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Dynamics of the opioid crisis in the Netherlands

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CHAPTER 7

Opioid epidemic: lessons learned and updated recommendations for misuse involving prescription versus non-prescription opioids

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Abstract

Introduction

In the past decades, the opioid crisis heavily impacted parts of the US society and has been followed by increase in use of opioids worldwide. It is of paramount importance that we explore the origins of the US opioid epidemic to develop best practices to tackle the rising tide of opioid overdoses.

Areas covered

In this expert review we discuss opioid (over)prescription, change in perception of pain, and false advertisement of opioid safety as the leading causes of the US opioid epidemic. Then, we review the evidence about opioid dependence and addiction potential, and provide current knowledge about predictors of aberrant opioid-related behavior. Lastly, we discuss different approaches that were considered or undertaken to combat the rising tide of opioid-related deaths by regulatory bodies, pharmaceutical companies and health-care professionals. For this expert review we considered published articles relevant to the topic under investigation that we retrieved from Medline or Google scholar electronic database.

Expert opinion

The opioid epidemic is a dynamic process with many underlying mechanisms. Therefore, no single approach may be best suited to combat it. In our opinion, the best way forward is to employ multiple strategies to tackle different underlying mechanisms.

Background on the opioid crisis

In the United States (US) and other countries worldwide, the use of opioids has risen substantially in the past couple of decades [1]. According to a survey conducted between 1998 and 2016 in Boston, Massachusetts, US, approximately 5% of their inhabitants, representative of the US general population, used an opioid in the seven days preceding the interview [2]. In addition, opioids were prescribed to about 6% of the Dutch population at some time during a one-year period (2017) [3], to about 8% of the population in any Scandinavian country per year (period from 2006 and 2017) [4], and to about 9% of the general population (of age between 16 and 59 years) in a year's time in England and Wales (between 2006 and 2019) [5]. Although the use of (prescribed and illicit) opioids in Europe (in absolute numbers) is not as widespread as in the US yet [6], it affects more people each year. According to the European Pain Federation (EFIC), there is no evidence of an opioid crisis across countries in Europe at the present time [6]. However, a clear association between the use of opioids and opioid-involved overdose deaths has been established [7], so the upward trend in prescribing rates warrants prudent opioid prescribing and close monitoring of opioid overdose deaths in Europe and elsewhere. Here, healthcare professionals play a key role as they alone can guarantee appropriate, safe opioid therapy, when necessary, educate patients about harms, and prevent opioid use when the risks outweigh the benefits and there is no clear indication for prescribing opioids.

In this expert review, we will first discuss the historic events leading to the opioid crisis in the US and its changing characteristics since 1999. The intention here is to understand and to reflect upon the events that jointly brought about the health care crisis in the US (as a case study). We will also discuss addictive properties of opioid medications and factors that are associated with opioid use disorder, although the evidence is not always unambiguous. Lastly, we will discuss the measures that were undertaken to combat the rising tide of opioid overdose deaths in the US, from which we can learn to best prevent the next health care crisis elsewhere.

The (three) waves of the US opioid epidemic

The opioid crisis in the US has been closely monitored since 1999. It is generally accepted that it consists of three distinct waves: a first wave since 1999, a second wave since 2010, and third wave from 2013 onwards (the three waves are depicted in Figure 1) [8–15]. The first wave of the crisis was characterized by an increase in death

rates by commonly prescribed opioids (prescription opioid line in Figure 1) [8,13]. The next wave of the crisis was triggered by an increase in heroin use [9], and the last wave was initiated by an increase in the use of synthetic opioids (fentanyl and congeners), obtained either by prescription or illicitly [10–12].

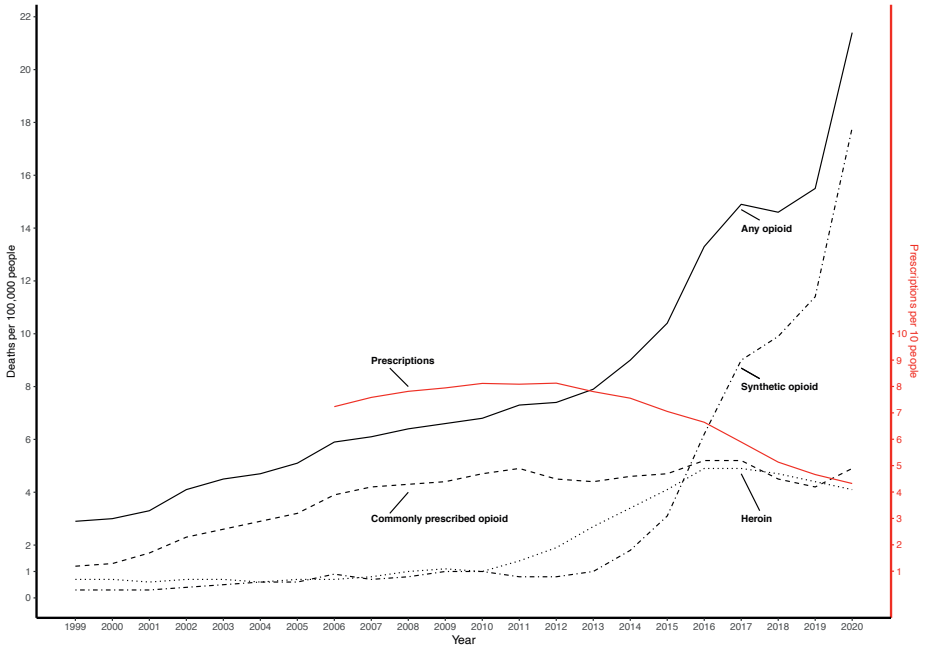

Figure 1. Opioid overdose deaths and opioid prescription rates in the United States, 1999-2019

