includes opioid abuse by proxies, which has been an important driver of opioid use in the US [25]. Finally, addiction is defined as a "Pattern of continued use with experience of, or demonstrated potential for, harm" (e.g., "impaired control over drug use, compulsive use, continued use despite harm, and craving"). Campbell et al. [26] empirically compared the ACTTION addiction definition with both ICD-11 dependence and DSM-5 substance use disorder definitions in patients using opioids for chronic non-cancer pain (CNCP). They found that the addiction definition captured a larger group of patients, showing fewer problem behaviours than the ICD-11

and DSM-5 criteria. Patients who only met the addiction criteria (and not ICD-11 or DSM-5 substance use disorder criteria) also had lower rates of psychological distress and substance use histories. Although a broad definition might be useful for epidemiological research and monitoring, it is less suitable for clinical practice since it could label people without problematic opioid use as addicted [26].

In addition to definitions for problematic opioid use, differences in measurement tools and the selection of populations deserve careful consideration. A review from Vowles et al. [24] found a broad range in opioid misuse in chronic pain patients (0.08%–81%), which was largely attributed to differences in study population selection and the measures of misuse that were used. The study with the highest rate was conducted in the USA in a population of chronic pain patients who presented to an emergency department seeking prescription opioid refills. Misuse was identified using a self-report questionnaire [27]. In contrast, the lowest rate was found in a Norwegian study which identified misuse in a nationwide prescription database using a definition based on opioid dose, duration, number of prescribers, and concurrent benzodiazepine use [28].

Thirdly, when investigating prescription opioid use, the medical indication should always be taken into consideration because the often-reported increase in the number of opioid prescriptions is not necessarily problematic. For example, an increase in short-term opioid use could result from improved post-operative pain management since opioids are effective in reducing short-term pain after surgery [29]. Similarly, whilst opioid use for chronic cancer pain or palliative care is effective [30], for CNCP other types of therapies are preferred [21]. Consequently, an increase in prescription opioid use could indicate inadequate non-evidence-based pain management when opioids are used for CNCP, or in contrast improved pain management and care for patients with acute pain or during palliation in terminal care. Hence, the contextual information and strict clinical indications are important to correctly interpret the specific use of an opioid in medical practice. Improvements in pain care can otherwise be falsely interpreted as unwarranted overprescribing.

Opioid Mortality

Between and within country differences in procedures used to establish cause-of-death statistics can significantly influence the number of registered overdose deaths, making opioid-related mortality rates within and between countries difficult to compare [31]. For example, in England, all unexpected deaths are investigated by a coroner, whilst in many other countries, this is less common. Since most drug-related deaths are classified based on toxicological screening, differences in post-

mortem toxicological screening methods and policy can also influence the reported number of drug-related and opioid-related deaths [32]. For instance, in Sweden, the number of fentanyl-related overdose deaths doubled after the introduction of routine toxicological fentanyl screenings [33]. Similarly, a reanalysis of post-mortem blood samples in Germany focussing on prescription opioids, found a 3.4-fold increase in the number of fentanyl-related overdose deaths compared to standard screening procedures [34]. These examples indicate that death rates for rare or difficult to detect compounds are highly dependent on regional procedures and available technology and funding. Consequently, comparing national opioid-related death rates, and interpreting trends over time is only possible when detailed information on country-specific procedures and possible changes in these procedures over time are considered. Although the EMCDDA regularly reports opioid related mortality for the entire EU, the data are still based on the cause-of-death statistics from individual countries.

Drivers

Drivers of Prescription Opioid Use

Increasing trends in prescription opioid use have been described for several European countries, including Germany [35], France [36], the United Kingdom [37], Spain [38], Poland [39], and the Netherlands [40]. Different drivers may have contributed to this increase.

Firstly, an important factor that could contribute to an increase in opioid use is an ageing population with more chronic pain problems and palliative care. Between 2004 and 2016, the proportion of people in the EU older than 80 increased from 3.9% to 5.4% [41] and is likely to increase even further. In addition, physicians might be reluctant to prescribe NSAID painkillers to the elderly due to the fear for severe gastrointestinal, cardiovascular, and renal side effects [42].

Secondly, some prescription opioids, such as oxycodone and fentanyl, are not associated with the same stigma as for instance morphine [43]. Patients often associate morphine with addiction, terminal illness, and imminent death [44]. Patients may not recognize oxycodone and fentanyl as being in the same category as morphine, thus potentially contributing to their acceptance and increasing use. Moreover, many of these newer opioids were introduced as patches, nasal sprays, and lollipops, which might – mistakenly – be perceived as safer than tablets or injections by both patients and prescribing physicians.

Thirdly, marketing of oxycodone is often cited as an important reason for increased oxycodone prescribing, especially in the USA. However, in contrast to the USA, marketing of drugs directly to patients is prohibited in Europe. Still, oxycodone consumption also increased in Europe with 47% between 2004 and 2016 [10]. It is unclear whether and to what extent other types of pharmaceutical marketing, like pharmaceutical support in medical curriculum development, doctor visits by pharma representatives, and congress presentations have been driving this increase in Europe.

Fourthly, increased opioid prescribing may also have been fuelled by increased attention for pain management (pain as fifth vital sign) [45, 46], decreased acceptance of pain by patients, a lack of physician training in and access of non-pharmacological pain management (e.g., physical therapy or psychological support), and shorter or no in-hospital stay after certain surgical procedures. Whilst all these factors appear to be plausible drivers for the increased prescription opioid use in Europe, little research has been done to investigate their relative contributions.

Drivers of Illicit Opioid Use

Although heroin is still the most frequently abused opioid in Europe, there are a growing number of reports on the abuse of other – mainly synthetic – opioids. A notable example is Estonia, where IMF addiction has overtaken heroin addiction [46]. In 2012, 87% of patients entering treatment for drug addiction in Estonia listed fentanyl as their primary drug of abuse [47]. Another example is Southern Bavaria where diversion of fentanyl patches from legal sources caused a temporary increase in fentanyl overdoses between 2005 and 2014.

In the EU, methadone, buprenorphine, fentanyl, codeine, morphine, tramadol, and oxycodone abuse and dependence now account for 22% of all treatment-seeking primary opioid use disorder patients [48]. This suggests that opioid abuse and dependence in some European countries are shifting from heroin towards prescription opioids and illegally produced synthetic opioids. Interestingly, the sources of the fentanyl and the drivers for its illicit use can differ between countries. In Estonia, a decrease in heroin availability was the main driver for increased use of IMF and opioid-related overdose deaths [49]. Compared to heroin, IMF is easier to smuggle, has a lower cost per dose, and has a more reliable supply than heroin [50]. In contrast, in Southern Bavaria, the fentanyl involved in the increased opioid overdose rate was sourced from diverted fentanyl patches [51] and an increase in its prescription use was the main driver for its illicit use.

Diversion and doctor shopping, both considered illegal, may also play an important role as drivers of illicit opioid use. For example, a US study found evidence of drug diversion in more than half of all unintentional prescription drug overdose deaths. Receiving prescriptions from multiple prescribers (doctor shopping) was present in about a fifth of all opioid-related deaths [25]. Obtaining opioid prescriptions from multiple doctors is possible in the USA due to the decentralized healthcare system. The centralized and single-payer system in most EU countries make doctor-shopping more difficult and could limit the emergence of iatrogenic opioid disorders, opioid diversion, and opioid overdose deaths from prescription opioids.

Recommendations and Conclusions

Quantitative trends in prescription opioid use and misuse of illicit opioids in Europe are rather well described and serious concerns have been raised about the possible negative consequences of the increase in opioid prescribing in Europe. However, comparative research into the underlying drivers of opioid use and the related harm in Europe appears to be lacking. Further research is needed for the development of adequate monitoring and adequate policy responses.

Firstly, policy makers aiming to reduce availability of illicit opioids should distinguish between illicitly manufactured opioids and diverted prescription opioids. Both are manufactured by different means and reach the illegal marketplace via different routes. Research into the source of illicit opioids is thus needed for an adequate policy response. Examples of policy responses to prevent prescription opioid diversion are prescription monitoring programs to detect fraud, legislation to regulate prescribers [52], and the introduction of abuse-deterrent formulations such as combinations with naloxone or formulations that are difficult to crush and resist chemical extraction [53]. Actions aiming to reduce the availability of illegally manufactured opioids (e.g., heroine and IMF) are more in the realm of traditional law enforcement. Research on prescription opioid diversion is currently lacking, precluding any policy response.

Secondly, although heroin is still the most used illicit opioid, serious concerns have been raised about potential harms from prescribed opioid use in Europe. In some parts of Europe, the prevalence of heroin addiction is decreasing and addiction to other types of (prescription) opioids is increasing. Policymakers aiming to reduce harm from prescription opioid use could include risk-mitigation strategies for patients who have an increased risk for opioid-related harm, switching chronic

opioid users to safer opioids such as (long-acting) buprenorphine (with or without naloxone), development of opioid-tapering guidelines and expanding treatment for iatrogenic opioid use disorders. In addition, adequate availability and accessibility of treatment for people with opioid use disorder should be provided, with special consideration given to patients with an iatrogenic opioid use disorder. Regions with high illicit opioid use should also implement adequate harm reduction strategies targeting this population (e.g., take-home naloxone kits or supervised self-injection rooms) [11, 12].

Thirdly, comparing data on opioid use and related harms within and across countries requires shared and meaningful definitions, distinguishing between non-problematic prescription opioid use and problematic opioid use. When examining problematic prescription opioid use, researchers should distinguish between misuse, abuse, and addiction/dependence. The latter can either be defined broadly by using the ACTTION addiction definition or narrower and more clinically relevant by using ICD-11 dependence or DSM-5 (moderate/severe) opioid use disorder. When using healthcare registration data to investigate opioid use, careful consideration should be given to the definition of chronic opioid use. The definition should at least identify continuous use over a specific minimum period (e.g., >3 months) and include criteria for a minimum opioid dose (e.g., >90 OME). Opioid dose or consumption should preferably be expressed in OME, a clinically relevant unit that allows comparing doses of different opioids and different routes of administration.

Although we advocate the use of shared definitions, it must be acknowledged that researchers cannot always choose an ideal definition, especially when using data that were collected for a different purpose. For example, exact opioid doses and durations are often difficult to extract from healthcare registration data, which complicate the identification of chronic high-dose opioid use. In such instances, a distinction between the (shared) ideal definition for an outcome, and a practical definition for identifying this outcome should be made and reported explicitly. This optimises comparability of research on different types of data. In addition, limitations of the practical definition should always be discussed, including the direction of potential biases.

Fourthly, the specific procedures for establishing a national death statistic can greatly influence the number of opioid-related deaths that are found. Consequently, researchers interpreting and comparing opioid mortality should consider the methods used to establish the death statistic and discuss the direction of potential consequences.

Fifthly, studies on the drivers of increased opioid prescribing are needed because little is known about this topic, hindering policy responses aimed at reducing unwarranted prescribing of opioid painkillers. Examples of possible policy responses are (1) improving physician knowledge on pain treatment, (2) development of evidence-based prescribing guidelines, and (3) expanding the access to non-pharmacological pain treatments. Finally, sudden discontinuation of opioid treatment should be avoided since withdrawal symptoms may lead patients to seek out illicit opioids to ameliorate these symptoms [54]. Without better knowledge of the specific drivers of prescription opioid use, a targeted policy response is impossible.

Sixthly, comparable to the CDC in the USA, the EMCDDA should expand its monitoring and reporting of opioid-related harm in Europe, and specifically make a distinction between illicit and prescription opioids. Monitoring of prescription opioid-related harm should include rates of misuse/abuse, diversion of legal prescription opioids into the illegal marketplace, treatment demand for iatrogenic opioid addiction, and mortality from prescription opioids.

Finally, we must recognize that there are many indications for which opioids provide unparalleled pain relief. Policy aimed at reducing unwarranted opioid prescribing or related harm should not, as a side effect, get in the way of opioid prescribing for patients with severe cancer pain or acute post-operative pain.

In summary, shared and meaningful definitions for prescription opioid use and related harms are needed to understand the opioid situation in Europe. Knowledge of the country-specific drivers for the increased opioid use and related harms is needed for an adequate policy response. Continuous close monitoring is warranted to guarantee early warnings and take timely actions. Finally, physicians should take a balanced approach to prescribing opioid pain killers, not avoiding them when there is a proper indication, without prescribing them too easily without full awareness of their potential risks.

Conflict of Interest Statement

W.v.d.B. reports personal fees from Angelini, non-financial support from Camurus, personal fees from Takeda, personal fees from Opiant, personal fees from Indivior, non-financial support from D&A Pharmaceuticals, outside the submitted work. A.S. is an Editorial Board Member of European Addiction Research. All other authors have nothing to disclose.

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Author Contributions

G.K., A.S., and W.v.d.B. conceptualized the paper, and drafted and revised the manuscript. M.P., F.A., K.V., H.S., R.v.D., and C.K. provided critical input and discussion for the manuscript.

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Chapter 4

Practice variation in opioid prescribing for non-cancer pain in Dutch primary care: A retrospective database study

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Abstract

Background

Prescription opioid use has increased steadily in many Western countries over the past two decades, most notably in the US, Canada, and most European countries, including the Netherlands. Especially the increasing use of prescription opioids for chronic non-cancer pain has raised concerns. Most opioids in the Netherlands are prescribed in general practices. However, little is known about variation in opioid prescribing between general practices. To better understand this, we investigated practice variation in opioid prescribing for non-cancer pain between Dutch general practices.

Methods

Data from 2017–2019 of approximately 10% of all Dutch general practices was used. Each year included approximately 1000000 patients distributed over approximately 380 practices. The primary outcome was the proportion of patients with chronic (>90 days) high-dose (≥90 oral morphine equivalents) opioid prescriptions. The secondary outcome was the proportion of patients with chronic (<90 oral morphine equivalents) opioid prescriptions. Practice variation was expressed as the ratio of the 95th/5th percentiles and the ratio of mean top 10/bottom 10. Funnel plots were used to identify outliers. Potential factors associated with unwarranted variation were investigated by comparing outliers on practice size, patient neighbourhood socioeconomic status, and urbanicity.

Results

Results were similar across all years. The magnitude of variation for chronic high-dose opioid prescriptions in 2019 was 7.51-fold (95%/5% ratio), and 15.1-fold (top 10/bottom 10 ratio). The percentage of outliers in the funnel plots varied between 13.8% and 21.7%. Practices with high *chronic high-dose opioid prescription proportions* were larger, and had more patients from lower income and densely populated areas.

Conclusions

There might be unwarranted practice variation in chronic high-dose opioid prescriptions in primary care, pointing at possible inappropriate use of opioids. This appears to be related to socioeconomic status, urbanicity, and practice size. Further investigation of the factors driving practice variation can provide target points for quality improvement and reduce inappropriate care and unwarranted variation.

Introduction

Prescription opioid use has increased steadily in the past two decades, most notably in the United States (US), Canada, and many European countries [1] including the Netherlands [2, 3]. In the US, increased opioid prescribing contributed to a sharp increase in opioid-related harm (the so-called "opioid epidemic") [4]. Though in the Netherlands levels of opioid-related harm are not comparable to the US, concerns have been raised about the increased medical use of prescription opioids, mainly oxycodone [2, 3]. In The Netherlands, the percentage of inhabitants being prescribed an opioid nearly doubled from 4.1% in 2008 to 7.5% in 2017 [3], after which it stabalised [5]. This can be attributed to increased prescribing by both general practitioners and medical specialists, however general practitioners prescribe the vast majority of opioids [6]. Most of these opioids are being prescribed for non-cancer pain [7] and evidence for their effectiveness in this type of pain is lacking [8]. In addition, chronic opioid use increases the risk for opioid addiction, overdose, and mortality, especially when high doses are prescribed [9].

Previous research has shown that large variation in opioid prescribing exists between geographical regions in the US [10], general practices in England [11], hospitals in the US [12], and physicians within the same hospital in the US [13]. This variation may be an important signal for the inappropriate use of opioids. When looking at medical practice variation, a distinction should be made between warranted and unwarranted sources [14]. In general, variation attributed to factors related to disease incidence or patient preferences is considered warranted because it affects the need for treatment. In contrast, variation attributed to provider-related factors or unclear clinical standards is considered unwarranted [14]. Large unwarranted variation may indicate over- or underuse of healthcare services and may provide an important signal for suboptimal care [15]. In-depth insight in these patterns within European countries is needed and will provide input for targeted strategies to improve quality of care.

Until now, most research on variation in opioid prescribing has been conducted in the United States and is unlikely to be generalizable to European countries due to differences in health care organisation and opioid situation. For example, a general practitioner is the cornerstone of healthcare in many European countries and functions as a gatekeeper to specialist care [16]. More than 80% of opioids in the Netherlands are prescribed by general practitioners [6]. In contrast, opioid prescribing in the US is more fragmented. Primary care physicians are also the top opioid prescribers in the US, but they only account for a third of all opioids [17]. To our knowledge, the only in-depth studies examining opioid prescribing in primary

care were conducted in the United Kingdom [11, 18]. However, investigating practice variation in opioid prescribing was not the main objective of these studies.

In the present study we therefore investigated practice variation in chronic opioid prescribing for non-cancer pain by general practitioners in the Netherlands. The primary outcome measure was the proportion of patients with chronic high-dose (≥90 oral morphine equivalents [OME]) opioid prescriptions, and the secondary outcome was the proportion of patients with chronic <90 OME opioid prescriptions. Opioid use for a period of 90 days or longer was considered chronic [19]. These outcomes were chosen because they represent different types of opioid prescribing according to the Dutch College of General Practitioners (NHG) guideline for Pain treatment [20]. It states that short term treatment with opioids for non-cancer pain can be initiated when non-opioid treatments provide insufficient relief. Chronic treatment with opioids should only be initiated when patients clearly benefit from opioids and the benefits outweigh the harms. Daily doses above 90 OME should be avoided to limit potential harm. To our knowledge, practice variation in opioid prescribing in this detail, by using outcomes that reflect duration, dose, and indication, has not yet been examined. Furthermore, a novelty of this study is that we aimed to understand the variation by comparing characteristics of high and low prescribing practices.

Methods

Data source

We used pseudonymised electronic health record data from Dutch general practices collected in the Nivel Primary Care Database (Nivel-PCD) for the calendar years 2017 to 2019. Nivel-PCD collects longitudinal data on patient characteristics, drug prescriptions, and disease episodes from approximately 10% of all general practices in the Netherlands [21]. Data belonging to the same patient within a general practice can be uniquely identified. Participating general practices were geographically spread across the Netherlands and their patients were representative for the entire Dutch population [22]. Prescriptions were coded according to the Anatomical Therapeutic Chemical [23] (ATC) classification system and information on the specific drug formulation, start date and dose is available. Disease episodes were coded according to the International Classification of Primary Care version 1 (ICPC-1) [24].

The use of personal data for research purposes in the Netherlands is regulated under the Dutch Medical Treatment Contracts Act (WGBO). The WGBO stipulates that explicit consent is not required if a) requesting consent is not reasonably possible

(if for example the patient is deceased) or- if b) the request for permission cannot reasonably be expected from the caregiver. The latter can refer to situations in which too great effort an effort is needed from health care providers, or when asking for permission would lead to a selective response. However, data collection should take place taking into account all possible organizational and technical measures needed. In addition, the Medical Research Involving Human Subjects Act (WMO), stipulates that approval by one of the national medical ethical committees is required only if the research involves humans subjected to actions or if rules of behavior are imposed on them. This is not the case in our study. General practices that participate in Nivel-PCD are contractually obliged to: (i) inform their patients about their participation in Nivel-PCD and (ii) to inform patients about the option to opt-out for inclusion of their data in the database. Data were pseudonymized before leaving the health care organization's premises and did not comprise any directly identifying personal information such as names, addresses and citizen service number [23]. Neither obtaining informed consent from patients nor approval by a medical ethics committee is obligatory for observational studies containing no directly identifiable data (Dutch Civil Law, Article 7: 458). The study was approved according to the governance code of Nivel-PCD under number: NZR-00319.034, and all legally required technical and organizational measures were applied to avoid real life identification of subjects.

Population

For each year, all general practices were included for which high-quality data was available. The quality criteria were: 1) data covering a period of at least 46 weeks, 2) at least 85% of prescriptions had a valid ATC code, 3) at least 75% of contacts had a valid ICPC code, 4) at least 500 patients were registered, and 5) at least 80% of a practice's patients were registered with that practice for the entire year. These criteria exclude general practices with poor or incomplete data registration.

From these practices, all patients were included who 1) were at least 20 years old, 2) were registered with their practice for the entire year, and 3) did not have a cancer diagnosis (e.g., not having a cancer diagnosis that was active in the year of analysis). Flowcharts describing the number of patients included and excluded are presented in S1 Fig.

Definitions and variables

Opioid prescriptions were identified using ATC codes N02A (Opioids) and N07BC (Drugs used in opioid dependence). Codeine was excluded, since it is predominantly used for cough. OME's were calculated based on the type of opioid, the amount

prescribed, and the route of administration. The OME conversion ratio's from Nielsen et al. [25] were used when possible.

The primary outcome was the proportion of patients of the total general practice population receiving a long-term high-dose opioid prescription, which was defined as opioid prescriptions covering a period of at least 90 consecutive days with an average daily dose of 90 mg OME or greater. The secondary outcome was the proportion of patients within general practices with chronic opioid use in general (without focussing on high douse use), which defined as opioid prescriptions covering a period of at least 90 consecutive days with an average daily dose of <90 OME. Patients with opioid prescription patterns that met both the definition for chronic and chronic high-dose in a single year were only classified as chronic high-dose. Details on the method for identifying patients with chronic (high-dose) opioid prescriptions can be found in S1 Text.

Age was calculated at the first of January of a year and was provided in 5-year age groups. The number of chronic diseases was defined as the number of registered patient diagnoses that were present in a predefined list of chronic diseases [26].