Figure was created based on publicly available data provided by the Centers of Disease Control and Prevention, US [13,16]. A similar figure is freely available and can be found on the website of the Centers of Disease Control and Prevention. [17] This figure shows the age adjusted annual death rates using the direct method and standard population (n= 2,000 individuals) between 1999 and 2020. Deaths are classified using the International Classification of Diseases, Tenth Revision (ICD-10). Drug overdose deaths are identified using underlying cause of death codes X40-X44, X60-X64, X85, and Y10-Y14. Some deaths may involve multiple opioid drugs. Furthermore, with the red line and by the right-side y-axis the annual prescription rates of opioids per 10 US residents is depicted. The annual prescription rate was calculated based on the number of dispensed opioid prescriptions in a calendar time and the size of the US population.

In more recent years, the US opioid epidemic seems to have transformed once again. In 2018, a brief decrease in overdose deaths was followed by an increase (Figure 1) that persisted until and including 2020 (the last reported rate of opioid overdose deaths) when over 20 deaths per 100,000 individuals were reported [13,14]. Based on this finding, it has been proposed that another wave, the fourth wave, has commenced in the US [15]. The recent rise in overdose deaths has been characterized by use of stimulants, methamphetamine and cocaine, and by concomitant use of stimulants and opioids, still mostly synthetic (e.g., benzo dope, a combination of fentanyl and etizolam; tranq dope, a combination of fentanyl and xylazine) [18].

The US opioid crisis – the perfect storm

Available evidence suggests that the US opioid epidemic was initiated by (over) prescribing of opioids in the 1990s and 2000s [8,19]. Any increase in use of a substance is either stimulated by an increase in demand, e.g., people are in more pain and therefore require more analgesics, or supply has suddenly increased. In the first wave of the US opioid crisis both demand and supply were altered in a way that has resulted in widespread opioid use.

Changed perception of pain and false reassurance of opioid effectiveness and safety

Since the 1960s, many efforts have been made to prioritize pain management in patient care [20]. The World Health Organization (WHO) added opioids to the Model list of essential medicines in 1977, which further cemented the unique position opioids hold in modern medicine [21]. Later, in 1986, the Expert Committee on Cancer Pain Relief and Active Supportive Care introduced the WHO 'pain ladder' for the treatment of malignant pain [22]. The novelty of the WHO Pain ladder was in the stepwise approach to pain management – starting with a non-opioid analgesic, continuing with weak opioids for a mild to moderate pain, and as a last resort, strong opioids for moderate to severe pain. The end goal of the proposed approach was a pain-free patient [22]. Unfortunately, being completely pain-free is unattainable for many chronic pain-inducing conditions. Here, reduction of pain and thus quality of life improvement may be of greater importance to the patients [23–26].

A discussion about the efficacy and particularly the safety of opioids in the treatment of chronic non-malignant pain started with a rather short letter published in the ***New England Journal of Medicine*** in 1980, reporting that just 4 out of about 12,000

hospitalized patients (less than 0.1%), who received at least one opioid during their hospitalization and had no prior history of addiction, developed addiction [27]. Unfortunately, the message of this letter was misinterpreted by many, including pharmaceutical companies, and it was falsely assumed that addiction is rare in patients receiving opioids in all settings [28]. Thereafter, at a meeting of the American Pain Society (APS) in 1995, James Campbell gave a talk about benefits and safety of opioid analgesics in the treatment of chronic non-malignant pain [29]. Later that year, the APS published the 'Quality improvement guidelines for the treatment of acute and cancer pain', further cementing the 'safe and effective' policy of opioids in the treatment of chronic non-malignant pain [30]. Furthermore, the APS proclaimed pain as a "fifth vital sign" in 1996, joining body temperature, pulse rate, respiration rate, and blood pressure in the assessment of one's wellbeing, while other countries followed suit [31]. In 2001, the Joint Commission for Accreditation of Healthcare Organizations (JCAHO; from now on mentioned as the Joint Commission) published a new pain management standard that changed the standard of care by making adequate pain relief a patient's right, by improving education and training of healthcare professionals about pain relief, and by emphasizing the importance of qualitative pain assessment and safe pain management [32]. Although the intention of the JCAHO standard was not to overtreat pain, it did probably have such an effect [33]. A close reader may have noticed that the strategy to combat pain (including educational material) proposed by the WHO never concerned non-malignant pain, but it is still widely used as the goal for the treatment of any type of pain (including non-malignant pain) in medical schools worldwide. Only recently, new guidelines concerning just chronic non-malignant pain are being developed [34,35].