Statistical analysis

All analyses were performed separately for each year to assess robustness of the analyses over separate years.

Descriptive statistics

Basic descriptive statistics for patients and practices are shown separately for all years: total number of patients and practices, number of patients per practice (mean, minimum, and maximum), number of observed outcomes, age and sex distribution, and mean number of chronic diseases per patient.

Practice variation analyses

Proportions of patients with chronic use and chronic high-dose use within general practices were indirectly standardized for patient age, sex, and number of chronic diseases. To do this, observed (unadjusted) proportions were calculated for each practice separately. Subsequently, a logistic regression model was performed to predict each patient's probability of experiencing an outcome (chronic use and chronic high-dose) based on the adjustment factors and to calculate the expected proportions of chronic use and chronic high-dose use per practice. The logistic regression was performed separately for both outcomes (chronic use and chronic high-dose use). The indirectly standardized proportion was obtained by calculating

the observed/expected ratio per practice and multiplying this ratio by the overall proportion. To avoid standardized proportions of zero, only practices with at least one patient with the outcome were included. Practices without any patients with the outcome were therefore reported separately.

Magnitude of variation

For each outcome (adjusted and unadjusted), a 95%/5% percentile ratio was calculated per year to quantify the amount of variation between practices. Similarly, a mean top 10/bottom 10 ratio was calculated.

Funnel plots were constructed to graphically represent practice variation on the outcome measures. The observed-expected ratios per practice were plotted against the expected number of patients with the outcome, and control limits (95% and 99.8%) were drawn around the target value (O/E = 1) [27]. Practices outside of the control limits are considered outliers. To account for uncontrolled variation control limits were adjusted for overdispersion by the method of Spiegelharter, which is a default functionality of the FunnelplotR package in R. [27, 28].

Understanding variation

To interpret the variation, general practices that were outliers in the funnel plot (both above and below control limits) or had no outcome (i.e. had extreme values) for chronic high-dose opioid prescriptions in 2019 were compared with respect to practice size, patient socioeconomic status (SES), and urbanicity. These factors were chosen because they are known to be related to opioid prescribing [11] and were present in our dataset. Urbanicity (in house addresses per km2) and SES (in percentage of people with a high or low income within a zip code area) were based on the first 4 digits of a patient's zip code and were retrieved from Statistics Netherlands (CBS). Data from 2017 was used, as this was the most recent dataset containing SES information. Per group (no outcome, low, and high outliers), mean practice size, mean adjusted proportions of chronic use, mean high-/low-income percentages, and mean urbanicity were reported.

All statistical analyses were done using R version 4.0.1. [29]. The package FunnelPlotR was used to construct the funnelplots, which includes a command to adjust for overdispersion by the method of Spiegelharter [30].

Results

Descriptive practice and patient characteristics per year are shown in Table 1. Overall, differences between descriptives across years were clinically unimportant. Flowcharts describing the number of patients included and excluded are presented in S1 Fig. An OME value could be calculated for 98.3% of all opioid prescriptions. In 2019 the overall percentages of patients with chronic and chronic high-dose prescriptions were 1.43% and 0.16% respectively.

Table 2 shows the variation (95/5% and mean top 10/bottom 10) for the primary and secondary outcomes. The number of practices without any patients with chronic high-dose (≥90 OME) opioid prescriptions were 27 (7%), 31 (8%), and 34 (9%) in 2017, 2018, and 2019 respectively. There were no practices without chronic <90 OME opioid prescriptions.

In 2019, the adjusted variation for chronic high-dose (≥90 OME) prescriptions was 7.51, meaning there was a 7.51-fold variation in proportions between the 95th percentile general practices and the 5th percentile general practices. This variation was slightly larger in previous years, with a 9.90-fold and 9.93-fold variation in 2017 and 2018 respectively. In 2019, there was a 15.1-fold variation between the highest 10 general practices and the lowest 10 general practices in the proportion of patients with chronic high-dose prescriptions. In 2017 and 2018, there were a 22.6-fold and 20.9-fold variation, respectively.

Funnel plots for both outcomes (chronic high-dose (≥90 OME) and chronic <90 OME opioid prescriptions) are shown in Fig 1 for the year 2019. Figs for 2018 and 2017 were comparable and can be found in S2 Fig. Overdispersion was present and corrected for in all years and outcomes, except for chronic high-dose (≥90 OME) prescriptions in 2019. The percentage of outliers was similar across all years and outcomes, varying between 13.8% and 21.7% (Table 3), with most outlying practices being low prescribers.

Table 4 shows a comparison of outlying practices with respect to the proportion of patients with chronic high-dose opioid prescriptions. Overall, practices with a high proportion of patients with *chronic high-dose opioid prescriptions* were the larger general practices, had more patients with a lower SES, and from higher urbanicity areas. In addition, these practices also prescribed more chronic <90 OME opioid therapy, compared to practices with a low proportion of chronic high-dose prescriptions.

Table 1. Basic patient and practice characteristics per year

	2017	**2018**	**2019**
Patients (n)	1 052 288	1 097 670	1 024 466
Practices (n)	378	388	361
Patients included per practice			
Mean	2 784	2 829	2 838
Min - max	855 - 12 143	943 - 12 177	1 093 - 12 262
Opioid prescriptions			
Chronic <90 OME	17 199 (1.63%)	17 731 (1.62%)	14 614 (1.43%)
Chronic high-dose (≥90 OME)	1 816 (0.17%)	1 830 (0.17%)	1 599 (0.16%)
Male (%)	516 812 (49.1%)	539 766 (49.2%)	504 890 (49.3%)
Age			
20 – 39	326 132 (31.0%)	339 340 (30.9%)	313 217 (30.6%)
40 – 59	397 393 (37.8%)	410 033 (37.4%)	376 860 (36.8%)
60 – 79	274 619 (26.1%)	291 456 (26.6%)	278 962 (27.2%)
80+	54 144 (5.2%)	56 841 (5.2%)	55 427 (5.4%)
Number of chronic diseases			
0	495 674 (47.1%)	589 126 (53.7%)	417 577 (40.8%)
1	231 347 (22.0%)	208 323 (19.0%)	248 217 (24.2%)
2	132 661 (12.6%)	121 042 (11.0%)	144 812 (14.1%)
3	78 908 (7.50%)	72 522 (6.6%)	86 285 (8.4%)
≥4	113 698 (10.8%)	106 657 (9.7%)	127 575 (12.5%)

OME= Oral morphine equivalent

Table 2. Variation scores for chronic high-dose (≥90 OME) use and chronic <90 OME prescriptions across years. The proportions on which the ratios are based is shown in brackets

	95%/5% ratio[b]			mean top 10/mean bottom 10 ratio[c]		
	2017	**2018**	**2019**	**2017**	**2018**	**2019**
Chronic <90 OME						
Unadjusted	3.9 (=2.78% / 0.72%)	4.1 (=2.88% / 0.71%)	3.9 (=2.42% / 0.63%)	9.4 (=3.64% / 0.39%)	9.9 (=3.70% / 0.37%)	9.4 (=3.41% / 0.36%)
Adjusted[a]	4.4 (=3.06% / 0.69%)	4.4 (=3.22% / 0.74%)	4.2 (=2.61% / 0.62%)	11.5 (=4.90% / 0.43%)	9.8 (=4.74% / 0.49%)	9.4 (=3.75% / 0.40%)
Chronic high-dose (≥90 OME)						
Unadjusted	9.0 (=0.42% / 0.05%)	8.4 (=0.39% / 0.05%)	6.9 (=0.34% / 0.05%)	17.1 (=0.52% / 0.03%)	19.2 (=0.53% / 0.03%)	14.8 (=0.53% / 0.04%)
Adjusted[a]	9.9 (=0.44% / 0.05%)	9.9 (=0.44% / 0.04%)	7.5 (=0.35% / 0.05%)	22.6 (=0.67% / 0.03%)	20.9 (=0.57% / 0.03%)	15.1 (=0.52% / 0.04%)

The proportions on which the ratios are based is shown in brackets.

[a] Adjusted for ages, sex, cancer, and number of chronic diseases

[b] 95%/5% ratio was calculated by dividing the proportion of the 95th percentile general practice by the proportion of the 5th percentile general practice

[c] mean top 10/mean bottom 10 ratio was calculated by dividing the mean proportion of the top 10 general practices by the mean proportion of bottom 10 general practices

Table 3. Number of outliers in the funnel plots for all years and outcomes

	2017	2018	2019
Outliers outside 95% overdispersed limits			
Chronic <90 OME	74 (19.6%)	77 (19.8%)	71 (19.7%)
Chronic high-dose (≥ 90 OME)	63 (17.9%)	61 (17.1%)	45 (13.8%)
Outliers above 95% overdispersed limits			
Chronic <90 OME	22 (5.8%)	28 (7.2%)	24 (6.7%)
Chronic high-dose (≥ 90 OME)	13 (3.7%)	6 (1.7%)	14 (4.3%)
Outliers below 95% overdispersed limits			
Chronic <90 OME	52 (13.8%)	49 (12.6%)	47 (13.0%)
Chronic high-dose (≥ 90 OME)	50 (14.2%)	55 (15.4%)	31 (9.5%)

Table 4. Comparison of outlying practices in 2019

	No patients with chronic high-dose (≥90 OME) prescriptions	**Low outliers (below 95% control limits)**	**High outliers (above 95% control limits)**
Practice			
N	34	31	14
Median practice size (IQR)	3 016 (2 348 - 3 108)	4 684 (2 790 - 6 290)	5 760 (2 696 - 7 675)
Median proportion of chronic <90 OME prescriptions (IQR)	1.05% (0.68% – 1.29%)	0.95% (0.70% – 1.08%)	2.22% (1.91% – 2.60%)
Median proportion of chronic ≥ 90 OME prescriptions (IQR)	-	0.046% (0.042% - 0.051%)	0.46% (0.37% - 0.51%)
Patient			
Median percentage low income (IQR)	34% (29% - 38%)	32% (26% - 36%)	44% (35% - 55%)
Median percentage high income (IQR)	24% (19% - 28%)	26% (20% - 34%)	15% (9% - 20%)
Median urbanicity in addresses / km^2 (IQR)	1 242 (361 - 1 461)	1 334 (720 - 1 621)	1 688 (981 - 1 971)

Practices with a high proportion of patients with high-dose opioid prescriptions versus practices with a low proportion of patients with high-dose opioid prescriptions. Practices were grouped into three categories: practices without any chronic high-dose prescriptions, and low and high outliers on the funnel plot.

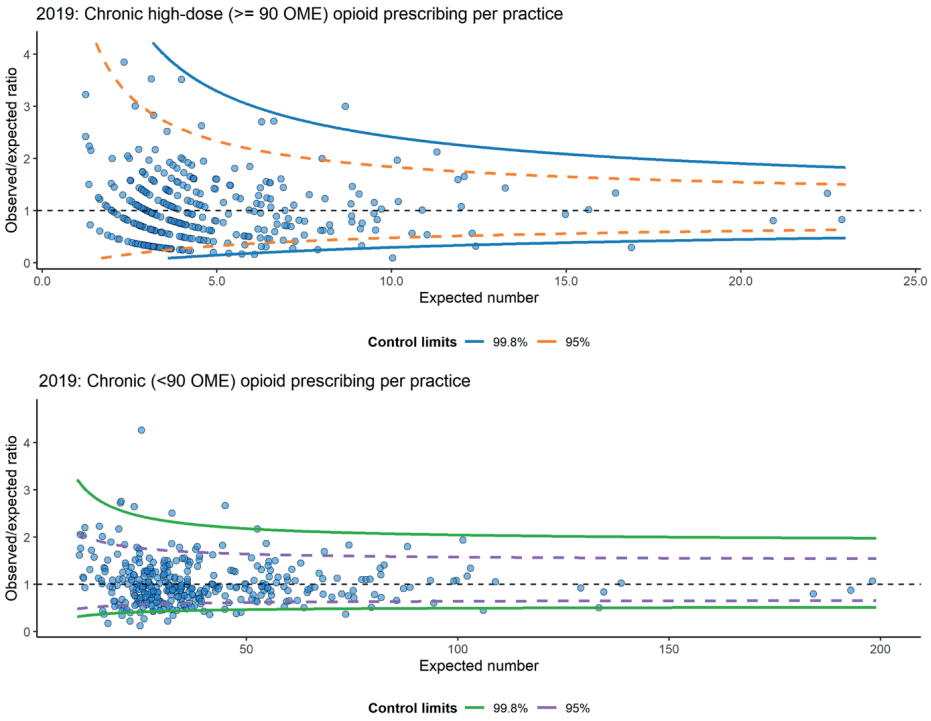

Figure 1. Funnel plots for both outcomes for 2019

Control limits for the outcome chronic < 90 OME were corrected for overdispersion. The horizontal black dotted line (O/E = 1) represents the target value where the observed proportion equals the expected proportion based on case-mix. Each dot represents a single practice. Variation between practices that lie between the 95% control limits is considered to be caused by random variation. Practices above or below the 95% control limits are considered outliers and were categorised as either high or low prescribers, respectively.

Discussion

In this study we explored practice variation in the proportion of patients within a general practices with opioid prescriptions for chronic non-cancer pain in Dutch primary care. In 2019 there was a 7.51-fold (95%/5%) practice variation in adjusted proportions of patients with chronic high-dose (≥90 OME) opioid prescriptions. For chronic <90 OME prescriptions, the adjusted variation was 4.19-fold. This finding is further supported by the larger than expected number of outliers (13.8% of practices in 2019). For 2017 and 2018 results were comparable, showing that the variation is consistent across the years. Moreover, the variation could not be attributed to sources of warranted variation (age, sex, and number of chronic diseases).

According to a recent systematic review by Sutherland et al., unwarranted variation can be explained using three domains: agency, evidence, and capacity [31]. Variation explained by medically irrelevant patient characteristics is seen as unwarranted from an agency perspective. For example, SES might influence the choice of pain therapy. Many non-pharmacological pain therapies (e.g. physical therapy) are not always covered by the Dutch mandatory basic health insurance and often require additional insurance. Opioids are always covered and might therefore be preferred by patients with a lower SES. Our data suggests this might be the case, as practices with a high proportion of chronic high-dose opioid prescriptions had more patients from low-income areas. Our results are in line with research by Curtis *et al.*, who found wide variation in opioid prescribing in England, which was related to practice size, rurality, and poverty [11]. Research has also shown that lower SES is associated with increased prevalence of pain [32] and ineffective coping styles [33] which could drive demand for opioids in this population. Although this might partly explain the variation, it should be questioned if this justifies increased opioid prescribing in this population.

Unwarranted variation may also emerge when clinical practice is not supported by the evidence. For example, differences in the interpretation of the NHG guideline for Pain management could result in important differences between practices. The guideline states that acute non-cancer pain can be treated with opioids when other treatments provide insufficient relief and daily functioning is severely inhibited. Chronic pain management with opioids for non-cancer pain should only be initiated when patients clearly benefit from opioids and the benefits outweigh the (potential) harms [20]. However, the guideline is unclear on what insufficient relief means, how to (objectively) measure this, and what to consider when weighing the harms and benefits. Different general practitioners might value the effectiveness of opioid

therapy differently and have different views on their benefits and risks. Research by Desveaux et al. showed that opioid prescribing by family physicians in Ontario, Canada was highly influenced by their personal beliefs on opioids and on their own capability to safely prescribe them. The subjective nature of opioid prescribing is further supported by Martens *et al*. [34] who found that Dutch physicians in long-term geriatric care based their choices for opioid therapy almost exclusively on personal experience, rather than guidelines or scientific evidence.

An important goal of practice variation research is to define target points to improve quality of care by decreasing unwarranted variation and by increasing appropriateness of care. First signalling and then explaining practice variation are the first steps towards achieving this goal [14]. However, explaining variation in healthcare utilisation and separating warranted from unwarranted variation remains challenging. Especially for chronic opioid prescribing, which requires balancing the benefits of therapy with the potential risks in collaboration with the patient [20]. In our study we corrected for several factors associated with warranted variation, and we compared outlying practices in an attempt to further grasp the variation we found. Even after correction the amount of variation remained similar, which suggests a high amount unwarranted variation. However, our data do not capture the many nuanced considerations that a physician might have when prescribing opioids. Future research is needed to further explain and understand the variation in opioid prescribing we found. Research using qualitative methods (e.g. in depth interviews and focus groups) that focusses on high and low opioid prescribers and their patients could reveal important additional information on how interpret the observed practice variation and to improve quality of care in patients with chronic pain. Different interpretation of guidelines, local policies, knowledge on pain therapy, beliefs on opioid therapy from both physicians and patients, the influence of SES, and views on non-opioid and non-pharmacological therapies should be investigated in more depth. In addition, future research should consider the quality of pain management in relation to opioid prescribing. A better understanding of the quality of pain management in high, average, and low prescribing practices would give insight into how much reduction in opioid prescribing is achievable without compromising quality of pain management. Especially the practices that prescribe no chronic high-dose opioids are interesting in this regard. However, optimising pain management should be the goal, not merely reducing the number of opioid prescriptions.

This study has strengths and limitations. Major strengths of this study are the use of a large, detailed dataset and the use of relevant outcome measures. The high level of detail in our dataset allowed us to use endpoints that distinguish between

higher (≥90 OME) and lower (<90 OME) daily opioid doses. This substantially adds to the clinical relevance of our findings because higher daily doses are associated with higher risks (e.g. addiction and overdose) and are treated differently in (inter) national guidelines [9, 20]. This study also has several limitations. First, our data only contains prescriptions by general practitioners. Prescriptions originating from other sources (e.g., hospitals) are not included in our dataset. However, research has shown that most of the opioids in the Netherlands are prescribed by general practitioners, so the underestimation of opioid use is likely to be small [6]. Second, we measured chronic opioid prescribing within calendar years. This means that chronic opioid use that starts during the last 3 months of a year could not be identified. Since this approach was used within all practices and years, biased results about variation are unlikely. However, outcome proportions may be somewhat underestimated. Third, our data only uniquely identifies patients within a practice. Switching of patients between practices cannot be detected. Patients visiting multiple doctors at the same time (doctor shopping) is highly unlikely to occur, because in the Netherlands a patient can only be registered with one general practice which provides routine care and acts a gatekeeper to secondary care. It is therefore unlikely that our results were biased by this. Fourth, the number of included patients dropped slightly in 2019, compared to previous years. This can be explained by a smaller number of practices that participated in the Nivel PCD. Data quality of the participating practices was, to our knowledge, not negatively affected, as our inclusion criteria also include data quality criteria. Fifth, we excluded cancer patients based on a cancer diagnosis. However, coded registration of cancer diagnosis in Dutch general practices is known to be poor [35], possibly resulting in the inclusion of some patients with cancer in our study. This could potentially reduce the amount of variation in our study because we expect there is less variation in opioid prescribing for cancer related pain than for non-cancer pain. Finally, our analysis includes opioids from ATC group N07BC (drugs used in opioid dependence) as these drugs are often used for pain, especially in general practice. We have conducted a sensitivity analysis whereby we excluded this ATC group. The results are presented in S2 Text. The main analysis (magnitude of variation and funnel plots) remains identical. Our exploratory analysis comparing the outliers shows a difference in the results for urbanicity. The sensitivity analysis showed higher urbanicity for practices with low or no chronic high-dose opioid prescribing, compared to the original analysis. Research using qualitative methods might provide more insight in the role of urbanicity in opioid prescribing.

In conclusion, this is the first Dutch study investigating practice variation in several key measures of opioid prescribing, revealing large unwarranted variation. This may point at suboptimal care and inappropriate opioid prescribing practices.

Further research should focus more in depth on the differences between high and low prescribing practices to further explain this variation, with special consideration given to the comparison of quality of pain management in low opioid prescribing practices versus high prescribing practices. Themes to investigate could be general practitioner's beliefs on opioid prescribing and pain management, interpretation of clinical standards, the influence of physician workload, and the role of patient preferences. Ultimately, increasing knowledge about causes of unwarranted variation may provide target points for improvement of quality of care and tackling inappropriate opioid use in patients with chronic pain.

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Supplements

S1. Text. Identification of chronic (high-dose) opioid use

Opioid prescriptions were identified using ATC codes N02A (Opioids) and N07BC (Drugs used in opioid dependence). Prescriptions for the same drug were considered repeat prescriptions when their active compound, formulation (eg. tablet, patch, capsule etc.) and strength were the same, and the prescription start dates were less than 90 days apart. The end date of a (repeat) prescription was defined as the start date of the next repeat prescription. The duration of the last prescription in a series of repeat prescriptions was calculated as the average duration of the previous prescriptions in the series. For non-repeat prescriptions, the duration was fixed at 14 days, which is the standard duration of a first prescription in the Netherlands. A similar method was previously used on the same database by Weesie et al.[26] For each prescription an average daily dose was calculated by dividing the amount prescribed (e.g. number of pills) by the prescription duration and converting this to OME. For each day, a patient's total opioid use was calculated by summing the daily dose of all active prescriptions. Chronic high-dose use was defined as a period of 90 subsequent days on which the average daily dose exceeded 90 OME, and this dose was exceeded on a majority (>45) of days.