The APS had a key role in the US opioid epidemic – by advising 'safe and effective' opioid pain treatment they drove sales of opioid analgesics, manufactured by different pharmaceutical companies, including Purdue Pharma [36,37]. The APS was dissolved in 2019 after facing several lawsuits due to their financial ties with the pharmaceutical industry [38]. Furthermore, the pharmaceutical industry, particularly Purdue Pharma, employed an aggressive marketing strategy to promote oxycodone (OxyContin®) prescription for treatment of chronic non-malignant pain, while the addictive properties of the medication were downplayed. Addiction to OxyContin® was considered highly unlikely, a claim that was mostly based on the letter by Porter and Jick [27], as well as assumed because of the controlled-release formulation of OxyContin® [39]. However, it has been shown that controlled-release formulations do

not have favorable safety profiles over other formulations [40]. When controlled-release oxycodone was introduced in clinical practice in Ontario, Canada, the associated overdose mortality increased about five-fold between 2000 and 2003 [41]. Physicians were led to believe (by the pharmaceutical industry, and the medical and scientific community) that opioids have low addictive potential that provided false reassurance of opioid safety profile in the treatment of chronic non-malignant pain. This is considered to be one of the reasons behind the US opioid epidemic [28].

Further deterioration of opioid use

Given the above, it is evident that the stage was set for the supply of opioids to follow the increasing demand, creating the perfect storm. In addition to over-prescription of opioids, drug diversion, i.e., use for other purposes than intended by the prescribing physician, contributed to uncontrolled opioid use in the US [42,43]. Diversion happened both at the level of a patient and of a prescriber. First, the patients were able to acquire a prescription from a second physician when the initial opioid treatment was stopped by their personal physician ('doctor shopping') [44], and second, some medical professionals (physicians and pharmacists) identified the increased demand for opioids as an ideal business opportunity. They began selling opioid prescriptions and opioids themselves ('pill mills') [45]. However, the transition towards problematic opioid use did not stop there; patients to whom opioid were prescribed began distributing their analgesic medication to family and friends with an intention to help them ease their pain or for financial gains. Kennedy-Hendricks et al. [46] reported that about 20% of all participants in their study shared their prescribed opioids with others, mostly with the intention to help alleviate their pain. Abusers of prescription opioids considered their behavior to be safer compared with the use of illicit opioids, e.g., heroin, because their opioids were licensed by the medication authority and are therefore "legal". Furthermore, they contained predictable doses (unlike illicit drugs) so their overdose potential was considered lower [47].

Subsequently, probably due to prescription monitoring programs and efforts to close 'pill mills' [47], the use of heroin and synthetic opioids increased, and the number of opioids overdose deaths associated with them quadrupled (Figure 1) [13]. Initially, heroin and illicit synthetic opioids were used by those initially misusing prescription opioids [48]. However, the increase in demand did not go unnoticed by manufacturers of illicit drugs, and they increased the supply of illicit opioids. In 2015, first-time opioid users were 4-times as likely to initiate opioid use with heroin than they were in 2005

[49]. Since the first wave of the opioid epidemic in 1999, it has been estimated that collectively more than 800,000 people died from a drug overdose in the US [50]. Currently, opioids are the main cause of drug overdose deaths with opioid overdoses accounting for about 70% of all drug overdose deaths in 2019 [51]. In 2016 alone more than 60,000 lives were lost due to an opioid overdose, after which the US opioid epidemic was declared a national emergency by President Donald Trump [52,53].

However, opioid use is not only associated with fatal opioid overdoses but also with non-fatal opioid overdose [54], increased risk of motor vehicle accidents [55], falling from standing height [56], addiction [57], tolerance [58], and many more. Besides that, opioid use disorder impairs the physical and mental component of the quality of life [59], and causes members of the active population to miss on average 29 workdays per year (work absenteeism) compared with those without an opioid use disorder [60]. Finally, the cost of opioid epidemic in the US was estimated to be about one trillion US dollars in 2017 alone [61].

Although the decision to include opioids within the armamentarium of pain management for chronic non-malignant pain was not based on sound scientific evidence [34], opioids are often prescribed to treat pain not related to cancer for longer periods of time despite the clear and well-known association between prolonged opioid use (more than 3 months) and opioid dependence and abuse [62].

What makes opioids prone to abuse?

Modern medicine relies heavily on opioids; without opioids anesthesia and management of postoperative pain would be more difficult and perhaps even impossible. The chemical structure of opioids shares many similarities with endogenous opioid receptor ligands. These ligands specifically bind to opioid receptors that are ubiquitously present throughout the central nervous system [63–65]. The biologic effects of opioids are considerable, and the individual biologic response to them varies considerably [66–68]. The complexity and the role of the pharmacokinetics and pharmacodynamics of opioids in the development of analgesic and adverse effects has been given much attention in the literature and is discussed in detail elsewhere [69–72]. Here we provide an overview of the mechanisms that are involved in short- and long-term adaptations to repeated activation of opioid receptors and other targets,

to guide the discussion about the potential of opioids to produce tolerance and addiction.

Short- and long-term adaptations to opioid use

Tolerance

Cellular changes in response to opioids use begin immediately after the initial exposure. Opioids bind to opioid receptors, which are G-protein-coupled receptors, that upon activation regulate many downstream biochemical pathways [73]. Both cytoplasmic G-protein subunits of the receptor interact with several cellular-effector mechanisms, inhibiting adenylyl cyclase and voltage-gated calcium channels, and stimulating inwardly rectifying potassium channels (GIRKs) and phospholipase C beta (PLCB) [74,75]. Ultimately, these biochemical changes are inhibitory on a cellular level, but can produce diverse effects based on receptor location (i.e., at pre- or post-synaptic neurons) [74,76]. Although four different opioid receptor subtypes have been identified, the analgesic and adverse actions of morphine (and morphine-like agonists) require predominantly activation of the mu-opioid receptor (MOR) subtype, as demonstrated in knockout mice models [77].

Various receptor and cellular, short- and long-term, adaptations during (repeat) opioid exposure are associated with the development of tolerance. One such adaptation is receptor desensitization that can occur within seconds to minutes after the initial opioid exposure. This particular mechanism includes the cytoplasmic decoupling of the effector (G-protein) from the opioid receptor by phosphorylation (by different kinases) and recruitment of beta-arrestin (and other proteins) and is followed either by receptor endocytosis, degradation, or recovery [75,76,78]. Initially, the receptors are able to quickly recover from acute desensitization, but upon repeat activation (by prolonged opioid use) the recovery potential is attenuated and desensitization is accelerated, probably by up-regulation of intracellular kinases and beta-arrestin [76]. This ultimately shifts the equilibrium between active and desensitized MORs and eventually leads to acute and long-term tolerance [76,79]. Other mechanisms involved in development of opioid tolerance are increased adenylate cyclase activity, activation of N-methyl-D-aspartate (NMDA) receptors, and glia cell activation, that all strive to restore the signaling process despite continued opioid exposure [80,81].

Reward

The addictive potential of opioids most probably originates from long-term adaptations in neuronal circuits that receive input from dopaminergic midbrain neurons [82,83]. Natural rewards and addictive substances (including opioids) are able to influence behavior by increasing extracellular dopamine levels within the mesocorticolimbic system [75,84,85] that is involved in reward and establishment of behavioral changes necessary to experience reward [83]. After an initial surge in dopamine levels, the concentration of dopamine returns to baseline levels. However, it has been proposed that chronic exposure to addictive substances, changes the homeostatic dopamine set point outside of its normal range [86,87]. This hypothesis has been further supported by results from imagining studies [87,88]. In a positron emission tomography (PET) imaging study by Volkow et al. [88], it was observed that two weeks after discontinuation of substance use, dopamine levels in the basal ganglia were depleted in individuals with an opioid (heroin) use disorder.

Opioid use disorder: clinical considerations

Tolerance, defined as the need to increase drug dose over time to produce the same biologic effect, and physical dependence can develop within days of opioid treatment (short-term effects) [89]. Dependence is characterized by withdrawal symptoms that can present as irritability, dysphoria, insomnia, diarrhea, runny nose, shivering, loss of weight, tremor, writhing, agitation, and aggression [90,91], and may last for several days, even weeks [92]. Although the withdrawal symptoms upon discontinuation of opioids may be perceived as severe, they are not life-threatening and can be reduced by opioid tapering [34]. Furthermore, tolerance can not only affect opioid analgesia, but can also influence the adverse effect potential [93].

According to the most recent edition of the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association [94], the clinical manifestation of opioid tolerance, dependence, and addiction is summarized in 'opioid use disorder' and defined as a disorder that "includes signs and symptoms that reflect compulsive, prolonged self-administration of opioid substances that are used for no legitimate medical purpose or, if another medical condition is present that requires opioid treatment, that are used in doses greatly in excess of the amount needed for that medical condition." [94]. The clinical picture will differ between patients depending on personal characteristics and the duration of opioid treatment, which is reflected in a wide range of symptoms included in the diagnostic criteria. Furthermore, when

opioids are used under appropriate medical supervision, symptoms of tolerance and withdrawal (dependence) are not considered in the evaluation of the disorder [94].

Until recently, it seemed improbable that an opioid use disorder (formerly named 'addiction') could be present in a clinical setting because the compulsive need for opioids, with disregard of any negative consequences, was rarely observed in patients [95]. However, dependence and complementary withdrawal symptoms are neither necessary nor sufficient for the manifestation of opioid use disorder in a clinical setting [96,97]. For example, it is common for dependence to occur without a concomitant opioid use disorder, in the treatment of malignant pain [98]. Still, recent evidence suggests that opioid use disorder may be common among cancer survivors and patients in remission [99,100]. Presence of substance use disorder in any clinical setting is not improbable and may very well be more prevalent than originally considered. In a 2015 review study [57], 38 different studies on opioid misuse and "addiction" from diverse clinical settings were included. The authors concluded that rates of "addiction" varied between 8% and 12% and appeared to be highest in pain clinics.