S2. Text Sensitivity analysis where opioids with ATC N07BC were excluded

Basic patient and practice characteristics per year:

	2017	2018	2019
Patients (n)	1 052 288	1 097 670	1 024 466
Practices (n)	378	388	361
Outcome			
Chronic < 90 OME	17 108 (1.63%)	17 641 (1.61%)	14 522 (1.42%)
Chronic high-dose (≥ 90 OME)	1 413 (0.13%)	1 469 (0.13%)	1 280 (0.12%)

Variation scores for chronic high-dose (≥90 OME) use and chronic <90 OME prescriptions across years

	95%/5% ratio[b]			mean top 10/mean bottom 10 ratio[c]		
	2017	**2018**	**2019**	**2017**	**2018**	**2019**
Chronic <90 OME						
Unadjusted	3.9 (=2.79% / 0.71%)	4.1 (=2.87% / 0.71%)	3.8 (=2.40% / 0.63%)	9.4 (=3.59% / 0.38%)	10.0 (=3.66% / 0.37%)	9.8 (=3.38% / 0.34%)
Adjusted[a]	4.4 (=3.07% / 0.69%)	4.4 (=3.21% / 0.74%)	4.2 (=2.61% / 0.62%)	11.4 (=4.82% / 0.42%)	9.9 (=4.72% / 0.48%)	9.6 (=3.73% / 0.39%)
Chronic high-dose (≥90 OME)						
Unadjusted	8.5 (=0.34% / 0.04%)	7.3 (=0.32% / 0.04%)	7.1 (=0.30% / 0.04%)	15.4 (=0.45% / 0.03%)	17.7 (=0.45% / 0.03%)	17.3 (=0.46% / 0.03%)
Adjusted[a]	9.5 (=0.37% / 0.04%)	9.6 (=0.39% / 0.04%)	7.8 (=0.31% / 0.04%)	18.5 (=0.55% / 0.03%)	20.0 (=0.53% / 0.03%)	16.8 (=0.45% / 0.03%)

The proportions on which the ratios are based is shown in brackets.

[a] Adjusted for ages, sex, cancer, and number of chronic diseases

[b] 95%/5% ratio was calculated by dividing the proportion of the 95th percentile general practice by the proportion of the 5th percentile general practice

[c] mean top 10/mean bottom 10 ratio was calculated by dividing the mean proportion of the top 10 general practices by the mean proportion of bottom 10 general practices

Number of outliers in the funnel plots for all years and outcomes

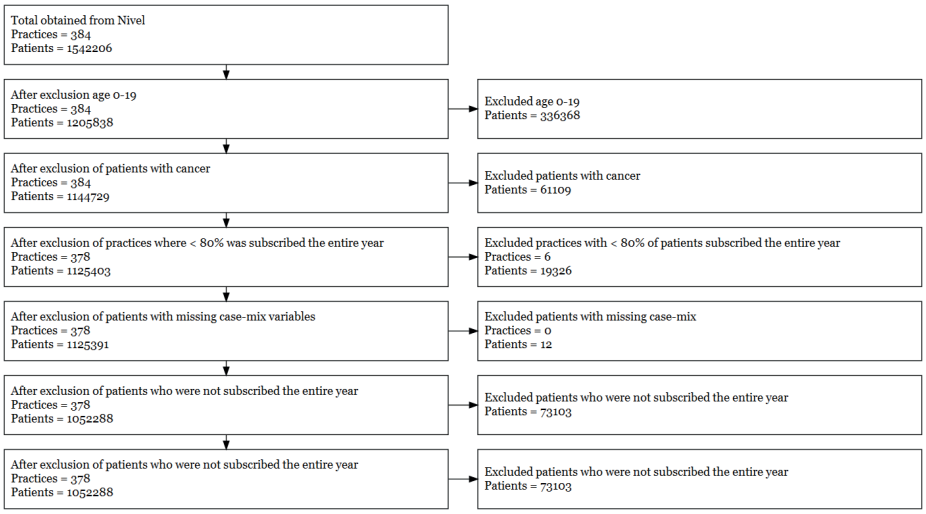
	2017	2018	2019
Outliers outside 95% overdispersed limits			
Chronic < 90 OME	75 (19.8%)	79 (20.4%)	72 (19.9%)
Chronic high-dose (≥ 90 OME)	51 (15.2%)	54 (15.7%)	40 (12.7%)
Outliers above 95% overdispersed limits			
Chronic < 90 OME	23 (6.1%)	28 (7.2%)	25 (6.9%)
Chronic high-dose (≥ 90 OME)	24 (7.1%)	19 (5.5%)	16 (5.1%)
Outliers below 95% overdispersed limits			
Chronic < 90 OME	52 (13.8%)	51 (13.1%)	47 (13.0%)
Chronic high-dose (≥ 90 OME)	27 (8.0%)	35 (10.2%)	24 (7.6%)

Comparison of outlying practices in 2019

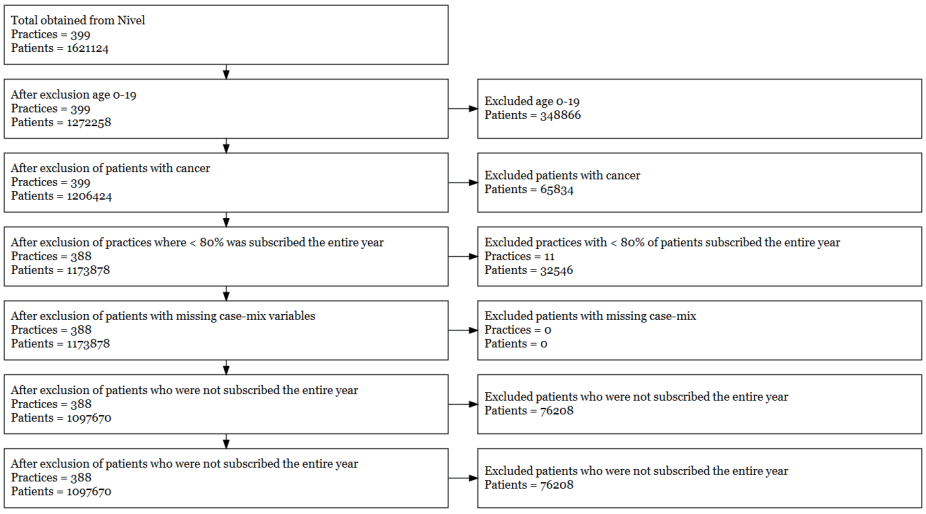
	No patients with chronic high-dose (≥90 OME) prescriptions	Low outliers (below 95% control limits)	High outliers (above 95% control limits)
Practice			
N	46	24	16
Median practice size (IQR)	2 966 (2 360 - 3 126)	5 592 (3 384 - 7 789)	5 841 (3 016 - 7 916)
Median proportion of chronic < 90 OME prescriptions (IQR)	1.12% (0.74% - 1.33%)	0.94% (0.77% - 1.08%)	2.22% (1.91% - 2.58%)
Median proportion of chronic ≥ 90 OME rate prescriptions (IQR)		0.04% (0.03% - 0.04%)	0.37% (0.30% - 0.43%)
Patient			
Median percentage low income (IQR)	36% (29% - 44%)	35% (26% - 43%)	43% (32% - 54%)
Median percentage high income (IQR)	22% (16% - 28%)	25% (17% - 34%)	15% (9% - 20%)
Median urbanicity in addresses / km² (IQR)	1 578 (370 - 1 775)	2 105 (1 031 - 2 382)	1 585 (981 - 1 796)

S1. Fig. Flowcharts describing the number of patients included and excluded per year

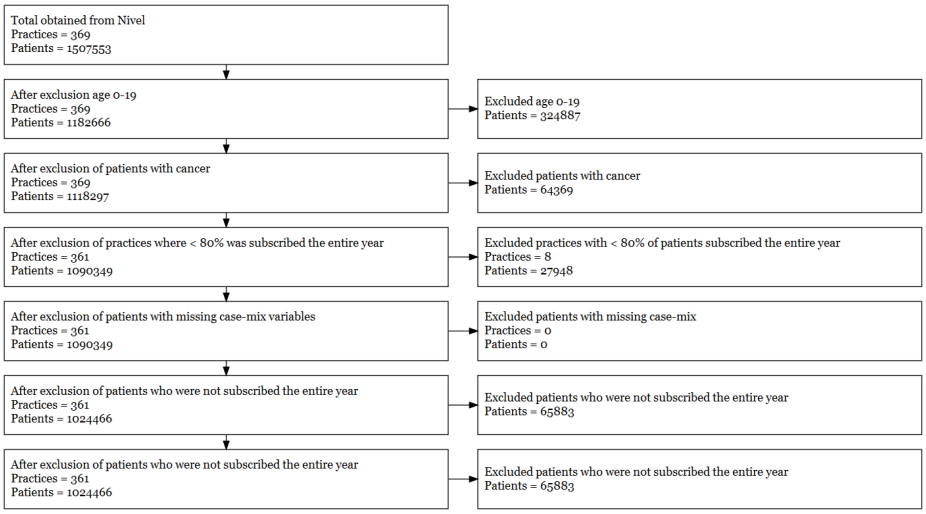
2017



2018

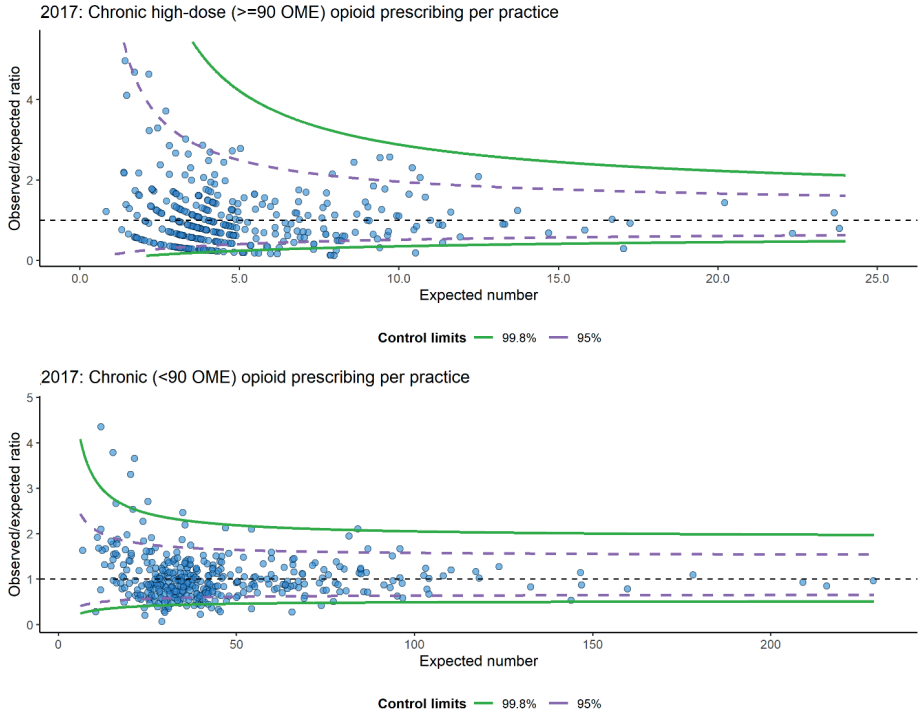


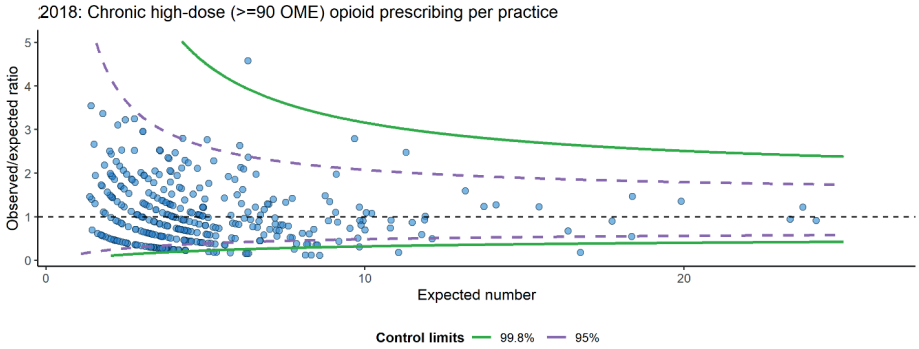
2019

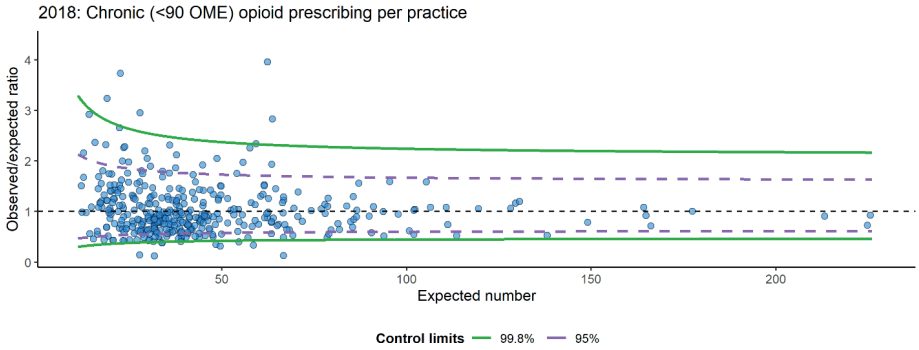

Total obtained from Nivel
Practices = 369
Patients = 1507553
After exclusion age 0-19
Practices = 369
Patients = 1182666
Excluded age 0-19
Patients = 324887
After exclusion of patients with cancer
Practices = 369
Patients = 1118297
Excluded patients with cancer
Patients = 64369
After exclusion of practices where < 80% was subscribed the entire year
Practices = 361
Patients = 1090349
Excluded practices with < 80% of patients subscribed the entire year
Practices = 8
Patients = 27948
After exclusion of patients with missing case-mix variables
Practices = 361
Patients = 1090349
Excluded patients with missing case-mix
Practices = 0
Patients = 0
After exclusion of patients who were not subscribed the entire year
Practices = 361
Patients = 1024466
Excluded patients who were not subscribed the entire year
Patients = 65883
After exclusion of patients who were not subscribed the entire year
Practices = 361
Patients = 1024466
Excluded patients who were not subscribed the entire year
Patients = 65883

S2. Fig. Funnel plots for outcomes from 2017 and 2018

Outcome rates were adjusted for age, sex, and number of chronic diseases. Control limits were corrected for overdispersion. The horizontal black dotted line (O/E = 1) represents the target value where the observed outcome rate equals the adjusted rate based on case-mix. Each dot represents a single practice.




2018: Chronic high-dose (>=90 OME) opioid prescribing per practice
Observed/expected ratio
0
1
2
3
4
5
0
10
20
Expected number
Control limits
99.8%
95%


2018: Chronic (<90 OME) opioid prescribing per practice
Observed/expected ratio
0
1
2
3
4
50
100
150
200
Expected number
Control limits
99.8%
95%

Chapter 5

Psychiatric risk factors for chronic high-dose opioid prescribing: register-based cohort study

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Abstract

Background

Chronic high-dose (CHD) prescription opioid use is a major public health concern. Although CHD opioid use has been associated with psychiatric disorders, the causality could go both ways. Some studies have already linked psychiatric disorders to an increased risk of transitioning to chronic opioid use, and longitudinal data identifying psychiatric disorders as predictors of CHD opioid use could shed further light on this issue.

Aims

To prospectively examine the relationship between the presence of a psychiatric disorder and subsequent development of CHD opioid use in primary care patients newly receiving opioids.

Method

Data were included from 137 778 primary care patients in The Netherlands. Cox regression modelling was used to examine the association between psychiatric disorders prior to a new opioid prescription and subsequent CHD opioid use (≥90 days; ≥50 mg/day oral morphine equivalents) in the subsequent 2 years.

Results

Of all patients receiving a new opioid prescription, 2.0% developed CHD opioid use. A psychiatric disorder before the start of an opioid prescription increased the risk of CHD opioid use (adjusted hazard ratio HR = 1.74; 95% CI 1.62–1.88), specifically psychotic disorders, substance use disorders, neurocognitive disorders and multiple co-occurring psychiatric episodes. Similarly, pharmacotherapy for psychosis, substance use disorders and mood and/or anxiety disorders increased the risk of CHD opioid use. Psychiatric polypharmacy conferred the greatest risk of developing CHD opioid use.

Conclusions

Psychiatric disorders increase the risk of developing CHD opioid use in patients newly receiving prescription opioids. To reduce the public health burden of CHD opioid use, careful monitoring and optimal treatment of psychiatric conditions are advised when opioid therapy is initiated.

Introduction

Prescription opioids are highly effective analgesics, although evidence for long-term use in chronic non-cancer pain is lacking.[1] In Europe, the number of people receiving opioid prescriptions has increased sharply in recent years.[2] For instance, the number of opioid prescriptions in The Netherlands nearly doubled over the past decade, mainly due to the substantial increase in oxycodone use.[3] Similar to other countries,[2] the increase in opioid prescriptions was paralleled by an increase in opioid-related harm, including opioid use disorder and opioid-related mortality.[3] Although not comparable to the opioid epidemic in the USA, the increased use of prescription opioids in Europe is considered a public health concern.[2] The risks associated with long-term prescription opioid use, including misuse, overdose and addiction, against the limited evidence for their long-term effectiveness stresses the importance of carefully balancing the benefits and risks when prescribing opioids.[4] Identifying patients at risk for chronic high-dose (CHD) use of prescribed opioids could help reduce opioid-related harm.[1,4,5] Several studies show that psychiatric disorders are associated with chronic opioid use and misuse. For example, a cross-sectional study in the USA showed that over half of all opioids were being prescribed to patients with psychiatric disorders, while these patients only make up 16% of the total population.[6] However, the relationship between CHD prescription opioid use and psychiatric disorders could be bidirectional.[7] Indeed, most studies investigating the association between psychiatric disorders and chronic opioid use rely on cross-sectional data from the USA collected from specific populations (e.g. insured patients, military veterans or patients with specific conditions).[5] To our knowledge, the only longitudinal studies on this topic are by Olopoenia et al[8] and Quinn et al.[9,10] Olopoenia et al found that in patients with chronic non-cancer pain, having a psychiatric disorder was a strong risk factor for receiving CHD opioid prescriptions.[8] The study was conducted in a US sample of insured patients aged 18–65, which limits generalisability to other (European) countries. Quinn et al found a similar relation between psychiatric disorders, initiation of opioid therapy and subsequent transition to long-term opioid use in both a US and a Swedish population.[9,10] Further longitudinal studies based on representative community samples, including some from Europe, are needed to substantiate current evidence on the role of psychiatric disorders as a major risk factor for chronic opioid use.

This study aimed to prospectively examine the relationship between psychiatric disorders and the development of CHD opioid use in Dutch primary care patients receiving a new opioid prescription. More specifically, we investigated whether the presence of a psychiatric disorder before a new opioid prescription increased the risk of CHD opioid use. This relationship was further explored for each psychiatric disorder separately and for different categories of psychiatric drug.

Method

Data and study design

We conducted a register-based cohort study with data from the Nivel Primary Care Database (Nivel-PCD), covering 2011–2019. The Nivel-PCD contains pseudonymised routine care data from approximately 10% of all general practitioners (GPs) across The Netherlands, which forms a representative sample of the total population of Dutch GPs.[11,12] All Dutch residents are registered with one GP who oversees their medical records, provides primary care and is a gatekeeper to specialist care. The Nivel-PCD thus includes representative nationwide patient data.

The available medical information is coded using the International Classification of Primary Care, version 1 (ICPC-1) for diagnoses and the Anatomical Therapeutic Chemical Classification (ATC) for prescriptions. Data from the Nivel-PCD can be used for research purposes. According to Dutch civil law (article 7:458), no informed consent or medical ethics committee involvement is required for studies without direct personal identifiable data. As a result, this study has been approved by the applicable governance bodies of Nivel-PCD under number NZR-00319.048.

Data on median income, as an indicator of socioeconomic status, were based on the first four digits of a patient's postcode and collected from Statistics Netherlands.[13]

Sample and follow-up

Between 2011 and 2017 all patients with at least one opioid prescription were included and indexed by date of the first opioid prescription. Exclusion criteria were: (a) missing data 6 months before the index prescription, (b) enrolment in a primary care practice with less than 90% of the prescriptions coded with a valid ATC code and (c) treatment of opioid use disorder. Because of the required 6 months without opioid prescribing before the index prescription, only patients with an index prescription in July 2011 and onward were included. To allow for a 2-year follow-up period after the index prescription, data from 2011–2019 were obtained. Patients were categorised as having treatment for opioid use disorder if the first opioid prescription was for an opioid used in treatment of opioid use disorder (ATC N07BC). This selection resulted in 137 778 included participants (Fig. 1).

Psychiatric disorders

Participants with psychiatric disorders were defined as having ≥1 psychiatric episode recorded or having ≥1 prescription for a psychiatric drug 6 months before a first opioid prescription. The comparison group comprised all other participants

receiving a new opioid prescription. Seven categories of psychiatric episode were created: mood and anxiety disorders; substance use disorders; psychotic disorders; neurocognitive disorders; somatisation or eating disorders; personality or gambling disorders; and multiple psychiatric episodes. Owing to limitations in the ICPC-1 coding system, the 'somatisation and eating disorders' and 'personality and gambling disorders' categories could not be subdivided into the individual disorders. Psychiatric drugs were grouped into five categories: mood and anxiety disorders (antidepressants, benzodiazepines, antiepileptics and buspirone); attention-deficit hyperactivity disorder (ADHD) (amphetamines and atomoxetine); substance use disorders (acamprosate, disulfiram, nalmefene, naltrexone, nicotine and varenicline); antipsychotics (atypical and typical antipsychotics); and multiple psychiatric drugs. Participants with more than one type of psychiatric episode or more than one type of psychiatric drug were categorised as having 'multiple psychiatric episodes' or 'psychiatric polypharmacy' respectively. Participants using tricyclic antidepressants, carbamazepine or duloxetine were not categorised as having a psychiatric disorder when there was a registered episode of neuropathy. Similarly, participants using anti-epileptics were not categorised as having a psychiatric disorder when they had an episode of epilepsy. The complete list of codes (ATC and ICPC-1) used to identify psychiatric drugs and episodes is given in Supplementary Tables 1 and 2.

Chronic high-dose opioid use

Participants were followed for a maximum of 2 years on the development of CHD opioid use (Supplementary Fig. 1 shows examples). Opioids were identified using ATC codes N02A (opioids) and N07BC (drugs used in opioid dependence). CHD opioid use was defined as opioid prescriptions covering ≥90 days with an average daily dose ≥50 mg oral morphine equivalents (OME).[1] The threshold of 50 mg OME was chosen because doses above this threshold carry increased risks for adverse events.[14] The method for identifying CHD opioid use in our data-set is described in the Supplementary Methods.