The probability of substance use disorder increases with the increase in their availability [101]. Above, we described that the availability and ease with which the substance can be procured, especially opioids, has increased considerably in the US since the 1990s [102]. Exposure is, in itself, the single most important risk factor for any substance use disorder, including obviously opioid use disorder. For example, it has been demonstrated by a large US population-based study that the respondents of the survey (n = 9,279) who use prescribed opioids had an increased risk (odds ratio of 3.1 after correcting for confounding variables) of any opioid misuse compared with nonusers [103]. Moreover, the daily dose of prescribed opioids, the number of filled opioid prescriptions, and prolonged opioid use are all positively associated with the risk of opioid misuse [104–106], although the benefit of prolonged exposure to opioids for the treatment of chronic non-malignant pain (in comparison to nonsteroidal anti-inflammatory agents, NSAIDs) has not been supported in a well conducted randomized clinical trial [107].

For advances in safe opioid treatment, it is of paramount importance to assess the individual patient's predisposition for opioid use disorder before an opioid is prescribed [108]. Furthermore, when prolonging opioid treatment is deemed necessary, the risk of

aberrant opioid-related behavior needs to be continuously evaluated and the opioid treatment properly tailored to ensure safe and effective treatment [109].

Who is at risk for opioid misuse, abuse and addiction?

Although not to prescribe opioids may protect from an opioid use disorder, in many clinical scenarios this option is simply not feasible and the uncontrolled pain itself may further exacerbate the potential for aberrant opioid-related behavior [110]. We must therefore prescribe opioids with careful consideration of the individual patient's characteristics [109,111].

Predictors of opioid use disorder

Several risk factors of aberrant opioid-related behavior have been identified. They may be grouped by demographic differences, psychiatric comorbidities (presence ***versus*** absence), substance misuse factors, and other factors [109,110].

Evidence on demographic factors of aberrant opioid-related behavior is particularly highly heterogeneous, and population, setting, and outcome definition dependent [112]. Although more women are being prescribed opioids than men [113], it appears that illicit opioid misuse is more prevalent in the younger age groups and is associated with male sex [114,115]. For example, when population-based data on opioid-related hospital admissions and deaths in the Netherlands were examined, it was found that patients with opioid prescriptions were on average ten years older and more often women (54.4 %) than in those without an opioid prescription (male sex in 66.3% of cases) [116]. Women are also more likely to report substance use and abuse than men, but that does not necessary translate into prevalence of misuse [117]. In addition to age and sex, other variables, for example, gender identity, ethnicity, marital and socio-economic status may be important, but the evidence is sparse, and many population groups were not included in studies [112].

An association between chronic pain, concurrent psychiatric comorbidities and opioid misuse has been identified [109]. A small double blind, placebo controlled randomized trial (n = 81 with a 25% drop out rate) on negative affect, a constellation of anxiety, depression, and a catastrophizing cognitive style, found that patients with chronic low back pain with high negative affect during six months of follow-up were likely to be

prescribed higher doses of opioids, had lesser improvement in pain, and greater rate of opioid misuse than those with low negative affect [118]. Depression in particular increases the risk of abuse of prescription opioids [119], but a similar increase in risk of prescription opioid abuse was also identified in patients with an anxiety disorder [120], panic attacks, post-traumatic stress disorder, and personality disorders [121]. However, a well-treated psychiatric disorder is considered a protective factor for opioid misuse in adolescents [19].

Above all other risk factors, a personal history of substance misuse and abuse preceding a long-term opioid treatment is a strong predictor of aberrant opioid-related behavior [122]. A study in which electronic health records were investigated for signs of opioid dependence in patients with chronic non-malignant pain, predicted an increased risk of current dependence, particularly in patients with a history of severe dependence and prescription opioid abuse (odds ratio 56) [123]. Personal history of any substance (alcohol, tobacco, marijuana) abuse is associated with an aberrant opioid-related behavior [124]. The non-opioid abusive substances serve as introductory drugs to prescription opioids. In a study in adolescent cannabis and tobacco users (age 14 years), a positive association with opioid use at age 19 years was identified [125]. Furthermore, it is now widely accepted that prescription opioids serve as a gateway drug toward abuse of heroin and other illicit opioids [48]. In the US, the majority of heroin users report having started their addiction trajectory with prescription opioids [48,126]. Besides the history of personal substance abuse, familial substance abuse is also an important risk factor [127]. In families where one of the parents was a current marijuana user, the offspring had higher risk of binge alcohol use, tobacco, and marijuana use [128].

Other risk factors of substance abuse include sexual abuse, particularly in the preadolescent period, legal problems and being a victim of an injury, as well as genetic factors (although genetic screening is currently not implemented in routine clinical practice) [122,129–131]. In a recent study, 55 pregnant women that were opioid users were interviewed about childhood trauma and abuse. When childhood sexual abuse was reported, the risk of current opioid misuse in pregnancy was increased (odds ratio 3.5) [132]. Similar findings were observed for any type of childhood abuse, including physical and emotional abuse [133]. As we already established that non-opioid abusive substances are often introductory drugs to prescription opioid misuse, it may be

worthwhile to enforce efforts of drug awareness and prevention programs in children of all ages.

Why are research findings on predictors of opioid misuse diverse?

There is much attention to research on the safety of opioid use. The breadth of provided evidence can be appreciated by quick Medline search; an algorithm consisting of keywords 'risk factors', 'opioid', 'misuse', 'addiction' and 'abuse' yields nearly 200,000 hits with exponential growth in number since the 1990s. However, the general lack of high-quality evidence and highly heterogenous findings have been recognized by many authors [112,134]. Findings not only depend on the internal validity of the study (considering confounding, information and selection bias), but also on the population under observation (children, adolescents, adults, elderly), country of origin (with differences in healthcare systems), year of research, setting (surgery, intensive care unit, pain clinic, street) and other, thus limiting generalizability of the study findings. Furthermore, conditional on the type of opioid misused (prescription or illicit drugs), the operational definition of the outcome under observation, and on the type of pain studied (malignant ***versus*** non-malignant pain ***versus*** no pain), predictors and other outcomes found to be associated with aberrant opioid-related behavior may differ substantially [112,135].

To improve our understanding of mechanisms behind opioid misuse, abuse, and addiction and to develop valid, useful clinical tools to aid in recognizing high risk patients in practice, we need to especially improve internal validity of opioid safety research, which is particularly challenging in observational studies, since clinical trials are mostly insufficiently powered to detect safety signals [136]. Based on our experience in conducting large-scale observational research on opioid safety, we recognized the presence of confounding by indication to be challenging to control for in this research field. Furthermore, the information on opioid use, outcomes, and other variables in registry-based studies is imperfect, which could have a profound impact on detecting safety signals [137].

The majority of opioid safety studies utilize an inactive comparator (no use) to study the safety profile of opioids. The 'no use' is there as an observational equivalent of a placebo control in a randomized clinical trial, however, in that setting the randomization ensures that if the two arms differ, it is only by chance. This does not hold for observation comparisons: patients to whom opioids were prescribed must be different from those

not requiring such medication; opioid users typically have an indication for opioid use. We can correct for these differences by controlling for them with various proposed techniques, e.g., multivariable regression models, propensity score adjustments, matching, but these may be insufficient at completely removing group differences in prognostic factors. Even though advanced methods have been proposed, e.g., high dimension propensity score, self-controlled series and external confounding adjustment [138–140], that are promising a high degree of control over measured and unmeasured (by proxy) confounding variables, they are seldom utilized [134]. Another approach would be to make use of an active comparator design [141]. However, it remains unclear what would the optimal comparator be in the research on opioid safety. A choice of an active comparator in opioid research very much depends on the research question, and even then, it may well be that one specific opioid (or another analgesic) is preferentially prescribed to more vulnerable patients that also have a poorer outcome prognosis.

Data utilized in opioid safety studies have rarely been collected for the purpose of scientific research. Therefore, we must assume a high variability in the reporting of opioid-related outcomes, opioid use, and other variables within and between medical centers. Although the information about opioid use is most often gained by examination of pharmacy claims which tend to be quite accurate, even the most sophisticated algorithms used to identify the duration of opioid treatment fail to address the issue of compliance with therapy being prescribed. Therefore, we do not know whether a patient actually ingested the medication, whether illicit opioids are used, or whether patients are buying opioids over the counter [134]. Although availability of opioids as an over the counter medicine may vary between countries, and the exposure prevalence due to over the counter opioids is assumed to be small compared with prescription opioids and may therefore not have substantial impact on the effect estimates [142], the structure of misclassification (and its association with other errors) introduced by over the counter use may be difficult to anticipate [143]. Similarly, various disease classifications (most often international classification of diseases, ICD) are utilized to identify outcomes and even populations in different settings and countries. For example, the F-series are not used for coding of drug-related deaths in the US, whereas in Europe this is standard practice [7]. When a new study, based on data collected in Europe, is being planned, but the code series from US are utilized, a serious underestimation of outcomes will occur. Furthermore, to identify individual opioid-related outcomes, a set of codes or even individual codes are used,

e.g., heroin poisoning. This may lead to serious misclassification, since the probability of accurate reporting may be reduced and the identification of individual opioid poisoning by a physician may be challenging (e.g., due to unreliable urine testing) [111,144,145]. Incomplete or missing information on the exposure, outcome, or other variables, and the underlying mechanism that led to the inaccurate information may have various consequences for the investigated outcome of interest that even most experienced researchers may misjudge [146], and therefore needs to be formally explored [147].

What can be done to prevent further escalation or another opioid crisis?

Many interventions have been developed to counter the opioid epidemic, but many of them only targeted misuse of prescription opioids. Therefore, despite the fact that the number of opioid prescriptions has declined for over a decade now, the number of opioid deaths in the US is still rising. This 'opioid paradox' [148] shows clearly that the myriad preventive measures that were implemented over that same decade, did not have the desired effect.

Regulatory solutions

Because the opioid crisis was initially perceived as a public health problem [149], many of the first preventive measures were legislative and regulatory, aimed at decreasing the number of prescriptions and indirectly the number of pills available for misuse. In several healthcare settings, prescription drug monitoring programs (PDMPs) were intensified or expanded. These mostly automated systems with usually state-wide coverage enable prescribers to check whether a patient has already received a recent prescription for a certain drug. Use of these PDMPs prior to prescription of a monitored drug is now mandatory in many parts of the US. This has limited the number of drugs prescribed [150,151]. However, PDMPs intentionally targeted the prescription rates of opioids and did not have an influence on non-medical use of opioids and might even unintentionally have increased the use of heroin and other illicit opioids [152].