Covariates

The following confounding factors were considered in the analysis: age, gender, chronic condition (excluding cancer), cancer and median income by postcode. These covariates were corrected for because they might correlate with opioid use and psychiatric disorders.[15] Age was categorised as '0–19', '20–39', '40–59', '60–79' or '80+' years. Chronic condition was defined as having one or more of the following episodes: angina pectoris, heart attack, ischaemic heart disease, heart failure, hypertension, cerebrovascular accident, arthrosis/arthritis, osteoporosis, asthma/chronic obstructive pulmonary disease and diabetes mellitus. Finally, median income

by postcode was categorised as 'low–below middle', 'below middle', 'below middle–middle', 'middle', 'middle–upper middle', 'upper middle', 'upper middle–high', in line with Statistics Netherlands publications.[13]

Statistical analysis

Baseline characteristics were calculated at the index date, but were not statistically compared between participants with and without psychiatric disorders as this has no clinical meaning in large samples.[16]

Cox regression models were used to examine the association between psychiatric disorders and subsequent CHD opioid use within 2 years of follow-up, reported as hazard ratios (HRs) with a 95% confidence interval (CI). For each participant, the follow-up time in days was calculated from the index date to (a) fulfilling the definition for CHD opioid use, (b) the end of the 2-year follow-up or (c) loss to follow-up, whichever occurred first. Immortal time bias could not occur because assignment to groups occurred before the follow-up began. The proportional hazards assumption was tested by examination of the Kaplan–Meier and log-minus-log plots, which showed that the proportional hazards assumption holds.

To examine the effect of type of psychiatric disorder on CHD opioid use, Cox regression analyses were performed for psychiatric episodes and psychiatric drugs separately. Participants with only an ICPC-1 code for a personality disorder or a gambling disorder were excluded (n = 662) because a distinction between these disorders could not be made as they have the same ICPC-1 code. Furthermore, those with only a record for somatisation and eating disorders were excluded because of the small sample size (n = 289) relative to the other groups (n > 400).

A P-value of <0.05 was considered statistically significant. All analyses were conducted with R.4.0.2 for Windows. The packages survival, survminer and coxphw were used to perform Cox regression.

Results

Of the 137 778 participants with an opioid prescription, 44 949 (32.6%) had a psychiatric disorder before the first opioid prescription (Table 1, Fig. 1). The average follow-up time was 595 days. Of all participants receiving a new opioid prescription, 2.0% developed CHD opioid use. Of the 44 949 participants with a psychiatric disorder and 92 829 without, 1314 (2.92%) and 1494 (1.61%) respectively developed CHD opioid use (Table 2). Participants with a psychiatric disorder were more likely to be female, older and to have more chronic conditions, cancer and a low income than those without (Table 1). Of the participants receiving an opioid, 95 675 (69%) reached the full follow-up time of 2 years.

A psychiatric disorder was associated with an increased risk of subsequent CHD opioid use (adjusted HR = 1.74, 95% CI 1.62–1.88) (Table 2). Adjusted analysis per psychiatric episode showed that psychotic disorders were associated with the highest risk of CHD opioid use (adjusted HR = 2.05, 95% CI 1.21–3.47). Substance use disorder (adjusted HR = 1.65, 95% CI 1.38–1.98), neurocognitive disorder (adjusted HR = 1.47, 95% CI 1.20–1.80) and multiple psychiatric episodes (adjusted HR = 1.83, 95% CI 1.41–2.37) also increased the risk of subsequent CHD opioid use (Table 2).

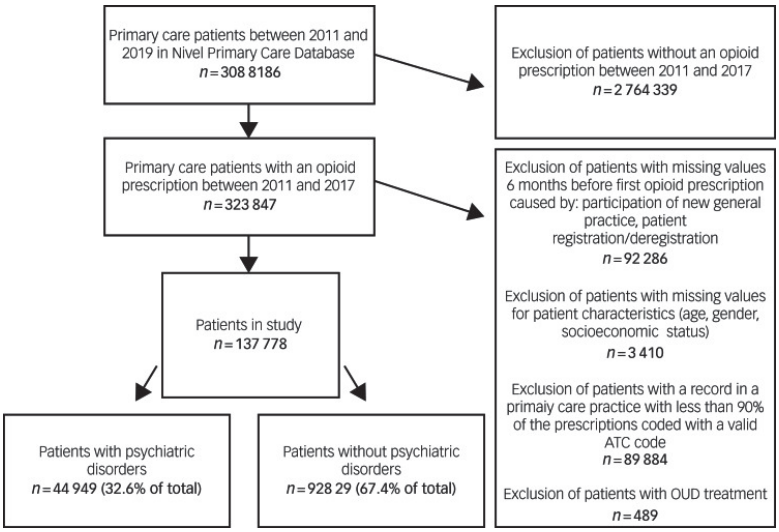

Figure 1. Flowchart of patients in the Nivel Primary Care Database (2011–2019), excluded and included in this study. OUD, opioid use disorder.

Table 1. Baseline characteristics of 137,778 primary care patients receiving an opioid

Characteristics	Patients with psychiatric disorders (N=44 949)	Patients without psychiatric disorders (N=92 829)
	N (%)	N (%)
Age (years)		
0-19	460 (1.02)	2650 (2.85%)
20-39	6148 (13.68)	17019 (18.33%)
40-59	15130 (33.66)	31859 (34.32%)
60-79	15515 (34.52)	31658 (34.10%)
80+	7696 (17.12)	9643 (10.39%)
Gender		
Male	16706 (37.17%)	42013 (45.26%)
Female	28243 (62.83%)	50816 (54.74%)
Chronic condition[a]		
No	15776 (35.10%)	40730 (43.88%)
Yes	29173 (64.90%)	52099 (56.12%)
Cancer		
No	37054 (82.44%)	81453 (87.75%)
Yes	7895 (17.56%)	11376 (12.25%)
Median income by zipcode		
low – below middle	271 (0.60%)	405 (0.44%)
below middle	8808 (19.60%)	16799 (18.10%)
below middle – middle	1020 (2.27%)	2052 (2.21%)
middle	25657 (57.08%)	52011 (56.03%)
middle – upper middle	2882 (6.41%)	7026 (7.57%)
upper middle	6177 (13.74%)	14268 (15.37%)
upper middle - high	134 (0.30%)	268 (0.29%)
Follow-up time[b]	559 (730)	612 (730)

[a] 'Yes' if one or more of the following comorbidities: angina pectoris, heart attack, ischemic heart disease, decompensatio cordis, hypertension, CVA, arthrosis/arthritis, osteoporosis, asthma/COPD, diabetes mellitus.

[b] Mean (median)

Table 2. Association between psychiatric disorders (episode and/or psychopharmacotherapy) and chronic high dose (CHD) opioid use

Psychiatric disorders	N	CHD opioid use N (%)	HR (95% CI) Unadjusted	HR (95% CI) Adjusted[a]
No	92829	1494 (1.61)	1 [reference]	1 [reference]
Yes	44949	1314 (2.92)	1.97 (1.83-2.12)	1.74 (1.62-1.88)
Psychiatric episode[b]				
No psychiatric episode	118046	2290 (1.94%)	1 [reference]	1 [reference]
Mood and/or anxiety disorder	9736	202 (2.07%)	1.05 (0.91-1.21)	1.12 (0.97-1.29)
Substance use disorder	3800	122 (3.21%)	1.65 (1.37-1.97)	1.65 (1.38-1.98)
Psychotic disorder	463	14 (3.02%)	1.66 (0.98-2.81)	2.05 (1.21-3.47)
Neurocognitive disorder	3076	102 (3.32%)	2.58 (2.11-3.14)	1.47 (1.20-1.80)
Multiple psychiatric episodes	1706	58 (3.40%)	1.90 (1.46-2.47)	1.83 (1.41-2.37)
Psychiatric drug				
No psychiatric drug	100972	1669 (1.65%)	1 [reference]	1 [reference]
PhT mood and/or anxiety disorder	31184	981 (3.15%)	2.02 (1.87-2.19)	1.71 (1.58-1.85)
PhT substance use disorder	514	17 (3.31%)	2.00 (1.24-3.22)	2.06 (1.28-3.32)
Antipsychotics	1152	25 (2.17%)	1.97 (1.33-2.92)	1.64 (1.10-2.43)
PhT ADHD	460	3 (0.65%)	0.39 (0.13-1.21)	0.96 (0.31-2.98)
Psychiatric polypharmacy	3496	113 (3.23%)	2.46 (2.04-2.98)	2.49 (2.06-3.02)

CHD chronic high dose, HR hazard ratio, PhT pharmacotherapy.

[a]Adjusted for gender, age, median income by zip code, chronic condition (angina pectoris, heart attack, ischemic heart disease, decompensatio cordis, hypertension, CVA, arthrosis/arthritis, osteoporosis, asthma/COPD, diabetes mellitus), cancer

[b]Excluded: personality disorder and/or a gambling disorder (N=662) and somatization and eating disorders (N=289).

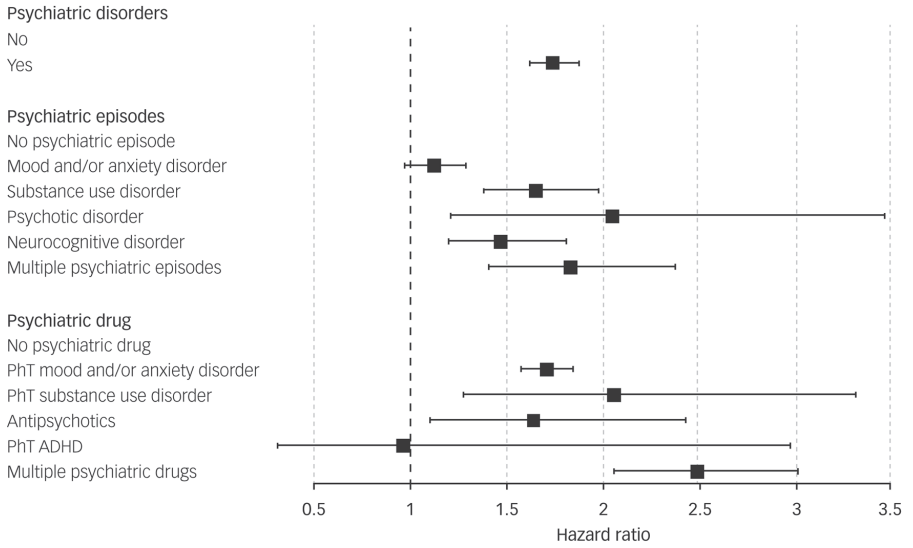

Figure 2. Association between psychiatric disorders (episode and/or psychopharmacotherapy) and chronic high-dose opioid use: adjusted hazard ratios

PhT, pharmacotherapy; ADHD, attention-deficit hyperactivity disorder.

Analysis by type of psychiatric drug showed that pharmacotherapy for mood and anxiety disorders (adjusted HR = 1.71, 95% CI 1.58–1.85), substance use disorders (adjusted HR = 2.06, 95% CI 1.28–3.32), antipsychotics (adjusted HR = 1.64, 95% CI 1.10–2.43) and psychiatric polypharmacy had an increased risk of subsequent CHD opioid use (Table 2). Psychiatric polypharmacy (adjusted HR = 2.49, 95% CI 2.06–3.02) carried the largest risk of developing CHD opioid use. A plot of the adjusted effect sizes of the main analysis and both sub-analyses is shown in Fig. 2.

In addition, two sensitivity analyses were performed to investigate (a) the effect of adding the total OME of the first prescription as a covariate and (b) the effect of excluding serotonin–noradrenaline reuptake inhibitors (SNRIs). The results of these analyses are presented in Supplementary Tables 3 and 4.

Discussion

This study aimed to prospectively investigate the association between psychiatric disorders and the development of chronic high-dose (CHD) opioid use in a representative large general population sample (n = 137 778).[17] In this cohort of primary care patients, 2.0% of those newly receiving an opioid prescription developed CHD opioid use during follow-up. Participants with psychiatric disorders were at greater risk of developing CHD opioid use than those without psychiatric disorders. Specifically, psychotic disorders, substance use disorder, neurocognitive disorders and multiple psychiatric episodes increase the risk for CHD opioid use. Similarly, the use of drugs for mood and anxiety disorders, psychosis and substance use disorder, and psychiatric polypharmacy, increased the risk for CHD opioid use. Overall, having a psychotic disorder and receiving psychiatric polypharmacy had the highest adjusted hazard ratios (2.05 and 2.49 respectively).

Our findings align with previous cross-sectional studies indicating an association between opioid misuse and psychiatric disorders.[18,19] Several mechanisms might explain this association. For example, the emotional distress associated with psychiatric disorders might predispose to chronic pain and subsequently prolonged opioid use.[7] Shared neurobiological mechanisms might also play an important role.[20] For instance, serotonin is involved in mood regulation, pain processing and analgesia.[21] Disruption of serotonergic pathways could contribute to psychiatric disorders (e.g. depression) as well as chronic pain.[21] Other shared risk factors for psychiatric disorders and chronic pain are traumatic childhood experiences and poor socioeconomic status.[20] Finally, decreased effectiveness of opioids in people with psychopathology might also play a role in the increased risk for CHD prescription opioid use in patients with psychiatric disorders.[7]

In this study, psychiatric polypharmacy showed the strongest association with subsequent CHD opioid use. Using multiple psychiatric drugs might indicate multiple or more severe psychiatric conditions. Therefore the observed highest hazard ratio in multiple psychiatric episodes and psychiatric polypharmacy might hint at a dose–response relationship, further suggesting causality.

Of the specific psychiatric disorders, participants with a psychotic disorder had the highest risk of developing CHD opioid use after an initial opioid prescription. This was confirmed by the medication analyses, which also showed this association for antipsychotic drug use. These findings contrast with previous research showing decreased pain sensitivity in people with a psychotic disorder.[22,23] Furthermore,

Owen et al[19] found that people with psychotic disorders are less often diagnosed with chronic pain conditions and less often receive opioids than the general population. A potential explanation for the discrepancies between the results of Owen et al and our data is a difference in study design. Our study examined the risk of CHD use after an initial opioid prescription, whereas Owen et al examined the initiation of opioid treatment. People with psychotic disorders might be less likely to receive an opioid, but once opioid treatment is initiated, they could have an increased risk for CHD use. This is in line with previous research showing an increased risk of overdose in people using antipsychotics and opioids concomitantly.[24]

An increased risk for CHD opioid use in people with psychotic disorders might be related to an increased addiction liability.[25] Indeed, the prevalence of substance use disorders is higher in people with a psychotic disorder than in the general population, in part due to shared genetic liability between the two conditions.[26] In addition, people with a psychotic disorder might continue using opioids to reduce psychotic symptoms.[27] Interestingly, antipsychotics have been shown to have a protective effect against substance use disorders in people with psychotic disorders.[28] This effect could be caused by reducing the rewarding effects of opioids by antipsychotics.[29] Our results show an increased risk of CHD opioid use in participants using antipsychotics, yet with a smaller hazard ratio than for a psychotic episode. However, the number of patients with a psychotic disorder and CHD opioid use in our data-set is limited, which precludes drawing strong conclusions.

In line with existing literature,[5] substance use disorder increased the risk of developing CHD opioid use. Previous research showed that approximately half of the people who use drugs illicitly reported pain as a reason for substance use.[30] Substance use disorder pre-dating CHD opioid use might thus reflect a type of self-medication before initiation of prescription opioids. Alternatively, people with pre-existing substance use disorder liability might also be at increased risk of CHD prescription opioid use or misuse when exposed to prescription opioids.[31]

We found an increased risk of CHD opioid use only in participants receiving pharmacological treatment for mood and anxiety disorders and not in those with an episode of a mood and anxiety disorder (irrespective of medication use). This contrasts with existing literature, showing rather consistently that people with mood and anxiety disorders have an increased risk of developing opioid misuse.[5] This association has been explained by overlapping stress-related mechanisms between pain and internalising disorders resulting in lower pain thresholds[5] and by the antidepressant properties of opioids.[32] That we only observed this association for

pharmacotherapy for mood and anxiety disorders might be explained by a difference in severity of the disorder. In The Netherlands, pharmacotherapy is mainly considered in people with severe depression or anxiety, whereas milder forms are usually treated with psychological interventions only.[33,34]

Our results also show an increased risk of CHD opioid use after an initial opioid prescription in participants with neurocognitive disorders (i.e. delirium, Parkinson's disease and dementia), although in the literature neurocognitive disorders are often associated with reduced prescription opioid use.[36] An inability to clearly express pain due to cognitive impairment might explain undertreatment with opioids.[35] But once opioid treatment is initiated it might also decrease the likelihood of discontinuation to avoid undertreatment.

Strengths and limitations and future research

When interpreting the current results, several strengths and limitations should be considered. A major strength of this study is the use of a large nationwide longitudinal data-set representative of a general population and a prospective study design. However, this study also has several weaknesses.

First, our data showed that 44% of the participants using psychiatric drugs did not have a registered psychiatric episode. Similarly, our sub-analyses showed more participants with prescriptions for psychiatric drugs (n = 36 806) than episodes of psychiatric disorder (n = 18 781). This is most likely caused by missing diagnoses. This might have affected our results, although we mostly overcame this limitation in our main analysis by defining psychiatric disorders using both registered episodes and psychiatric drug use. Second, some benzodiazepines were included as psychiatric drugs for anxiety or mood disorders, although they might be prescribed for mild sleeping problems. As a result, the current study might underestimate the influence of drugs for mood and anxiety disorders on CHD opioid use. Third, although we included registered drug use for ADHD, no reliable ICPC-1 code for ADHD was available. Our analyses on the effects of ADHD medication on subsequent CHD opioid use should therefore be considered explorative. Fourth, this study likely did not identify all participants with substance use disorder or those who use opioids illicitly. The resulting misclassification would probably lead to an underestimation of the overall risk of psychiatric disorders on subsequent CHD opioid prescribing. Fifth, our data do not include information on the reason for opioid prescribing. The risk for transitioning to chronic opioid use may vary per indication for the prescription opioids. For example, it might differ between postoperative and chronic pain. Future research should elucidate which patient populations and indications require

most attention, and whether this interacts with psychiatric comorbidity. Sixth, our sensitivity analysis showed that the total OME of the first prescription did not affect the effect of psychiatric disorders on the risk of CHD opioid use (Supplementary Table 3). Seventh, SNRIs can also be used to treat fibromyalgia. A sensitivity analysis excluding these drugs did not show substantial effects of SNRIs on the association between antidepressant use and receiving a CHD opioid prescription (Supplementary Table 4). Eighth, social factors such as living alone might influence the risk of transition to CHD opioid use. However, our data-set does not include such information and it could therefore not be used as a covariate. Finally, we could not provide insight into, or adjust for the effect of, non-pharmacological strategies for pain relief. Future studies should explore the potential mitigating effects of such interventions on the risk of developing CHD prescription opioid use in people with psychiatric conditions.

Clinical implications

The association between psychiatric disorders and CHD opioid use underscores the need for an integrated approach in pain management. Strategies to prevent opioid-related harm could include screening for psychiatric comorbidity prior to opioid initiation, psychiatric consultation in case of psychiatric comorbidity and, if indicated, ongoing involvement of a psychologist or psychiatrist to treat the psychiatric condition and prevent the development of chronic or escalating opioid use.[7] Indeed, adequate pain management includes optimal treatment of co-occurring psychiatric conditions and active monitoring.[1,7,37] However, this should not result in undertreatment of pain in people with a psychiatric disorder, and opioids should not be withheld when they are indicated.

Data availability

Access to the underlying data in this study can be requested from Nivel Primary Care Database.

Author contributions

M.M.C.H., A.S. and G.A.K. initiated the study. G.A.K. and Y.M.W. collected and prepared the data. M.M.C.H., G.A.K., F.A. and A.S. were responsible for the concept and design of the study and the analyses. All authors were involved in the interpretation of the results. M.M.C.H. and G.A.K. were responsible for the writing of the manuscript and the other authors contributed to revisions of the manuscript. G.A.K., M.M.C.H. and Y.M.W. had full access to all the data in the study. Other authors were not precluded from accessing data in the study, and they accept responsibility to submit for publication.

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Declaration of interest

None.