An important, nationwide step was taken when the Centers for Disease Control (CDC) published their 'Opioid prescribing guideline' in 2016 [34], focused on the treatment of chronic non-malignant pain with opioids. This guideline gave a series

of recommendations on whether or not to initiate opioid therapy for chronic pain, on which opioids to prescribe (it states a preference for immediate release opioid formulations as opposed to extended release formulations), which dose and for how long to prescribe (as low a dose as possible for the shortest period of time), and how to assess the risk of opioid related harm (e.g., not prescribing to patients with a history of substance abuse, or concomitant use of benzodiazepines). Similarly, some countries in Europe updated or developed new prescription guidelines, as for example the Netherlands [153], and the United Kingdom [35], that either rely more heavily on opioids in the post-operative period (the Netherlands) or were developed specifically for chronic non-malignant pain and therefore support also non-pharmacological interventions.

In the wake of the US guidelines, which were first and foremost intended as a set of clinical recommendations, many US states implemented laws limiting the duration of opioid prescriptions, and in some cases even the dose that could be prescribed [154]. Furthermore, restrictions were placed on 'doctor shopping' [155], and high-volume prescribers were sent letters informing them of their unusual prescription behavior [156]. These legal limitations have affected the prescription rates of opioids (the red line in Figure 1) and although they might have curbed the increasing rate of opioid overdoses associated with prescribed opioids (Figure 1), they have done little so far to limit the overall number of overdose deaths (these are now mainly driven by illicit opioids), and the question remains whether they are effective at all [157].

Pharmacological solutions

Pharmacological solutions to the opioid problem have also been presented over the past two decades. When the first signs of opioid misuse were starting to surface, several new pharmacological opioid formulations, targeted at decreasing abuse potential (so called abuse deterrent formulations or ADFs), entered the market. Furthermore, novel opioid-receptor agonists and of course new formulations of naloxone became used.

Abuse Deterrent Formulations

There are several ways in which a drug can be formulated in an abuse deterrent way, as described by the Food and Drugs Administration (FDA) [158]: adding a physical or chemical barrier to the drug in question, combining agonist/antagonist combinations, decreasing a drug's likability by including aversive substances that deter users from

using the drug in large amounts, and novel technologies such as unconventional delivery systems or using prodrugs that can only be activated by ingestion.

The best-known example of the first category, adding a chemic-physical barrier, is a reformulation of OxyContin® (ADF OxyContin®). The drug was marketed with a new shell which made crushing and extraction of the drug difficult. This decreased the number of opioid overdoses due to oxycodone [159], but only for a short while. A plateau was reached within a few years after reformulation, for which there are several possible explanations. First, it is possible that users used different ways to ingest the drug (orally as opposed to snorting and injecting), which would eventually lead to the same incidence of oxycodone overdoses. It is also possible that users changed their drug preference, and simply started to snort and inhale/inject other types of opioids. This would then decrease the number of oxycodone overdoses, but not the number of overall opioid overdoses. It is important to note that the number of heroin overdoses rose between 2010 and 2014 [160]. A study into the abuse of ADF OxyContin® in a large cohort of patients with an opioid use disorder showed that in a subsample only a small percentage of users stopped abusing oxycodone altogether [161]. Some switched to a different drug (heroin) but most did not change their behavior after the reformulation. The evidence for a massive switch to heroin is inconclusive: one study reported that the odds of heroin initiation did not change after the introduction of ADF OxyContin® [162], others have shown no decrease in overall opioid overdose deaths after the introduction of ADF OxyContin® [163,164], consistent with the idea that users simply switched to other opioid drugs. After the introduction of ADF OxyContin® several other abuse deterrent formulations were marketed [165]. We note, however, that not all ADF formulations hold the same physico-chemical properties that facilitate or deter alternative routes of administration [165].

Another way of deterring abuse is by combining antagonists with agonists. This has an interesting pharmacological rationale. Naloxone, together with naltrexone still the most important opioid antagonist, has poor bioavailability when swallowed orally, due to its high first pass effect. An opioid user swallowing the tablet as intended, would not suffer from the effects of the added naloxone, but if one were to snort or inject a crushed tablet, naloxone would work and limit the opioid' effects or even cause withdrawal symptoms. The use of agonist/antagonist combinations to deter opioid misuses goes back even further than addition of a physico-chemical barrier: already in the early 2000s a combination tablet of buprenorphine and naloxone was released [166]. Since then,

several other formulations, combining oxycodone or morphine with either naloxone or naltrexone became available [165].