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Supplementary materials

Table 1. International Classification of Primary Care (ICPC-1) codes identifying psychiatric episodes

Psychiatric episode	ICPC-1 code
***Mood and/or anxiety disorder**	
Panic disorders, including panic attack disorder and generalized anxiety disorder	1874
Other neurotic disorders, including phobias and compulsive disorders	1879
Depressive disorders, also including post-partum depression	1876
Bipolar disorder	1873
Suicide attempt	1877
Post traumatic stress disorder/crisis, and transient stress	1802
***Substance use disorder**	
Problematic alcohol use	1815
Acute alcohol abuse/intoxication	1816
Drug abuse	1819
Tobacco abuse	1817
Medication abuse	1818
***Psychotic disorder**	
Schizophrenia all types	1872
Other/unspec psychosis	1898
***Neurocognitive disorder**	
Parkinsonism	1787
Dementia senile/Alzheimer	1870
Delirium (excl. delirium tremens)	1871
***Eating disorder**	
Boulimia	2106
Eating problems in children	1811
***Somatic symptom disorder**	
Hysterical/hypochondriacal disorder	1875
***Personality disorder and/or gambling disorder**	1880
***Codes used in exclusion criteria**	
Epilepsy all types	1788
Neuropathy	1794

Table 2. Anatomical Therapeutic Chemical Classification (ATC) codes identifying psychiatric drug prescriptions

Psychiatric drug			**ATCcode**
Major drug class	**Minor drug class**	**Specific drug name**	
Amphetamines			
		Dexamphetamine	N06BA02
		Lisdexamphetamine	N06BA12
		Methylphenidate	N06BA04
		Amfetamine	N06BA01
Antiepileptics			
		Carbamazepine	N03AF01
		Lamotrigine	N03AX09
		Pregabalin	N03AX16
		Valproic acid	N03AG01
Antidepressants			
	SSRI (non-selective)	Duloxetine	N06AX21
		Trazodone	N06AX05
		Venlafaxine	N06AX16
	SSRI (selective)	Citalopram	N06AB04
		Dapoxetine	G04BX14
		Escitalopram	N06AB10
		Fluoxetine	N06AB03
		Fluvoxamine	N06AB08
		Paroxetine	N06AB05
		Sertraline	N06AB06
	Tricyclic antidepressants	Amitriptyline	N06AA09
		Clomipramine	N06AA04
		Dusolepin	N06AA16
		Doxepin	N06AA12
		Imipramine	N06AA02
		Maprotiline	N06AA21
		Nortriptyline	N06AA10
	Tetracyclic antidepressants	Mianserin	N06AX03
		Mirtazepine	N06AX11

Table 2. Continued

Psychiatric drug			**ATCcode**
Major drug class	**Minor drug class**	**Specific drug name**	
	AD, rest group (i.e. bupropion, vortioxetine)	Bupropion	N06AX12
		Vortioxetine	N06AX26
		Agomelatine	N06AX22
		Hyperici herba	N06AX25
	MAO A inhibitors (i.e. moclobemide)	Moclobemide	N06AG02
	MAO inhibitors, non-selective (i.e. phenelzine tranylcypromine)	Phenelzine	N06AF03
		Tranylcypromine	N06AF04
Benzodiazepine receptor agonists		Alprazolam	N05BA12
		Bromazepam	N05BA08
		Brotizolam	N05CD09
		Clobazam	N05BA09
		Clorazepate	N05BA05
		Diazepam	N05BA01
		Flunitrazepam	N05CD03
		Flurazepam	N05CD01
		Loprazolam	N05CD11
		Lorazepam	N05BA06
		Lormetazepam	N05CD06
		Midazolam	N05CD08
		Nitrazepam	N05CD02
		Oxazepam	N05BA04
		Prazepam	N05BA11
		Temazepam	N05CD07
		Zolpidem	N05CF02
		Zopiclone	N05CF01
		Clonazepam	N03AE01
		Chlordiazepoxide	N05BA02
Antipsychotics, atypical		Aripiprazole	N05AX12
		Brexpiprazole	N05AX16

Table 2. Continued

Psychiatric drug			ATCcode
Major drug class	**Minor drug class**	**Specific drug name**	
		Cariprazine	N05AX15
		Clozapine	N05AH02
		Lurasidone	N05AE05
		Olanzapine	N05AH03
		Paliperidone	N05AX13
		Quetiapine	N05AH04
		Risperidone	N05AX08
		Sertindole	N05AE03
		Chlorpromazine	N05AA01
Antipsychotics, typical		Amisulpride	N05AL05
		Bromperidol	N05AD06
		Chloorprothixene	N05AF03
		Flupenthixol	N05AF01
		Fluspirilene	N05AG01
		Haloperidol	N05AD01
		Penfluridol	N05AG03
		Periciazine	N05AC01
		Pimozide	N05AG02
		Pipamperone	N05AD05
		Sulpride	N05AL01
		Tiapride	N05AL03
		Zuclopenthixol	N05AF05
		Fluphenazine	N05AB02
		Perphenazine	N05AB03
		Droperidol	N05AD08
Antipsychotics, other		Lithium	N05AN01
Pharmacotherapy for alcohol addiction		Acamprosate	N07BB03
		Disulfiram	N07BB01
		Nalmefene	N07BB05
		Naltrexone	N07BB04

Table 2. Continued

Psychiatric drug			ATCcode
Major drug class	**Minor drug class**	**Specific drug name**	
Pharmacotherapy for nicotine addiction		Nicotine	N07BA01
		Varenicline	N07BA03
Psychiatric drug, rest group		Buspiron (indication: anxiety disorder)	N05BE01
		Atomoxetine (indication: ADHD)	N06BA09

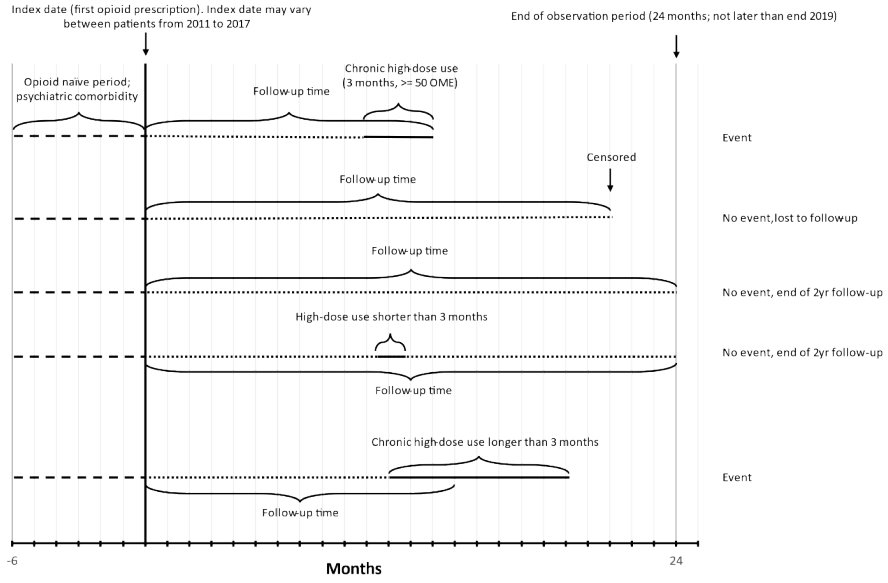

Figure 1. The follow-up period for each patient started with new opioid use (between 2011-2017) and was completed until the chronic high-dose (CHD) event occurred (between 2013-2019) or end of the 2 year follow-up. In case patients were deregistered, e.g. due to GP switch or death, censoring occurred. The CHD event comprise a minimal period of 3 months, but can comprise a longer period as illustrated.

Methods

CHD opioid use was identified by using the duration, dosage, and number of the prescribed opioids. The opioid prescription duration was calculated by identifying repeat prescriptions, and using the start date of the repeat prescription as stop date of the previous prescription, similar to Weesie et al. Prescriptions for the same drug were considered repeat prescriptions when their start date was less than 90 days apart. The end date of a prescription was defined as the start date of the next prescription. The duration of the last prescription in a series of repeat prescriptions was calculated as the average duration of the previous prescriptions. For non-repeat prescriptions the duration was fixed at 14 days, the standard duration of a first prescription in the Netherlands. For each prescription a daily dose was calculated by dividing the amount prescribed (e.g. number of pills) by the duration and converting this to oral morphine equivalents (OME). For each day the total opioid use was calculated by adding the daily dose of all active prescriptions. Chronic high-dose use was defined as a period of 90 subsequent days where the average daily dose was greater than 50 OME, and this dose was exceeded on a majority of days.

This method only depends on the type of drug prescribed, the starting date, and the total prescribed dose to identify CHD opioid use. Therefore, it is not sensitive to patient compliance to the prescribed dosing schedule and also accounts for prn (as needed) dosings.

Weesie YM, Hek K, Schermer TRJ, Schellevis FG, Leufkens HGM, Rook EJ, et al. Use of Opioids Increases With Age in Older Adults: An Observational Study (2005-2017). Front Pharmacol. 2020;11:648.

Table 3. Sensitivity analysis in which the total OME of first prescription was included as a correction factor. Total OME was first categorised into <100 OME, 100-200 OME, 200-300 OME, and ≥300 OME

Psychiatric disorders	N	CHD opioid use N (%)	HR (95% CI) Unadjusted	HR (95% CI) Adjusted[a]
No	92829	1494 (1.61)	1 [reference]	1 [reference]
Yes	44949	1314 (2.92)	1.97 (1.83-2.12)	1.67 (1.55-1.80)
Psychiatric episode				
No psychiatric episode	118046	2290 (1.94%)	1 [reference]	1 [reference]
Mood and/or anxiety disorder	9736	202 (2.07%)	1.05 (0.91-1.21)	1.12 (0.97-1.29)
Substance use disorder	3800	122 (3.21%)	1.65 (1.37-1.97)	1.59 (1.33-1.91)
Psychotic disorder	463	14 (3.02%)	1.66 (0.98-2.81)	2.21 (1.31-3.74)
Neurocognitive disorder	3076	102 (3.32%)	2.58 (2.11-3.14)	1.47 (1.20-1.80)
Multiple psychiatric episodes	1706	58 (3.40%)	1.90 (1.46-2.47)	1.94 (1.49-2.52)
Psychiatric drug				
No psychiatric drug	100972	1669 (1.65%)	1 [reference]	1 [reference]
PhT mood and/or anxiety disorder	31184	981 (3.15%)	2.02 (1.87-2.19)	1.71 (1.58-1.85)
PhT substance use disorder	514	17 (3.31%)	2.00 (1.24-3.22)	2.08 (1.29-3.36)
Antipsychotics	1152	25 (2.17%)	1.97 (1.33-2.92)	1.66 (1.12-2.47)
PhT ADHD	460	3 (0.65%)	0.39 (0.13-1.21)	1.00 (0.32-3.11)
Psychiatric polypharmacy	3496	113 (3.23%)	2.46 (2.04-2.98)	2.52 (2.08-3.05)

CHD chronic high dose, HR hazard ratio, PhT pharmacotherapy.

Table 4. Sensitivity analysis in which SNRI's were excluded

Psychiatric disorders	N	CHD opioid use N (%)	HR (95% CI) Unadjusted	HR (95% CI) Adjusted[a]
No	93139	1510 (1.62)	1 [reference]	1 [reference]
Yes	44639	1298 (2.91)	1.95 (1.81-2.10)	1.72 (1.60-1.86)
Psychiatric drug				
No psychiatric drug	100022	1696 (1.67%)	1 [reference]	1 [reference]
hT mood and/or anxiety disorder	29484	954 (3.13%)	2.00 (1.85-2.17)	1.68 (1.55-1.82)
PhT substance use disorder	504	17 (3.26%)	1.95 (1.21-3.14)	2.02 (1.25-3.26)
Antipsychotics	1207	26 (2.11%)	1.84 (1.25-2.71)	1.57 (1.06-2.31)
PhT ADHD	466	3 (0.64%)	0.38 (0.12-1.17)	0.93 (0.30-2.88)
Psychiatric polypharmacy	3287	112 (3.30%)	2.51 (2.07-3.04)	2.53 (2.09-3.06)

CHD chronic high dose, HR hazard ratio, PhT pharmacotherapy.

Chapter 6

A European perspective on the North American Opioid Crisis

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Background

The Stanford-Lancet Commission on the North American Opioid Crisis was formed to understand and propose solutions to the opioid crisis in the USA and Canada. The results (written by Humphreys et al.) were published in the Lancet in 2022. The commission provided a detailed analysis of the opioid epidemic subdivided into seven domains, and provided comprehensive recommendations for each. We noted that many of the recommendations by Humprey's et al were already a reality in many European countries. As a results, we submitted the letter below to the Lancet, which was published there after editorial review. Letters to the editor serve as a platform for researchers to offer additional insights, critique, support, or alternative interpretations of published research. These letters are not only important in maintaining scientific integrity, but also add depth to scientific discussions.

Contents of the letter

With great interest and enthusiasm we read the Commission led by Keith Humphreys and colleagues.[1] For the past few years, we have been investigating the use of prescription opioids, and prescription opioid-related harm in Europe.[2,3,4,5] Similar to the Humphreys and colleagues' analysis, we found an increasing trend in prescription opioid use in almost all European countries.[3] However, we generally found no evidence for a substantial increase in opioid-use-related adversities (eg, hospitalisations, opioid dependence, and opioid overdose deaths) or an opioid crisis that is similar in magnitude or nature to the crisis in the USA.[3] The one important exception is Scotland, UK, which is reporting opioid-related overdose deaths similar to North America.[3]

Many of the Commissioners' recommendations are already a reality in most European countries. Furthermore, the role of widely implemented universal health care in Europe, including addiction care, is, in our opinion, underappreciated by Humphreys and colleagues. Universal health care has been a major factor in preventing an opioid crisis of US proportions across Europe for several reasons. First, universal health care provides access to appropriate care without high costs for the individual. This ensures that people never have to choose between high-cost (appropriate) care or cheaper (less appropriate) care such as, for example, a hip or knee replacement instead of chronic pain management with opioid painkillers. Second, European health-care systems are much more centralised than in the USA. In many European countries, general practitioners (GPs) are central to health care, important gate keepers to specialist

care, and integrate all patient care. GPs thereby minimise fragmentation of care, resulting in fewer solitary sources of prescription opioids, subsequently preventing opioid diversion, development of iatrogenic opioid disorders, and opioid overdose deaths from prescription opioids. For example, 80% of opioids in the Netherlands are prescribed by a GP.[5] in contrast, primary care physicians in the USA account for only a third of all opioid prescriptions.[6] Third, evidence-based addiction care covered by health insurance (including opioid substitution treatment) is more widely available in European countries than in the USA.[3] As Humphreys and colleagues state, availability of low-threshold addiction care is inevitable to counteract an opioid epidemic and lower opioid overdose mortality.

We strongly support the analyses and recommendations by Humphreys and colleagues and would like to complement them with this European perspective, given the major differences in the opioid epidemic between the USA and Europe. The availability of universal health care in the broadest sense, including professional addiction care, is a cornerstone of European health-care systems and contributes greatly to preventing and tackling an opioid epidemic of US proportions.

WvdB reports personal fees for consultation and presentations from Camurus. All other authors declare no competing interests.

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Chapter 7

Summary and general discussion

The aim of this thesis was to 1) investigate the magnitude of prescription opioid use and misuse in the Netherlands, 2) provide an overview of different definitions of opioid use and types of opioid-related harm, and give an analysis of possible drivers for prescription opioid use and related harm, 3) find targets for quality improvement in pain management by investigating practice variation in opioid prescribing, and 4) investigate possible psychiatric risk factors for chronic high-dose opioid prescribing.

Chapter 2: Trends in use and misuse of opioids in the Netherlands

To investigate current prescription opioid use and possible negative consequences in the Netherlands, we obtained data from several nationwide databases. Our results show that between 2008 and 2017, the number of prescription opioid users nearly doubled from 4109 to 7489 per 100.000, mainly because of the strong increase in oxycodone use. Opioid-related hospital admissions tripled from 2,5 to 7,8 per 100.000 in the same period. The number of patients in addiction care for opioid use disorders other than heroin increased from 3,1 per 100.000 in 2008 to 5,6 per 100.000 in 2015. Opioid-related mortality was stable between 2008 and 2014, with approximately 0,21 deaths per 100.000, but increased to 0.65 per 100.000 in 2017. Overall, the results show an increase in prescription opioid use paralleled by an increasing trend in several proxies for misuse. However, compared to the United States, Canada and several other European countries, opioid-related harm in the Netherlands is still low.

Chapter 3: Monitoring opioids in Europe: The need for shared definitions and measuring drivers of opioid use and related harms

This commentary explores how different definitions of opioid use, misuse, abuse and mortality can complicate research. In addition, we discuss several potential drivers for opioid use and related harms in Europe. Finally, we recommend harmonising definitions and further investigating the factors that drive opioid use and misuse in Europe to better understand the state of opioid use and misuse in Europe.

Chapter 4: Practice variation in opioid prescribing for non-cancer pain in Dutch primary care: a retrospective database study

This research examines variation in opioid prescribing for chronic non-cancer pain in Dutch primary care. Data from approximately 10% of all Dutch general practices, corresponding to roughly one million patients across 380 practices from 2017 to 2019, was used. In the most recent year (2019), there was a 7.5-fold variation in the proportion of patients prescribed chronic high-dose opioids between the top and bottom 5% of practices. In addition, 14% of practices were considered statistical outliers. Practices with a high proportion of patients with *chronic high-dose opioid prescriptions* were larger and had more patients from lower-income classes and more

densely populated areas. This high variation indicates possible inappropriate opioid prescribing and may provide target points for quality improvements.

Chapter 5: Psychiatric risk factors for chronic high-dose opioid prescribing: a register-based cohort study

This study aimed to investigate if the presence of a psychiatric disorder is associated with subsequent chronic high-dose opioid (≥90 days; ≥50mg oral morphine equivalents) prescribing in primary care patients newly receiving opioids. Data from 137.762 primary care patients who newly started an opioid between 2011-2017 were included from the Nivel Primary Care database. We found that the presence of a psychiatric disorder before initiating opioid therapy increases the risk of developing chronic high-dose opioid use. Patients with multiple psychiatric disorders are especially at risk. Therefore, careful monitoring and optimal treatment of psychiatric conditions are advised when opioid therapy is initiated.

Chapter 6: A European perspective on the North American Opioid Crisis

Chapter 6 discusses the North American opioid crisis from a European viewpoint, emphasizing that many of the Stanford-Lancet Commission's recommendations for the US and Canada are already implemented in Europe. We highlight the role of universal healthcare and the availability of evidence-based addiction care in preventing an opioid epidemic in Europe.

General discussion

Understanding the increase in prescription opioid use in the Netherlands

In Chapter 2, we used a combination of national registries to assess the extent of prescription opioid use and related harms in the Netherlands. Although our results showed an increasing trend in prescription opioid use, paralleled by increases in opioid-related harm, including mortality, these rates are still very low compared to the US. In 2017, opioid-related mortality in the Netherlands was 0,65 per 100.000, compared to 14.9 in the US.[1]

After 2017, the number of patients being prescribed an opioid decreased and dropped by 8.1% in 2020 compared to 2017. However, their number increased again afterwards, possibly due to the effects of the COVID-19 pandemic. In 2022, the number of patients being prescribed an opioid had increased again by 6.2% compared to 2020. However, a slightly different trend emerges when looking at the total number of prescriptions instead of the number of patients. The trend in total number of opioid prescriptions increases up until 2017, decreases until 2020, and then stabilises. When this is combined with the increasing number of patients from 2020 onward, there are fewer prescriptions per patient, which suggests more short-term use and less chronic use of opioids.

This could indicate that, while the number of patients using opioids has risen, they are potentially being prescribed opioids more cautiously, with doctors prescribing opioids for shorter durations to address immediate pain needs rather than long-term chronic pain management. However, definitive data on this topic is lacking, and further research would be needed to elucidate the effect of the COVID-19 pandemic on prescription opioid use and other changes in prescribing practices from 2018 onward.

Concerning opioid-related mortality, the Dutch National Drug Monitor (NDM) reports fluctuating opioid-relating mortality from 2017 onward that seems to stabilise in 2020-2021.[2] Compared to 2017, opioid-related deaths increased by 14% in 2021, which is still low compared to the rest of Europe and the US. However, these data should be cautiously interpreted as they do not distinguish between illegal and prescription opioids. In addition, they are subject to changes in registration procedures and post-mortem toxicological investigations. Overall, there appear to be no signs of escalating opioid-related mortality in the Netherlands.

Although an opioid epidemic of US proportions does not appear to be developing in the Netherlands, we still observe a substantial increase in opioid prescriptions and explaining this increase is therefore still imperative. We speculate that several factors might have contributed. First, the population of the Netherlands is ageing, which is associated with more painful conditions (e.g. osteoarthritis and low back pain) for which an opioid could be prescribed. Indeed, research shows that most opioids are prescribed to older patients.[3] However, ageing can only explain a small part, as the percentage of people aged 65+ only increased from 15% to 19% between 2007-2018.[4] Second, increased awareness of the harm caused by other analgesics, mainly non-steroidal anti-inflammatory drugs (NSAIDs; e.g. ibuprofen or diclofenac), likely plays a role. For example, NSAIDs can cause gastrointestinal bleeding, kidney damage, and increase cardiovascular risks, especially in elderly patients. Doctors might, therefore, prefer to prescribe opioids rather than NSAIDs in this population. Bedene et al. indeed found that between 2013 and 2017, NSAID prescribing decreased and opioid prescribing increased,[5] suggesting a shift in prescribing from NSAIDs to opioids. Third, attention to pain management in hospitals has increased since the early 90s. Subsequently, a program was started in 2009 to increase the early recognition and treatment of pain in Dutch hospitals, which called for frequent measurements of pain scores and timely treatment of pain. The pain scores recorded during hospital stays were also used as quality indicators to benchmark hospitals.[6]

A parallel between this Dutch program and the "Pain as the Fifth Vital Sign" campaign in the US can be drawn. The American Pain Society introduced this campaign in the late 1990s to raise healthcare professionals' awareness of adequate pain management. The campaign similarly called for routine measurement of pain scores in various healthcare settings, including hospitals and outpatient clinics.[7] However, in hindsight, this campaign inadvertently contributed to overprescribing of opioids and the subsequent opioid epidemic.[8] Finally, the marketing of opioids (especially oxycodone) might have contributed to an increase in opioid prescribing. However, direct marketing to patients is not allowed in The Netherlands. Yet, Dutch data on the role of marketing to physicians is lacking, making it difficult to estimate the impact.

Is there a European opioid epidemic?

Prescription opioid use also increased in most European countries over the past decades. However, as in the Netherlands, most European countries do not appear to experience as much harmful effects from increased opioid prescribing as the US. According to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), mortality from opioid overdose in the EU was approximately 1.2 per 100.000 inhabitants in 2017.[9] However, Europe is a heterogeneous region with

considerable variation between countries. An analysis by Pierce et al.[10] shows high opioid-related mortality in some European nations. The British Isles, in particular the region of Scotland, have especially high rates. In 2018, Scotland had 22.7 fatal opioid overdoses per 100.000 inhabitants, which was higher than the US (14.6 per 100.000 in 2018[11]). However, in contrast to the US, there are no signs that opioid prescribing for pain is driving opioid-related mortality in Scotland.[12] Instead, the risk factors that increase opioid-related mortality in Scotland are the co-use of opioids with other psychotropic drugs (benzodiazepines, gabapentinoids, and Z-drugs such as zolpidem and zopiclone), limited access to addiction care, the high mean age of people who misuse opioids, and poverty and deprivation.[12,13] Another example of high opioid-related mortality in Europa is Estonia, which had high mortality from illicitly manufactured fentanyl (IMF) between 2003 and 2017. The peak was reached in 2012, with a mortality rate of 13 per 100.000 inhabitants.[14] The main driver of the increased IMF use was a decrease in heroin availability, and IMF filled the gap in the market[14] . Overall, Europe is currently not facing an opioid epidemic similar to the US, although Scotland has a high opioid-related mortality rate.

Why is there no European opioid epidemic?

It is plausible that the differences between Europe and the United States regarding opioid-related harm stem from fundamental differences in healthcare systems, prescription practices, drug regulations, and cultural differences.[15] The structure of the healthcare system in most European countries, in particular universal coverage with low cost for patients, likely plays an important role in preventing harm from opioid prescriptions (Chapter 6). With accessible, low-cost care, patients can opt for the most appropriate treatment for chronic conditions without incurring a financial burden. The central role of general practitioners in most European healthcare systems also minimises fragmentation of care and increases oversight on opioid prescribing, thereby reducing risks of doctor shopping and misuse. Additionally, the widespread availability of addiction care, covered by insurance, ensures support for those struggling with opioid addiction, further reducing the likelihood of escalating harm.

Is there a risk for a future European opioid epidemic?

It could be argued that complacency played an important role in allowing the US opioid epidemic to emerge and escalate, and it could also pose a risk for Europe. The risks of opioids, including oxycodone, were already known in the 60's[16], yet important warning signs of an upcoming problem were ignored. For example, a publication in the Lancet from 2000[17] signalled a strong increase in oxycodone consumption in the US, but it concluded that it was a reflection of better pain management. This aligns

perfectly with the thinking of that time, that especially chronic pain was undertreated and opioids were not addictive when used in a medical context. In hindsight, the early signs of an emerging crisis were there. Still, they were ignored or misinterpreted in favour of the easy conclusion that opioids were the cure for an epidemic of pain; a conclusion strongly supported by the pharmaceutical industry[18]. This historical complacency underscores how overlooking early warning signs and settling for convenient narratives can hinder early interventions, allowing a manageable problem to escalate into a full-blown crisis.

Although European healthcare systems and current opioid trends differ from those in the US, the situation in Estonia highlights that shifts in illicit drug markets can quickly result in increased mortality. Especially the influx of IMF or other synthetic opioids could pose a risk.[19] These compounds are highly potent and cheap to manufacture[20], and their emergence in European drug markets could cause a rapid escalation of opioid-related mortality, as seen in the US and Estonia. Therefore, despite the absence of an opioid epidemic, Europe should not become complacent about this potential illicit use. It remains crucial to monitor shifts in drug trends and quickly address potential threats. The focus should not only be on prescription opioids, acknowledging that a crisis can manifest in various ways.

Quality of opioid prescribing in the Netherlands

To further investigate the quality of opioid prescribing in the Netherlands, we examined variation in chronic opioid prescribing between general practices (Chapter 3). Two types of variation are distinguished in practice variation research: warranted and unwarranted. Warranted variation includes all variation that can be explained by patient preferences, medical needs, and dictates from evidence-based medicine.[21,22] In contrast, unwarranted variation is variation that cannot be explained by these factors.[23] Unwarranted variation is potentially problematic because it may indicate a lack of standardisation, leading to potential inappropriate use and health inequalities, thereby negatively impacting patient outcomes. Investigating unwarranted variation is relevant because it can provide target points for quality improvement by highlighting inconsistencies in healthcare utilisation and healthcare providers' behaviour.[23]

In Chapter 4, we examined practice variation in chronic (≥ 90 days) high-dose (≥ 90 oral morphine equivalents) opioid prescribing for non-cancer pain in Dutch primary care. The Dutch College of General Practitioners (NHG) guideline for Pain treatment strongly advises against long-term prescribing of opioids to patients with chronic pain, as the benefits generally do not outweigh the risks.[24] However, our results

show that this practice still occurs in many general practices. In addition, our results show high variability, with ~20% of practices being statistical outliers for chronic high-dose opioid prescribing. Most outliers had lower-than-average prescribing rates, and only a few practices prescribed more than average. On average, the high-prescribing practices were larger, with patients from lower socioeconomic status (SES) and higher urbanised areas than low-prescribing practices. We also found that chronic high-dose prescribing was entirely absent in many practices. This raises the question of whether this variation in prescribing is accompanied by a similarly large variation in the quality of pain care and what level of opioid prescribing could be considered "optimal". For example, if there were no differences in the quality of pain care between average practices and low prescribing practices, this would suggest that a strong reduction of opioid prescribing would be possible without compromising pain care. A similar argument is made by Curtis et al. [25], who investigated geographic variation in high-dose opioid prescribing in England. They found that if every practice in England prescribed high-dose opioids at the same rate as the lowest decile, a reduction of over 90% in high-dose prescribing could be achieved. However, this study did not consider the quality of care, making it difficult to directly correlate prescribing rates with patient outcomes.

Other observational research suggests that a reduction in opioid prescribing is indeed possible without compromising the quality of pain care. For example, a recent Dutch study in a large academic hospital observed a 41% reduction in the number of patients being discharged with an oral opioid after a surgical procedure when oxycodone was replaced by morphine in their guidelines.[26] The transition from oxycodone to morphine disrupted the habitual prescription of oxycodone, potentially making healthcare providers more cautious and aware. In addition to reducing post-operative prescribing, the switch resulted in a 35% drop in the total oral morphine equivalents (OME) administered during hospital admission. Pain intensity scores were not affected, suggesting a degree of unnecessary prescribing pre-intervention. Further research into the difference in the quality of pain care between high, low, and average prescribers of opioids across various healthcare settings could further clarify the relationship between chronic prescribing patterns and patient outcomes. However, it should be noted that reducing opioid prescribing should not be seen as a goal in and of itself and that improving pain management and reducing risks should be the primary objectives.

Non-pharmacological pain management and patient engagement

Non-pharmacological treatments are increasingly recognised as the preferred approach for treating chronic pain, owing to their effectiveness in the long-term

and absence of negative effects, such as tolerance and addiction.[27] However, these therapies, including cognitive-behavioural therapy, physical therapy, graded exposure, mindfulness, and distraction techniques, differ from pharmacological options in that they require active engagement by the patient. In contrast, pharmacological options only require the patient to take a pill according to schedule. Therefore, the success of non-pharmacological therapies relies heavily on the patient's willingness to commit to these therapies. It is, therefore, vital to emphasise the advantages of non-pharmacological treatments in chronic pain and stress the patient's role in the success of these therapies. Moreover, if medication is prescribed, it should always be part of a multimodal approach that includes non-pharmacological treatments.[28] Although choosing the appropriate type of therapy is important, it is equally important to establish what constitutes a successful outcome. In some cases, a (strong) reduction in pain might not be achievable, making pain scores a poor metric for success.[28] Instead, treatment success should be evaluated broadly and include improved functionality, quality of life, and increased ability to do daily activities.

Psychiatric risk factors for chronic opioid use

An important step in reducing opioid-related harm is identifying patients at risk of developing chronic opioid use. Several studies show that patients with a psychiatric disorder might be a particularly at-risk population. For example, a US study showed that more than half of all opioids were prescribed to patients with a psychiatric disorder. At the same time, this group only makes up 16% of the total population.[29] In Chapter 5, we investigated if patients with a psychiatric disorder had a greater risk of transitioning into chronic opioid use after a first opioid prescription than patients without such disorders. Our results show that patients with a psychiatric disorder had nearly double the risk of transitioning into chronic high-dose opioid use. The increased risk was especially prominent in patients with specifically psychotic disorders, substance use disorders, neurocognitive disorders, and multiple co-occurring psychiatric episodes. When these results are viewed in a broader context, they further support the notion that pain and psychiatry are closely related[30,31] and that treating psychiatric disorders and managing pain requires an integrated, multidimensional approach. When doing so, it is key to recognise that patients with psychiatric disorders have an equal right to effective pain management, including opioids when indicated, as any other patient. Pain management in these patients should be more closely monitored to prevent chronic high-dose opioid use, and mental health professionals should be consulted at an early stage to treat psychiatric conditions where possible.

Tackling And Preventing the Opioid Epidemic (TaPtOE) consortium

Although this thesis systematically explores opioid use and misuse in the Netherlands, it is limited in scope because of its epidemiological focus. The broader Dutch TaPtOE consortium (which includes this project) aims to provide a more comprehensive view of the opioid situation in the Netherlands. It was funded by the Dutch Research Council (NWO), aiming to prevent an opioid crisis in the Netherlands. Its research goals include all aspects of prescription opioid use and misuse in the Netherlands. This includes examining everything from the initial prescription to long-term use and eventual discontinuation. To reduce chronic opioid use and misuse, the project aims to develop tools to identify patients at risk and develop alternative (non-opioid) treatments for pain and interventions to reduce misuse. In addition to the medical domain, TaPtOE also aims to provide insight into the extent of illicit prescription opioid use and how they are acquired, for example, via the dark web. Although this thesis focuses on the epidemiological aspects of opioid use and its harms, the broader scope of TaPtOE is invaluable when discussing prescription opioid use in the Netherlands. For example, a study by Davies et al. qualitatively examined personal factors and trajectories leading to prescription opioid use disorder.[32] The study revealed that patients often received insufficient information about opioid risks and safe usage and highlighted how ineffective pain management drives patients toward misuse. At the same time, a lack of effective monitoring allows for easy access to refills. They stress the need for patient education, prescription oversight, and proper guidance. This qualitative study offers a detailed and personal view of the risks associated with prescription opioid use, complementing the broader epidemiological focus presented in this thesis.

Current initiatives across the Netherlands

In addition to TaPtOE, various other initiatives were launched in the Netherlands to address unnecessary opioid prescribing.[33] These initiatives primarily aim to educate healthcare providers and patients about responsible opioid use, monitor prescriptions, offer guidance on opioid tapering, provide specialised care for problematic opioid use, and enhance awareness. In the Arnhem-Nijmegen region, two new guidelines specifically stand out. First, the regional perioperative pain protocol adopts a multidimensional approach to pain management. Instead of relying primarily on pain scores (NRS scores), it emphasises patient satisfaction, restoration of functionality, non-pharmacological approaches, and patient education. The specialist in the hospital should prescribe the initial post-operative pain medication. It can contain opioids but is limited to the expected duration of the post-operative pain. If patients require additional analgesia beyond this initial post-discharge prescription, the GP should only prescribe a limited amount or refer

back to the specialist. This approach ensures patients take home a limited quantity of opioids, minimising the risk of prolonged use or misuse.

Second, the guideline for tapering opioids in primary care describes how opioids should be discontinued in patients currently using opioids chronically. It emphasises a gradual taper adjusted to the patient's needs and stresses the need for patient guidance and support. A referral to secondary psychiatric or addiction care should be considered when psychiatric comorbidities are present. The nationwide development of new guidelines targeting various healthcare domains underscores the urgency felt in addressing the rise of opioid prescriptions. Many of these guidelines underscore the significance of psychological or psychiatric guidance, especially for patients with complex needs, thereby acknowledging the connection between pain management and psychiatry.

Methodological and data challenges

Research into opioid use, misuse, and policy effectiveness faces various methodological and data challenges, in particular when relying on retrospective data from sources not specifically designed for opioid research. An important challenge is data quality and detailedness, as research that uses healthcare data is often limited to structurally recorded data, such as ATC-coded prescriptions or ICPC-coded disease episodes. Important data, such as the reason for prescribing or the prescriber's considerations, are usually missing from these datasets (Chapters 4 and 5). However, much extra detail is contained in the free-text portion of medical files, such as notes or letters. Traditionally, human interpretation is needed to extract these details in a suitable research format. However, this is impractical to do on a large scale (e.g. tens of thousands of files) because it is time-consuming and thus costly. Recent developments in artificial intelligence might change this, as current large language models (e.g. GPT-4) can comprehend and interpret free text much faster and more cheaply than humans. This technological advancement could unlock a vast amount of currently impractical data, allowing for a wider range of research questions to be answered.[34]

Future directions

Given the limited rates of opioid-related harm in the Netherlands, future research and interventions here should mainly focus on a) preventing unneeded (initiation of) opioid therapy, b) minimising transition to chronic opioid use after the start of therapy, and c) decreasing current chronic opioid use.

First, pain management guidelines should contain stricter criteria for starting opioid therapy, giving a more prominent position to alternative non-opioid and non-pharmacological pain management strategies. Regularly updating these guidelines should be part of a continuous quality improvement process. After a prescription for opioids, the risk of transitioning to chronic opioid use can be reduced by carefully monitoring patients and limiting post-operative prescribing. Periodic evaluation of the risks and benefits is key, especially in those at risk of chronic use. Current guidelines are vague on how this should be done and what factors should be considered. Pain management guidelines should provide further clarification on this topic. This could be done by establishing clear thresholds for initiating opioid therapy based on pain intensity, duration, and functional impairment. Guidelines should also outline monitoring strategies, including frequency of follow-ups, quantifiable parameters to monitor, signs of misuse, and ways to adjust therapy based on these follow-ups. Integrating risk assessment tools to identify patients prone to chronic use will help determine an appropriate monitoring strategy.

Second, future research should focus on the specific patient populations in which opioid prescribing can be safely reduced. Although current studies suggest that opioids are overprescribed, they do not detail the types of patients in which initiation of opioid use can be avoided. A deeper analysis of existing data from hospitals or general practices that reduced their opioid prescribing using a simple intervention (e.g. prescribing morphine instead of oxycodone or limiting the number of pills prescribed) could help elucidate the characteristics of patients in which prescribing could be reduced. An important prerequisite is that the intervention did not disproportionately affect the quality of pain care.

Another aspect to investigate is to what extent the specific type of opioid contributes to the development of chronic opioid use. Pharmacological effects or stigma associated with specific opioids could affect their propensity for chronic use or addiction. For example, there are signs that oxycodone is more addictive than other opioids[35], and morphine is still generally associated with end-stage illness.[36] However, research investigating the influence of these effects on practice is scarce and has thus far not resulted in a strong preference for a specific opioid in guidelines. Moreover, research indicates that, currently, the choice of opioid type is mostly subjective and strongly guided by the personal experience of the prescriber.[37]

Third, a problem central to research into prescription opioid use is the lack of a clear idea of what "inappropriate" or "unnecessary" use is. This problem partly stems from a lack of solid evidence for the efficacy of opioids for various types of pain, particularly

chronic non-cancer pain and the mere fact that pain is a subjective personal experience. Without a better understanding of the situations in which opioids provide benefits and what the universal outcome measures are to describe this situation, it becomes difficult to assess the degree of unnecessary opioid use. Conversely, assessing underprescribing is equally problematic. The appropriateness of an opioid prescription is also dependent on the range of pain treatment options available to both the physician and the patient. Without a clear framework to assess the appropriateness of an opioid prescription, prescription rates can only be high or low relative to other rates (e.g. rates from other countries), hindering a nuanced understanding of opioid use and its implications. As outlined in chapter 3, the use of uniform data and consistent definitions is crucial for advancing research in this field.

Conclusions

Although the Netherlands remains shielded from high levels of opioid-related harm compared to the US, the increase in prescription opioid use cannot be ignored. The variation in opioid prescribing in primary care suggests inconsistent healthcare quality regarding pain management, and the relationship between psychiatric disorders and chronic high-dose opioid use underscores the need for a multidimensional approach to pain, especially in patients with psychiatric comorbidities.

Going forward, it is imperative to develop pain guidelines that steer away from opioids as much as possible in situations where they have no benefit. At the same time, we must ensure that those who benefit from them retain access while preventing misuse.

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Chapter 8

Nederlandse samenvatting en algemene discussie

Opioïden zijn pijnstillers die in de geneeskunde al lange tijd gebruikt worden voor het behandelen van matig tot ernstige pijn. Ze worden gewonnen uit de papaver somniferum plant of chemisch gesynthetiseerd en omvatten stoffen zoals morfine, oxycodon en fentanyl. In de gezondheidzorg worden ze gebruikt voor het verlichten van pijn tijdens chirurgische ingrepen, bij de behandeling van kanker, tijdens palliatieve zorg en voor verschillende soorten acute pijn. Hoewel opioïden effectieve pijnstillers zijn, zijn ze door hun potentieel voor misbruik, afhankelijkheid en overdosering zowel een zegen als een vloek.

Het gebruik van receptplichtige opioïden is in Nederland sterk toegenomen tussen 2008 en 2015, voornamelijk door een toename in het gebruik van oxycodon. In 2015 werd oxycodon het meeste gebruikt van alle opioïden met ongeveer 350.000 mensen die het middel gebruikten. Dit was een verdubbeling ten opzicht van 2012. Andere veelgebruikte opioïden waren fentanyl, morfine en buprenorfine. In totaal waren er meer dan een half miljoen mensen die in 2015 een receptplichtig opioïd gebruikten.

Er zijn verschillende signalen die erop wijzen dat deze toename zorgwekkend kan zijn en een potentieel probleem voor de volksgezondheid. Nieuwsberichten in nationale media hebben bijvoorbeeld het gebruik van receptplichtige opioïden in verband gebracht met verslaving en overdosering. Deze zorgen zijn niet ongegrond, aangezien de toenemende trend van opioïdgebruik op recept in Nederland sterk lijkt op het beginstadium van een probleem wat al langere tijd verwoestende gevolgen heeft in de Verenigde Staten: de zogeheten “opioïdencrisis”.

Het verloop van de opioïdencrisis in de Verenigde Staten kan opgedeeld worden in drie golven die elk gekenmerkt worden door sterfte aan verschillende soorten opioïden. De eerste golf begon rond 2000 en werd gekenmerkt door verslaving en overdoseringen door receptplichtige opioïden, met name oxycodon. De oorzaak hiervan was vooral marketing door de farmaceutische industrie waarin benadrukt werd dat opioïden niet verslavend zijn mits gebruikt onder medisch toezicht. Als reactie op de stijgende verslavings- en sterftecijfers werden maatregelen geïntroduceerd om het voorschrijven te beperken. Dit had echter als onbedoeld effect dat veel mensen die verslaafd waren geraakt aan receptplichtige opioïden overstapten naar illegale opioïden zoals heroïne. Dit luidde rond 2007 de tweede golf in, die gekenmerkt werd door een sterke toename in sterfte door heroïne. De derde golf, die begon in 2015, werd gekenmerkt door een toename in synthetisch gesynthetiseerde opioïden, voornamelijk illegaal gesynthetiseerde fentanyl. Deze synthetische opioïden kwamen op de illegale markt omdat ze goedkoper zijn om te produceren. Daarnaast zijn ze veel potenter dan heroïne, waardoor zelfs kleine hoeveelheden een

overdosering kunnen veroorzaken. Deze ontwikkelingen samen hebben geleid tot een voortdurende stijging van opioïd gerelateerde sterfte in de Verenigde Staten, waarbij er in 2020 meer dan 70.000 mensen overleden aan opioïden.

De stijging van het opioïdgebruik op recept in Nederland, gecombineerd met signalen van verslaving en overdosering, tegen de achtergrond van de Amerikaanse opioïdencrisis, kan worden gezien als een potentieel probleem voor de volksgezondheid. Er zijn gegevens beschikbaar over trends in het voorschrijven van opioïden in Nederland, maar een grondige analyse van de mogelijke gevolgen, zoals misbruik, verslaving en sterfte ontbreekt en een dergelijke analyse is cruciaal om te bepalen óf, en wat voor, interventie nodig is.

Samenvatting van de hoofdstukken

Het doel van dit proefschrift was 1) het onderzoeken van de omvang van het gebruik en misbruik van voorgeschreven opioïden in Nederland, 2) het geven van een overzicht van verschillende definities van opioïdengebruik en soorten opioïd-gerelateerde schade, en een analyse geven van mogelijke drijfveren voor het gebruik van voorgeschreven opioïden en gerelateerde schade, 3) aanknopingspunten vinden voor kwaliteitsverbetering in pijnbehandeling door praktijkvariatie in het voorschrijven van opioïden te onderzoeken, en 4) mogelijke psychiatrische risicofactoren voor chronisch hoog gedoseerd opioïdengebruik te onderzoeken.

Hoofdstuk 2: Trends in gebruik en misbruik van opioïden in Nederland

Om het huidige gebruik van receptplichtige opioïden en mogelijke negatieve gevolgen in Nederland te onderzoeken, hebben we gegevens verkregen uit verschillende landelijke databases. Uit onze resultaten blijkt dat tussen 2008 en 2017 het aantal opioïdengebruikers op recept bijna verdubbelde, voornamelijk vanwege een sterke toename in het gebruik van oxycodon. Het aantal opioïd-gerelateerde ziekenhuisopnames verdrievoudigde in dezelfde periode van 2,5 naar 7,8 per 100.000. Het aantal patiënten in verslavingszorg voor opioïde gebruikstoornissen, anders dan heroïne, nam toe van 3,1 per 100.000 in 2008 naar 5,6 per 100.000 in 2015. Opioïd-gerelateerde sterfte was stabiel tussen 2008 en 2014, met ongeveer 0,21 sterfgevallen per 100.000, maar steeg naar 0,65 per 100.000 in 2017. Over het algemeen laten de resultaten een toename in het gebruik van voorgeschreven opioïden zien, met parallel daaraan een toenemende trend in verschillende indicatoren voor misbruik. In vergelijking met de Verenigde Staten, Canada en verschillende andere Europese landen is de opioïd-gerelateerde schade in Nederland echter nog steeds laag.

Hoofdstuk 3: Het monitoren van opioïden in Europa: De noodzaak voor gedeelde definities en het meten van oorzaken van toegenomen opioïdengebruik en gerelateerde schades

Dit commentaar verkent hoe verschillende definities van opioïdengebruik, verkeerd gebruik, misbruik en sterfte onderzoek kunnen bemoeilijken. Daarnaast bespreken we verschillende mogelijke oorzaken voor toegenomen opioïdengebruik en gerelateerde schade in Europa. Ten slotte bevelen we aan om definities te harmoniseren en verder onderzoek te doen naar de factoren die het gebruik en misbruik van opioïden in Europa stimuleren, om zo een beter beeld te krijgen van opioïdengebruik en -misbruik in Europa.

Hoofdstuk 4: Praktijkvariatie in het voorschrijven van opioïden voor niet-kankerpijn in de Nederlandse eerstelijnszorg: een retrospectieve databasestudie

Dit onderzoek analyseert variatie in het voorschrijven van opioïden voor chronische niet-kankerpijn in de Nederlandse eerstelijnszorg. Er is hiervoor gebruik gemaakt van gegevens van ongeveer 10% van alle Nederlandse huisartsenpraktijken, wat overeenkomt met ongeveer een miljoen patiënten in 380 praktijken van 2017 tot 2019. In het meest recente jaar (2019) was er een 7.5-voudige variatie tussen de bovenste en onderste 5% van de praktijken in het percentage patiënten dat chronische hoog gedoseerde opioïden kreeg voorgeschreven. Daarnaast waren 14% van de praktijken statistische uitschieters. Praktijken met een hoog percentage patiënten met chronisch hoog gedoseerde opioïdenrecepten waren groter en hadden meer patiënten uit lagere inkomensklassen en dichter bevolkte gebieden. Deze grote variatie duidt op mogelijk ongepast voorschrijven van opioïden en kan aanknopingspunten bieden voor kwaliteitsverbetering.

Hoofdstuk 5: Psychiatrische risicofactoren voor chronisch hoog gedoseerd opioïden voorschrijven: een cohortstudie gebaseerd op huisartsendata

Deze studie had tot doel om te onderzoeken of de aanwezigheid van een psychiatrische stoornis geassocieerd is met daaropvolgend chronisch hoog gedoseerd opioïdengebruik (≥90 dagen; ≥50mg orale morfine-equivalenten) in patiënten in de eerstelijnszorg die nieuw opioïden startten. Gegevens van 137.762 eerstelijnspatiënten die tussen 2011-2017 nieuw met een opioïd begonnen, zijn geïncludeerd uit de Nivel Zorgregistraties Eerste Lijn database. We vonden dat de aanwezigheid van een psychiatrische stoornis voorafgaand aan het starten van opioïden het risico verhoogt op het later krijgen van chronisch hoog gedoseerd opioïden. Vooral patiënten met meerdere psychiatrische stoornissen lopen risico. Daarom wordt zorgvuldige monitoring en optimale behandeling

van psychiatrische aandoeningen geadviseerd wanneer er in deze populatie met opioïden wordt gestart.

Hoofdstuk 6: Een Europees perspectief op de Noord-Amerikaanse opioïdencrisis

Hoofdstuk 6 bespreekt de Noord-Amerikaanse opioïdencrisis vanuit een Europees perspectief, waarbij wordt benadrukt dat veel van de aanbevelingen die gedaan zijn door de Stanford-Lancet Commissie voor de VS en Canada, in Europa al een realiteit zijn. Verder benadrukken we de rol van universele gezondheidszorg en de beschikbaarheid van evidence-based verslavingszorg in het voorkomen van een opioïdencrisis in Europa.

Algemene discussie

Verklaring van de toename van het gebruik van voorgeschreven opioïden in Nederland

In Hoofdstuk 2 hebben we een combinatie van landelijke databases gebruikt om trends in het gebruik van receptplichtige opioïden en de daarmee samenhangende schade in Nederland te onderzoeken. Hoewel onze resultaten een stijgende trend lieten zien in het gebruik van receptplichtige opioïden, met parallel daaraan een toename in opioïdgerelateerde schade, waaronder sterfte, zijn deze getallen nog steeds erg laag in vergelijking met de VS. In 2017 bedroeg de opioïdgerelateerde sterfte in Nederland 0,65 per 100.000, vergeleken met 14,9 in de VS.[1]

Na 2017 nam het aantal patiënten dat een opioïd voorgeschreven kreeg af, en daalde het met 8,1% in 2020 ten opzichte van 2017. Hun aantal nam daarna weer toe, mogelijk als gevolg van de COVID-19-pandemie. In 2022 was het aantal patiënten dat een opioïd voorgeschreven kreeg weer met 6,2% toegenomen ten opzichte van 2020. Er ontstaat echter een iets ander beeld wanneer we kijken naar het aantal recepten in plaats van het aantal patiënten. Het aantal opioïdenrecepten neemt toe tot 2017, en neemt daarna af tot 2020 en stabiliseert daarna. Hoewel er dus een toename geweest is in het aantal patiënten, zijn er minder recepten per patiënt, wat duidt op meer kortdurend en minder chronisch gebruik van opioïden.

Dit zou kunnen betekenen dat, hoewel het aantal patiënten dat opioïden gebruikt is toegenomen, artsen wel voorzichtiger zijn geworden met voorschrijven. Definitieve gegevens hierover ontbreken, en verder onderzoek zou nodig zijn om het effect van de COVID-19 pandemie op het gebruik van opioïden, en andere veranderingen in voorschrijfgedrag sinds 2018 op te helderen.

Wat betreft opioïdgerelateerde sterfte rapporteert de Nederlands Drug Monitor (NDM) fluctuerende opioïd-gerelateerde sterfte vanaf 2017 die lijkt te stabiliseren in 2020-2021.[2] In vergelijking met 2017 namen opioïdgerelateerde sterfgevallen met 14% toe in 2021, wat nog steeds laag is vergeleken met de rest van Europa en de VS. Deze gegevens moeten voorzichtig worden geïnterpreteerd, aangezien ze geen onderscheid maken tussen illegale opioïden en receptplichtige opioïden. Bovendien zijn ze onderhevig aan veranderingen in registratieprocedures en post-mortem toxicologisch onderzoek. Al met al lijken er geen tekenen te zijn van een escalerende opioïdensterfte in Nederland.

Hoewel een opioïdencrisis van Amerikaanse omvang zich niet lijkt te ontwikkelen in Nederland, hebben we wel een substantiële toename van het voorschrijven van opioïden gezien en het verklaren van deze toename is nog steeds belangrijk. Wij denken dat meerdere factoren kunnen hebben bijgedragen. Ten eerste vergrijst de bevolking van Nederland, wat gepaard gaat met pijnlijkere aandoeningen (bijv. artrose en lage rugpijn) waarvoor een opioïde zou kunnen worden voorgeschreven. Onderzoek toont inderdaad aan dat de meeste opioïden worden voorgeschreven aan oudere patiënten.[3] Vergrijzing kan echter maar een klein deel verklaren, aangezien het percentage 65+'ers tussen 2007-2018 slechts is gestegen van 15% naar 19%.[4] Ten tweede speelt een verhoogd bewustzijn van de schade veroorzaakt door andere pijnstillers, voornamelijk niet-steroïde anti-inflammatoire geneesmiddelen (NSAID's; bijv. ibuprofen of diclofenac), waarschijnlijk een rol. NSAID's kunnen gastro-intestinale bloedingen, nierschade en cardiovasculaire problemen veroorzaken, vooral bij oudere patiënten. Artsen zouden daarom in deze populatie de voorkeur kunnen geven aan het voorschrijven van opioïden in plaats van NSAID's. Bedene et al. ontdekten inderdaad dat tussen 2013 en 2017 het voorschrijven van NSAID's afnam en het voorschrijven van opioïden toenam,[5] wat wijst op een verschuiving in het voorschrijven van NSAID's naar opioïden. Ten derde is de aandacht voor pijnbestrijding in ziekenhuizen sinds het begin van de jaren 90 toegenomen. Vervolgens is in 2009 een programma gestart om de vroege herkenning en behandeling van pijn in Nederlandse ziekenhuizen te vergroten, waarbij werd opgeroepen tot het regelmatig meten van pijnscores en tijdige behandeling van pijn. De pijnscores die tijdens ziekenhuisopnames werden geregistreerd, werden ook gebruikt als kwaliteitsindicatoren voor ziekenhuizen.[6]

Er is een parallel te trekken tussen dit Nederlandse programma en de campagne "Pain as the Fifth Vital Sign" in de VS. De American Pain Society introduceerde deze campagne eind jaren negentig om de gezondheidszorg bewust te maken van adequate pijnbehandeling. De campagne riep ook op tot het routinematige meten van pijnscores in verschillende settings, waaronder ziekenhuizen en poliklinieken.[7]

Achteraf gezien heeft deze campagne onbedoeld bijgedragen aan het overmatig voorschrijven van opioïden en de daaropvolgende opioïdencrisis.[8] Ten slotte kan marketing voor opioïden (met name oxycodon) hebben bijgedragen aan een toename van het voorschrijven van opioïden. Marketing van geneesmiddelen gericht op patiënten is in Nederland echter niet toegestaan. Nederlandse gegevens over de rol van marketing gericht op artsen ontbreken, waardoor het moeilijk is om de invloed hiervan in te schatten.

Is er een Europese opioïdencrisis?

Het gebruik van receptplichtige opioïden is de afgelopen decennia ook in de meeste andere Europese landen toegenomen. Net als in Nederland lijken de meeste Europese landen echter niet zoveel schadelijke effecten te ondervinden van deze toename in vergelijking met de VS. Volgens het Europees Waarnemingscentrum voor drugs en drugsverslaving (EMCDDA) bedroeg de sterfte als gevolg van een overdosis opioïden in de EU in 2017 ongeveer 1,2 per 100.000 inwoners.[9] Europa is echter heterogeen met aanzienlijke verschillen tussen landen. Een analyse van Pierce et al.[10] laat een hoge opioïd-gerelateerde sterfte zien in bepaalde Europese landen. De Britse eilanden, met name Schotland, hebben bijzonder hoge sterftecijfers. In 2018 had Schotland 22,7 fatale overdoses opioïden per 100.000 inwoners, wat hoger was dan de VS (14,6 per 100.000 in 2018[11]). In tegenstelling tot de VS zijn er echter geen tekenen dat het voorschrijven van opioïden voor pijn hiervan de oorzaak was.[12] In plaats daarvan zijn de risicofactoren die de opioïd-gerelateerde sterfte in Schotland verhogen, het gelijktijdig gebruik van opioïden met andere psychotrope geneesmiddelen (benzodiazepinen, gabapentinoïden en Z-drugs zoals zolpidem en zopiclon), beperkte toegang tot verslavingszorg, de hoge gemiddelde leeftijd van mensen die opioïden misbruiken, en armoede en kansarmheid.[12,13] Een ander voorbeeld van een hoge opioïd-gerelateerde sterfte in Europa is Estland, dat tussen 2003 en 2017 hoge sterfte had als gevolg van illegaal vervaardigde fentanyl (IMF). De piek werd bereikt in 2012, met een sterftecijfer van 13 per 100.000 inwoners.[14] De belangrijkste oorzaak van het toegenomen IMF-gebruik was een afname van de beschikbaarheid van heroïne, en IMF vulde het gat in de illegale markt.[14] Over het algemeen wordt Europa momenteel niet geconfronteerd met een opioïdencrisis die vergelijkbaar is met de VS, hoewel Schotland wel een hoog opioïd-gerelateerd sterftecijfer heeft.

Waarom is er geen Europese opioïdencrisis?

Het is aannemelijk dat de verschillen tussen Europa en de Verenigde Staten met betrekking tot opioïd-gerelateerde schade voortkomen uit fundamentele verschillen in zorgstelsels, voorschrijfpraktijken, geneesmiddelenregelgeving en culturele verschillen.[15] De structuur van het gezondheidszorgstelsel in de meeste Europese landen, met name

universele dekking met lage kosten voor patiënten, speelt waarschijnlijk een belangrijke rol bij het voorkomen van schade door het voorschrijven van opioïden (Hoofdstuk 6). Met toegankelijke, goedkope zorg kunnen patiënten kiezen voor de meest geschikte behandeling voor chronische aandoeningen zonder financiële lasten. De centrale rol van huisartsen in de meeste Europese landen minimaliseert ook de versnippering van de zorg en vergroot het toezicht op het voorschrijven van opioïden, waardoor het risico op dokter shopping (het bezoeken van meerdere artsen om een recept te bemachtigen) en misbruik worden verminderd. Bovendien zorgt de wijdverbreide beschikbaarheid van verzekerde verslavingszorg voor ondersteuning van mensen die worstelen met opioïdenverslaving, waardoor de kans op escalatie verder wordt verkleind.

Bestaat er een risico op een toekomstige Europese opioïdencrisis?

Men zou kunnen stellen dat een zekere nonchalance, en het idee dat het wel goed zat, een belangrijke rol heeft gespeeld bij het ontstaan en het laten escaleren van de opioïdencrisis in de VS, en dat dit ook een risico voor Europa zou kunnen vormen. De risico's van opioïden, waaronder oxycodon, waren al bekend in de jaren '60[16], maar belangrijke waarschuwingssignalen van een aankomend probleem werden genegeerd. Een publicatie in de Lancet in 2000[17] signaleerde bijvoorbeeld een sterke toename van de consumptie van oxycodon in de VS, maar concludeerde vervolgens dat dit een weerspiegeling was van verbeterde pijnbestrijding. Dit sluit perfect aan bij de gedachte van die tijd, dat chronische pijn onderbehandeld was en opioïden niet verslavend waren bij gebruik in een medische context. Achteraf gezien waren de eerste tekenen van een opkomende crisis er wel. Toch werden ze genegeerd of verkeerd geïnterpreteerd ten gunste van de gemakkelijke conclusie dat opioïden de remedie waren voor een epidemie van pijn; een conclusie die sterk werd gesteund door de farmaceutische industrie.[18] Deze historische nonchalance onderstreept hoe het negeren vroege waarschuwingssignalen en zich berusten in een verhaal wat goed uitkomt een snelle interventie kan belemmeren, waardoor een beheersbaar probleem kan escaleren tot een onbeheersbare crisis.

Hoewel de Europese zorgstelsels en de huidige opioïdentrends verschillen van die in de VS, laat de situatie in Estland zien dat verschuivingen op de illegale drugsmarkten snel kunnen leiden tot een hoger sterftecijfer. Vooral de instroom van IMF of andere synthetische opioïden kan een risico vormen.[19] Deze verbindingen zijn zeer potent en goedkoop om te produceren[20], en de opkomst ervan op de Europese drugsmarkt zou kunnen leiden tot een snelle escalatie van opioïd-gerelateerde sterfte, zoals in de VS en Estland. Daarom mag Europa, ondanks het ontbreken van een opioïdencrisis, niet nonchalant worden. Het blijft van groot belang om verschuivingen in drugstrends te volgen en potentiële bedreigingen snel aan te pakken. De focus moet niet alleen

liggen op voorgeschreven opioïden, beseffende dat een crisis zich op verschillende manieren kan manifesteren.

Kwaliteit van het voorschrijven van opioïden in Nederland

Om de kwaliteit van het voorschrijven van opioïden in Nederland verder te onderzoeken, hebben we gekeken naar variatie in het voorschrijven van chronisch hoog gedoseerde opioïden tussen huisartsenpraktijken (Hoofdstuk 3). Bij praktijkvariatieonderzoek worden twee soorten variatie onderscheiden: gerechtvaardigde en ongerechtvaardigde variatie. Gerechtvaardigde variatie omvat alle variatie die kan worden verklaard door voorkeuren van de patiënt, medische behoeften en richtlijnen uit evidence-based medicine.[21,22] Ongerechtvaardigde variatie daarentegen is alle variatie die niet door deze factoren kan worden verklaard.[23] Ongerechtvaardigde variatie is potentieel problematisch omdat het kan duiden op een gebrek aan standaardisatie in zorg, wat kan leiden tot ongepast gebruik en ongelijkheden op gezondheidsgebied, wat een negatieve invloed heeft op de behandeling van een patiënt. Het onderzoeken van ongerechtvaardigde variatie is relevant omdat het aanknopingspunten kan bieden voor kwaliteitsverbetering door inconsistenties in zorggebruik en het gedrag van zorgverleners aan het licht te brengen.[23]

In hoofdstuk 4 onderzochten we de praktijkvariatie van chronisch (≥ 90 dagen) hoog gedoseerde (≥ 90 orale morfine-equivalenten) opioïden voor niet-kankerpijn in de Nederlandse eerstelijnszorg. De richtlijn voor pijn van het Nederlands Huisartsen Genootschap (NHG) raadt het langdurig voorschrijven van opioïden aan patiënten met chronische pijn sterk af, omdat de voordelen over het algemeen niet opwegen tegen de risico's.[24] Uit onze resultaten (Hoofdstuk 4) blijkt echter dat dit in de praktijk nog steeds voorkomt. Bovendien laten onze resultaten een hoge variabiliteit zien, waarbij ~20% van de praktijken statistische uitschieters zijn voor het chronisch voorschrijven van hoog gedoseerde opioïden. De meeste uitschieters schreven dit echter minder vaak dan gemiddeld voor, en slechts een paar praktijken schreven meer dan gemiddeld voor. De bovengemiddeld vaak voorschrijvende praktijken waren gemiddeld groter, met patiënten met een lagere sociaaleconomische status (SES) en uit dichter bevolkte gebieden dan praktijken met een laag voorschrijfgedrag. We zagen ook dat chronisch voorschrijven van hoog gedoseerde opioïden in veel praktijken volledig afwezig was. Dit roept de vraag op of deze variatie in het voorschrijven gepaard gaat met een even grote variatie in de kwaliteit van de pijnbehandeling en welk niveau van het voorschrijven van opioïden dan als "optimaal" kan worden beschouwd. Als er bijvoorbeeld geen verschillen zouden zijn in de kwaliteit van de pijnzorg tussen gemiddelde praktijken en lage voorschrijfpraktijken, zou dit suggereren dat een sterke vermindering van het voorschrijven van opioïden

mogelijk zou zijn zonder dat dit ten koste gaat van de kwaliteit van pijnbehandeling. Een soortgelijk argument wordt aangevoerd door Curtis et al. [25], die de geografische variatie in het voorschrijven van hoog gedoseerde opioïden in Engeland onderzocht. Ze stelden dat als elke huisartsenpraktijk in Engeland hoog gedoseerde opioïden voorschreef in dezelfde mate als de laagste 10%, een vermindering van meer dan 90% in het voorschrijven van hoog gedoseerde opioïden zou kunnen worden bereikt. In deze studie werd echter geen rekening gehouden met de kwaliteit van de zorg, waardoor het moeilijk was om het voorschrijfpercentage direct te correleren met patiëntuitkomsten.

Ander observationeel onderzoek suggereert dat een vermindering van het voorschrijven van opioïden inderdaad mogelijk is zonder de kwaliteit van de pijnzorg in gevaar te brengen. Een recent Nederlands onderzoek in een groot academisch ziekenhuis constateerde bijvoorbeeld een vermindering van 41% in het aantal patiënten dat na een chirurgische ingreep met een opioïde werd ontslagen toen oxycodon werd vervangen door morfine in de richtlijnen.[26] De overgang van oxycodon naar morfine verstoorde het routinematig voorschrijven van oxycodon, waardoor artsen mogelijk voorzichtiger en bewuster werden. Naast het verminderen van postoperatief voorschrijven, resulteerde de overstap naar morfine in een daling van 35% in de totale orale morfine-equivalenten (OME) die tijdens ziekenhuisopname werden toegediend. Pijnscores werden niet beïnvloed, wat suggereert dat er vóór interventie onnodig veel werd voorgeschreven. Verder onderzoek naar het verschil in de kwaliteit van zorg tussen hoge, lage en gemiddelde voorschrijvers van opioïden in verschillende zorginstellingen zou de relatie tussen het voorschrijven van opioïden en patiëntuitkomsten verder kunnen verduidelijken. Echter, het verminderen van het voorschrijven van opioïden moet niet een doel op zich worden gezien. Het verbeteren van zorg en het verminderen van risico's omtrent opioïden zouden de voornaamste doelen moeten zijn.

Niet-medicamenteuze pijnbestrijding en betrokkenheid van de patiënt

Niet-medicamenteuze behandelingen worden steeds meer erkend als de voorkeursbehandeling van chronische pijn vanwege hun effectiviteit op de lange termijn en de afwezigheid van negatieve effecten, zoals tolerantie en verslaving.[27] Deze therapieën, waaronder cognitieve gedragstherapie, fysiotherapie, mindfulness en afleidingstechnieken, verschillen echter van farmacologische opties doordat ze actieve betrokkenheid van de patiënt vereisen. Farmacologische opties daarentegen vereisen alleen dat de patiënt een pil volgens schema inneemt. Daarom is het succes van niet-medicamenteuze therapieën sterk afhankelijk van de bereidheid van de patiënt om zich aan deze therapieën te committeren. Het is daarom van belang om de voordelen van niet-medicamenteuze behandelingen bij chronische

pijn te benadrukken en de rol van de patiënt zelf in het succes van deze therapieën te benadrukken. Als medicatie toch wordt voorgeschreven, moet deze altijd deel uitmaken van een multimodale aanpak die ook niet-medicamenteuze behandelingen bevat.[28] Afgezien van het kiezen van de juiste therapie, is het net zo belangrijk om vast te stellen wat een succesvol resultaat is. In sommige gevallen is een (sterke) vermindering van pijn mogelijk niet haalbaar, waardoor pijnscores een slechte maatstaf voor succes zijn.[28] In plaats daarvan moet het succes van de behandeling breed worden geëvalueerd en een verbeterde functionaliteit, kwaliteit van leven en een groter vermogen om dagelijkse activiteiten uit te voeren omvatten.

Psychiatrische risicofactoren voor chronisch opioïdengebruik

Een belangrijke stap in het verminderen van opioïd-gerelateerde schade is het identificeren van patiënten die het risico lopen chronisch opioïdengebruik te ontwikkelen. Verschillende onderzoeken tonen aan dat patiënten met een psychiatrische stoornis in het bijzonder risico kunnen lopen. Zo bleek uit een Amerikaans onderzoek dat meer dan de helft van alle opioïden werd voorgeschreven aan patiënten met een psychiatrische stoornis. Tegelijkertijd maakt deze groep slechts 16% uit van de totale bevolking.[29] In hoofdstuk 5 onderzochten we of patiënten met een psychiatrische stoornis een groter risico hadden op chronisch opioïdengebruik na een eerste opioïdenrecept dan patiënten zonder dergelijke stoornissen. Onze resultaten lieten zien dat patiënten met een psychiatrische stoornis bijna een twee keer zo groot risico hadden op chronisch hoog gedoseerd opioïdengebruik. Het verhoogde risico was vooral aanwezig bij patiënten met psychotische stoornissen, stoornissen in het gebruik van middelen, neurocognitieve stoornissen en patiënten met meerdere psychiatrische aandoeningen. Wanneer deze resultaten in een bredere context worden bekeken, ondersteunen ze het idee dat pijn en psychiatrie nauw met elkaar verbonden zijn[30,31] en dat het behandelen van psychiatrische stoornissen en het behandelen van pijn een geïntegreerde, multidimensionale aanpak vereisen. Daarbij is het van belang om te erkennen dat patiënten met psychiatrische stoornissen evenveel recht hebben op effectieve pijnbestrijding, inclusief opioïden indien nodig, als elke andere patiënt. Pijnbestrijding bij deze patiënten moet echter nauwlettender worden gevolgd om onnodig chronisch gebruik van opioïden te voorkomen, en professionals in de geestelijke gezondheidszorg moeten in een vroeg stadium worden geraadpleegd om psychiatrische aandoeningen waar mogelijk te behandelen.

Aanpakken en voorkomen van een opioïdencrisis (TaPtOE consortium)

Hoewel dit proefschrift systematisch het gebruik en misbruik van opioïden in Nederland onderzoekt, is het beperkt in reikwijdte vanwege de epidemiologische focus. Het bredere Nederlandse TaPtOE-consortium (waar dit project deel van

uitmaakt) heeft tot doel een uitgebreider beeld te geven van de opioïdensituatie in Nederland. Het werd gefinancierd door de Nederlandse Organisatie voor Wetenschappelijk Onderzoek (NWO), met als doel een opioïdencrisis in Nederland te voorkomen. De onderzoeksdoelen gaan over alle aspecten van het gebruik en misbruik van receptplichtige opioïden in Nederland. Dit omvat het onderzoeken vanaf een eerste recept tot langdurig gebruik en het uiteindelijk stoppen van opioïden. Om chronisch gebruik en misbruik van opioïden te verminderen, heeft het project tot doel instrumenten te ontwikkelen om risicopatiënten te identificeren en alternatieve (niet-opioïde) behandelingen voor pijn en interventies te ontwikkelen om misbruik te verminderen. Naast het medische domein wil TaPtOE ook inzicht geven in de omvang van het illegale gebruik van receptplichtige opioïden en hoe deze worden verkregen, bijvoorbeeld via het dark web. Hoewel dit proefschrift zich richt op de epidemiologische aspecten van opioïdengebruik en de schade ervan, is de bredere reikwijdte van TaPtOE noodzakelijk om een compleet beeld te krijgen van het gebruik van receptplichtige opioïden in Nederland. Een studie van Davies et al. onderzocht bijvoorbeeld kwalitatief hoe persoonlijke factoren en trajecten leiden tot een stoornis in het gebruik van receptplichtige opioïden.[32] Uit de studie bleek dat patiënten vaak onvoldoende informatie kregen over de risico's van opioïden en veilig gebruik en benadrukte hoe ineffectieve pijnbestrijding patiënten tot misbruik drijft. Tegelijkertijd zorgt een gebrek aan effectieve monitoring voor het gemakkelijk krijgen van herhaalrecepten. Ze benadrukken de noodzaak van patiëntenvoorlichting, toezicht op het voorschrijven en goede begeleiding. Deze kwalitatieve studie biedt een gedetailleerd en persoonlijk beeld van de risico's die gepaard gaan met het gebruik van opioïden op recept en vult de bredere epidemiologische focus aan die in dit proefschrift wordt gepresenteerd.

Lopende initiatieven in Nederland

Naast TaPtOE zijn er in Nederland diverse andere initiatieven gestart om onnodig voorschrijven van opioïden aan te pakken.[33] Deze initiatieven zijn in de eerste plaats gericht op het voorlichten van zorgverleners en patiënten over verantwoord opioïdengebruik, het monitoren van recepten, het geven van advies over het afbouwen van opioïden, het bieden van gespecialiseerde zorg voor problematisch opioïdengebruik en het vergroten van het bewustzijn voor de risico's. In de regio Arnhem-Nijmegen vallen twee nieuwe richtlijnen specifiek op. Ten eerste hanteert het regionale perioperatieve pijnprotocol een multidimensionale benadering van pijnbestrijding. In plaats van voornamelijk te vertrouwen op pijnscores (VAS-scores), legt het de nadruk op patiënttevredenheid, herstel van functionaliteit, niet- medicamenteuze benaderingen en patiëntenvoorlichting. De specialist in het ziekenhuis moet de eerste pijnmedicatie na een operatie voorschrijven. Het kan opioïden bevatten, maar is in ieder geval

beperkt tot de verwachte duur van de postoperatieve pijn. Als patiënten naast dit eerste recept na ontslag aanvullende pijnstilling nodig hebben, mag de huisarts slechts een beperkte hoeveelheid extra voorschrijven of terugverwijzen naar de specialist. Deze aanpak zorgt ervoor dat patiënten een beperkte hoeveelheid opioïden mee naar huis nemen, waardoor het risico op langdurig gebruik of misbruik wordt geminimaliseerd.

Ten tweede beschrijft de richtlijn voor het afbouwen van opioïden in de eerste lijn hoe opioïden moeten worden afgebouwd bij patiënten die momenteel chronisch opioïden gebruiken. Het legt de nadruk op een geleidelijke afbouw die is afgestemd op de behoeften van de patiënt en benadrukt de noodzaak van begeleiding en ondersteuning van de patiënt. Een verwijzing naar de tweedelijns psychiatrische of verslavingszorg kan worden overwogen wanneer er sprake is van een psychiatrische comorbiditeit. De landelijke ontwikkeling van nieuwe richtlijnen gericht op verschillende zorgdomeinen onderstreept de urgentie die wordt gevoeld bij het aanpakken van de toename in het gebruik van opioïden. Veel van deze richtlijnen onderstrepen het belang van psychologische of psychiatrische begeleiding, vooral voor patiënten met complexe behoeften, en erkennen daarmee het verband tussen pijnbestrijding en psychiatrie.

Methodologische en data-uitdagingen

Onderzoek naar het gebruik, misbruik en effectiviteit van opioïden kent verschillende methodologische uitdagingen, met name wanneer gebruik wordt gemaakt van retrospectieve gegevens uit bronnen die niet specifiek zijn ontworpen voor onderzoek. Een belangrijke uitdaging is de kwaliteit en gedetailleerdheid van de data, aangezien onderzoek waarbij gebruik wordt gemaakt van zorgdata vaak beperkt blijft tot structureel vastgelegde data, zoals ATC-gecodeerde recepten of ICPC-gecodeerde ziekte-episodes. Belangrijke gegevens, zoals de reden van het voorschrijven of de overwegingen van de voorschrijver, ontbreken meestal in deze datasets (hoofdstukken 4 en 5). Er zijn echter veel extra details opgenomen in het vrije tekstgedeelte van medische dossiers, zoals notities of brieven. Traditioneel is menselijke interpretatie nodig om deze details te extraheren. Dit is echter onpraktisch om op grote schaal te doen (bijvoorbeeld tienduizenden bestanden) omdat het tijdrovend en dus kostbaar is. Recente ontwikkelingen op het gebied van kunstmatige intelligentie kunnen hier verandering in brengen, aangezien de huidige grote taalmodellen (bijv. GPT-4) vrije tekst veel sneller en goedkoper kunnen begrijpen en interpreteren dan mensen. Deze technologische vooruitgang zou een enorme hoeveelheid momenteel onpraktische gegevens kunnen ontsluiten, waardoor een breder scala aan onderzoeksvragen kan worden beantwoord.[34]

Toekomstperspectief

Gezien de beperkte hoeveelheid opioïd-gerelateerde schade in Nederland, moeten toekomstig onderzoek en interventies vooral gericht zijn op a) het voorkomen van onnodige (start van) opioïden, b) het minimaliseren van de overgang naar chronisch opioïdengebruik na start, en c) het verminderen van huidig chronisch opioïdengebruik.

Ten eerste moeten richtlijnen voor pijnbestrijding strengere criteria bevatten voor het starten van opioïdentherapie, waarbij een belangrijkere plaats wordt gegeven aan niet-opioïde en niet-farmacologische behandeling. Het bijwerken van deze richtlijnen moet deel uitmaken van een continu kwaliteitsverbeteringsproces. Na een recept voor opioïden kan het risico op overgang naar chronisch opioïdengebruik worden verminderd door patiënten zorgvuldig te volgen en postoperatief voorschrijven te beperken. Periodieke evaluatie van de risico's en voordelen is van cruciaal belang, vooral bij mensen die het risico lopen om chronisch opioïden te gaan gebruiken. De huidige richtlijnen zijn vaag over hoe dit moet gebeuren en met welke factoren rekening moet worden gehouden. Richtlijnen voor pijnbestrijding moeten verdere verduidelijking over dit onderwerp bieden. Dit kan worden gedaan door duidelijke drempels vast te stellen voor het starten van opioïdentherapie op basis van pijnintensiteit, duur en functionele beperkingen. Richtlijnen moeten ook monitoringstrategieën beschrijven, inclusief frequentie van follow-ups, kwantificeerbare parameters om te monitoren, tekenen van misbruik en manieren om de therapie aan te passen op basis van deze follow-ups. Het integreren van risicobeoordelingsinstrumenten om patiënten te identificeren die vatbaar zijn voor chronisch gebruik, zal helpen bij het bepalen van een geschikte monitoringstrategie.

Ten tweede moet toekomstig onderzoek zich richten op de specifieke patiëntenpopulaties waarin het voorschrijven van opioïden veilig kan worden verminderd. Hoewel de huidige studies suggereren dat opioïden te veel worden voorgeschreven, beschrijven ze niet bij welke soorten patiënten het starten van opioïdengebruik kan worden vermeden. Een diepere analyse van bestaande gegevens van ziekenhuizen of huisartsenpraktijken die het voorschrijven van opioïden hebben verminderd met behulp van een eenvoudige interventie (bijvoorbeeld het voorschrijven van morfine in plaats van oxycodon of het beperken van het aantal voorgeschreven pillen) zou kunnen helpen bij het ophelderen van de kenmerken van patiënten waarbij het voorschrijven zou kunnen worden verminderd. Een belangrijke voorwaarde is dat de ingreep de kwaliteit van de pijnzorg niet onevenredig heeft beïnvloed.

Een ander aspect om te onderzoeken is in hoeverre het specifieke type opioïde bijdraagt aan de ontwikkeling van chronisch gebruik. Farmacologische effecten of stigma's die

verband houden met specifieke opioïden kunnen van invloed zijn op hun neiging tot chronisch gebruik of verslaving. Zo zijn er signalen dat oxycodon verslavender is dan andere opioïden[35], en morfine wordt nog steeds over het algemeen geassocieerd met het levenseinde.[36] Onderzoek naar de invloed van deze effecten op de praktijk is echter schaars en heeft tot nu toe niet geleid tot een sterke voorkeur voor een specifiek opioïd. Bovendien blijkt uit onderzoek dat de keuze van het type opioïd momenteel meestal subjectief is en sterk wordt bepaald door de persoonlijke ervaring van de voorschrijver.[37]

Ten derde is een centraal probleem in onderzoek naar het gebruik van receptplichtige opioïden het ontbreken van een duidelijk idee van wat "ongepast" of "onnodig" gebruik is. Dit probleem komt deels voort uit een gebrek aan bewijs voor de werkzaamheid van opioïden voor verschillende soorten pijn, met name chronische niet-kankerpijn en het feit dat pijn een subjectieve persoonlijke ervaring is. Zonder een beter begrip van de situaties waarin opioïden voordelen bieden en wat voor uitkomstmaten hiervoor gebruikt kunnen worden, blijft het moeilijk om de mate van onnodig opioïdengebruik te beoordelen. Omgekeerd is het beoordelen van te weinig voorschrijven net zo problematisch. De geschiktheid van een opioïdenrecept is ook afhankelijk van het scala aan pijnbehandelingsopties dat beschikbaar is voor zowel de arts als de patiënt. Zonder een duidelijk kader om de geschiktheid van een opioïdenrecept te beoordelen, kunnen de receptpercentages alleen hoog of laag zijn in vergelijking met andere getallen (bijv. getallen uit andere landen), wat een genuanceerd begrip van het gebruik van opioïden en de implicaties ervan belemmert. Zoals uiteengezet in hoofdstuk 3 is het gebruik van uniforme gegevens en consistente definities van cruciaal belang voor het bevorderen van onderzoek op dit gebied.

Conclusies

Hoewel Nederland in vergelijking met de VS beschermd lijkt tegen hoge niveaus van opioïd-gerelateerde schade, kan de toename van het gebruik van receptplichtige opioïden niet worden genegeerd. De variatie in het voorschrijven van opioïden in de eerstelijnszorg suggereert een inconsistente kwaliteit van de gezondheidszorg met betrekking tot pijnbestrijding, en de relatie tussen psychiatrische stoornissen en chronisch gebruik van hoge doses opioïden onderstreept de noodzaak van een multidimensionale benadering van pijn, vooral bij patiënten met psychiatrische comorbiditeiten.

In de toekomst is het noodzakelijk om pijnrichtlijnen te ontwikkelen die zoveel mogelijk wegblijven van opioïden in situaties waarin ze geen voordeel hebben. Tegelijkertijd moeten we ervoor zorgen dat degenen die er baat bij hebben, toegang behouden en tegelijkertijd het risico op misbruik zoveel mogelijk reduceren.

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Appendix

Research data management

This thesis is based on a combination of aggregated data obtained from several national databases, and pseudonymised electronic health record data from Dutch general practices.

Chapter 2 is based on aggregated open access data from GIP, and aggregated data that was requested from Dutch Hospital Data (DHD), National Alcohol and Drugs Information System (LADIS), and Statistics Netherlands (CBS). Individual patient data from the different databases were not used as only aggregated data was available. GIP allows use of their open access data when a reference to GIP is made. DHD, LADIS, and CBS provide data to third parties in accordance with Dutch privacy laws. DHD, LADIS, and CBS all allow publication of aggregated data when used in accordance with their specific protocols.[1] In line with Dutch law, no additional ethical review is needed in these cases.

Chapters 4 and 5 use pseudonymised electronic health record data from Dutch general practices collected in the Nivel Primary Care Database (Nivel-PCD). General practices that participate in Nivel-PCD are contractually obliged to: (i) inform their patients about their participation in Nivel-PCD and (ii) to inform patients about the option to opt-out for inclusion of their data in the database. Data were pseudonymised before leaving the health care organization's premises and did not comprise any directly identifying personal information such as names, addresses, and citizen service number. Neither obtaining informed consent from patients nor approval by a medical ethics committee is obligatory for observational studies containing no directly identifiable data (Dutch Civil Law, Article 7: 458). The study was approved according to the governance code of Nivel-PCD under number: NZR-00319.034, and all legally required technical and organizational measures were applied to avoid real-life identification of subjects.

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[1] The specific protocols can be found here:
GIP: https://www.gipdatabank.nl/veelgestelde-vragen/gebruik_2
DHD: https://www.dhd.nl/producten-diensten/registratie-data/aanvraag-van-ziekenhuisdata
CBS: https://www.cbs.nl/en-gb/about-us/organisation/privacy
LADIS: https://www.ladis.eu/nl/over-ladis/werken-met-ladis

Data collection and storage

The data for chapters 4 and 5 were analysed and stored in Nivel's secured digital environment.

Availability of data

All studies were published open access. The underlying datasets for chapters 4 and 5 cannot be shared publicly because of a confidentiality agreement with the database host (Nivel). Although the data are pseudonymised, the detail and amount of data would partly allow the de-identification of patients. Nivel granted access to the data under a strict confidentiality agreement which required on-site analysis of the data to prevent it from leaving Nivel's secured digital environment. Access to the underlying dataset can be obtained from Nivel under the same conditions.

Curriculum vitae

Arno Kalkman werd geboren op 8 oktober 1988 in Scheemda. Na het behalen van zijn VWO-diploma aan het Dollard College in Winschoten in 2007, ging hij Farmacie studeren aan de Rijksuniversiteit Groningen. In 2015 behaalde hij daar zijn masterdiploma. Tijdens zijn studie werkte hij parttime als softwareontwikkelaar bij Speciaaldrukkerij Lijnco in Groningen. Na het afronden van zijn studie begon hij als softwareontwikkelaar bij ChipSoft, een ontwikkelaar van zorgsoftware, om zijn ICT-expertise te combineren met zijn kennis van het apothekersvak. Hij miste echter de klinische praktijk en daarom zocht hij deze combinatie elders. In november 2015 ging hij aan de slag als apotheker ICT bij het Canisius Wilhelmina Ziekenhuis in Nijmegen. Na enkele jaren leidde zijn passie voor onderzoek ertoe dat hij in november 2018 begon aan een promotietraject bij het Canisius Wilhelmina Ziekenhuis en het Radboudumc. Tijdens zijn promotie bleef hij zijn werk als apotheker ICT parttime doen. Arno woont samen met zijn vriendin Kelly in Nijmegen en samen hebben ze een zoon, Jonas (2022).

Arno Kalkman was born on 8 October 1988 in Scheemda. After graduating from the Dollard College in Winschoten in 2007, he went on to study Pharmacy at the University of Groningen. He obtained his master's degree there in 2015. During his studies, he worked part-time as a software developer at Lijnco in Groningen. After completing his studies, he started as a software developer at ChipSoft, a developer of healthcare software, to combine his ICT expertise with his knowledge of the pharmacy profession. However, he missed clinical practice, which is why he looked elsewhere for this combination. In November 2015 he started working as an ICT pharmacist at the Canisius Wilhelmina Hospital in Nijmegen. After a few years, his passion for research led him to start a PhD program at the Canisius Wilhelmina Hospital and the Radboudumc in November 2018. During his PhD, he continued to do his work as an ICT pharmacist part-time. Arno lives with his girlfriend Kelly in Nijmegen and together they have a son, Jonas (2022).

List of publications

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Kalkman GA, Kramers C, Van Dongen RT, Schers HJ, Van Boekel RLM, Bos JM, et al. Practice variation in opioid prescribing for non-cancer pain in Dutch primary care: A retrospective database study. PLOS ONE. 2023;18(2):e0282222.

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Ali MIM, **Kalkman GA**, Wijers CHW, Fleuren HWHA, Kramers C, De Wit HAJM. External validity of an automated delirium prediction model (DEMO) and comparison to the manual VMS-questions: a retrospective cohort study. International Journal of Clinical Pharmacy. 2023;45(5):1128-35.

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Kalkman GA, Zhang Y, Monachino E, Mathwig K, Kamminga ME, Pourhossein P, Ommen PE, Stratmann SA, Zhao Z, van Oijen AM, Verpoorte E, Chiechi RC. Bisecting Microfluidic Channels with Metallic Nanowires Fabricated by Nanoskiving. ACS Nano. 2016;10(2):2852–9.

Pouwels KB, **Kalkman GA**, Schagen D, Visser ST, Hak E. Is combined use of SSRIs and NSAIDs associated with an increased risk of starting peptic ulcer treatment? British Journal of Clinical Pharmacology. 2014;78(1):192–3.

PhD portfolio

Department: **Pharmacology and Toxicology**
PhD period: **01/12/2018 – 09/10/2024**
PhD Supervisor(s): **Prof. Dr. C. Kramers, Prof. Dr. A.F.A. Schellekens**
PhD Co-supervisor(s): **Dr. F. Atsma, Dr. R.T.M. van Dongen**

Training activities	
Courses	
• RIHS - Introduction course for PhD candidates (2019)	15.00
• Radboudumc - Introduction day (2019)	6.00
• Statistical workshop on multilevel analysis (2019)	12.00
• Radboudumc - eBROK course (for Radboudumc researchers working with human subjects) (2019)	26.00
• Workshop writing a rebuttal (2021)	2.00
• Radboudumc - Scientific integrity (2022)	20.00
Seminars	
• Voorjaarsbijeenkomst NVKFB 2019 (incl oral presentation given) (2019)	14.00
• Dutch Pharmacology Day (2021)	8.00
• FIGON Dutch Medicine Days (incl poster) (2021)	20.00
• NISPA dag (incl oral presentation) (2023)	16.00
Conferences	
• Wennberg International Collaborative Spring Policy Meeting (incl. poster presentation) (2022)	32.00
Other	
• NISPA dag 2019 `op inhoud verbinden` (incl presentatie) (2019)	14.00
• NISPA schrijfretraite (2020)	24.00
• Review scientific paper (2020)	14.00
• Review scientific paper (2020)	14.00
• NISPA schrijfretraite (2020)	24.00
• NISPA schrijfretraite (2021)	16.00
• Review scientific paper (2021)	14.00
• Radboud research integrity round (2021)	2.00
• Radboud research integrity round (2021)	2.00
• NISPA schrijfretraite (2021)	24.00
• NISPA schrijfretraite (2022)	16.00
• NISPA schrijfretraite (2022)	24.00
Teaching activities	
Supervision of internships / other	
• Supervision of bachelor student (2020)	28.00
Total	**387.00**

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