Opioid alternatives

There are few true alternatives to the use of opioids for moderate to severe pain. When non-steroidal anti-inflammatory drugs (NSAIDs) have fallen out of favor because of their undesirable cardiovascular side-effect profile or because of limitation in the healthcare budget assigned to this widely used medication group (as for example in the Netherlands [116]), there are few opioid alternatives to alleviate both acute and chronic pain. The ultimate goal in opioid research, finding an opioid with all the advantages but none (or fewer) of the disadvantages, has thus far proven elusive. The opioid analgesics currently available all exert their main actions through the mu-opioid receptor (MOR) as opposed to the kappa and delta opioid receptors [77,167]. This receptor activation is responsible for both the desired (analgesic) and unwanted (respiratory depressant) effects of opioids, and therefore for the overdose deaths. A new investigative pathway has opened up a possible future pain therapy – biased opioid receptor ligands. After mu opioid receptor (MOR) activation, the analgesic effect is mostly mediated through the activation of the G protein, while it is assumed (but not fully proven) that the majority of side effects, such as respiratory depression, are mediated through activation of an auxiliary cytoplasmic transduction MOR protein, beta-arrestin [168,169]. Any pharmacological compounds favoring the G protein pathway over the beta-arrestin pathway would theoretically have analgesic properties while lower risk of side-effects: the biased ligands. Several candidate molecules have been tested in pre-clinical and clinical trials [170,171], from which oliceridine was the first to receive FDA approval for in-hospital use.

Naloxone for home use

Finally, a different way of preventing the loss of life from opioid overdoses is to treat overdoses promptly. An opioid overdose is easily treated when discovered early. Administration of 0.4 to 4 mg of naloxone (via intravenous, intramuscular or intranasal routes), depending on the opioid used and dose, can reverse opioid-induced respiratory depression and thus prevent coma, cardiac arrest and death. The caveat here is the availability of naloxone – while naloxone is readily available in hospitals and physician practices, it is not available in those places where most overdoses happen. An idea already developed in the early years of this century [172,173], to provide communities with improvised naloxone kits for home use, was more widely introduced

in the early 2010s. In 2014, the WHO issued a guideline on community management of opioid overdose, stating 'Naloxone needs to be available to anyone likely to witness an opioid overdose in the pre-hospital setting' [174]. To this effect, so-called 'take home naloxone' formulations (THN), such as an auto-injector pen and a nasal spray were introduced. In their opioid prescription guideline, the CDC [175] and US Surgeon General Public Health Advisory [176] recommend prescribing any form of THN to any patient with a high risk of overdose (i.e., a patient with a history of overdose or opioid use disorder, a patient with a high opioid dose or concurrent benzodiazepine use, or any individual using illegal opioids). McDonald et al. [177] conducted a systematic review of the observational evidence available for THN schemes. Not only did they show that THN schemes are successful in decreasing opioid overdose deaths, but they also showed that they are cost-effective, have a low risk of adverse events and are easily implemented over a wide range of social settings. They therefore conclude that THN distribution should be introduced as a standard of care in prevention of opioid overdose deaths [177].

Patient-centered solutions

Patients' expectations of both their pain levels and the effect of the analgesic therapy should be carefully managed by the physician. Patient education in pain and pain therapy during a pre-operative visit might be able to help decrease opioid need after the surgery [178,179]. Similarly, someone who receives an opioid prescription for non-surgical pain, should be informed of possible side-effects and the potential for misuse, by both the prescriber and the pharmacist dispensing the medication [180,181]. Patient awareness of the risks of opioid use might help with decreasing opioid use and consequent misuse.

Tailoring prescriptions, for example post-surgery, to the specific patient will also help in reducing leftover pills [182–184]. Any pills left at home are a risk for non-medical use, be it for self-medication, or diversion to others. Patients are likely to hold on to their leftover pills, for their own or other people's future use [185]. Furthermore, return of opioid tablets to the pharmacy (or the hospital) should be as easy as possible, and might even need to be financially rewarded [148], also to decrease the number of pills available for misuse.

Expert opinion

As we have tried to demonstrate in this review, the opioid crisis is a complex problem, and there does not seem to exist one definite solution. Not only has the general opinion on pain and what amount of pain is bearable changed, but also doctors' attitudes and possibilities, as well as possibilities of healthcare facilities. The rise in the number of opioid-related fatalities continues year upon year and shows no sign of slowing. As physicians, we are at least partially responsible for this 'rising tide of deaths' [186], and it is therefore also our responsibility to help find a solution for this problem. However, modern medicine without opioids is currently unthinkable. We are limited in therapeutic options when a patient is in serious pain. Anesthesia without opioids is very difficult and possibly unsafe [187]. We need to convince ourselves, but also all of our colleagues, as well as our patients that there is a fine line between responsible opioid use and misuse. In this respect, it is important to note that the need for opioids in pain therapy is subject to a high amount of variability. It is therefore difficult to develop a one-size-fits-all strategy for opioid therapy in both acute and chronic non-malignant pain settings. It is of paramount importance that therapy is individualized, and a good relationship between patient and prescriber is key here. Initiation of opioid therapy warrants close contact between patient and physician to enable monitoring of opioid effect, possible side-effects or signs of misuse. Where possible, prescriptions should be short-termed and refills only possible after close contact with the physician. Ideally, opioids should only be used as a 'pain circuit breaker' in non-malignant pain, much like a course of antibiotics. Cancer pain patients should, on the other hand, have access to opioid therapy when required, also on a long-term basis, but again with careful consideration of appropriate opioid therapy and with acknowledging the side effects. Opioid use should not be, however, extended beyond the intended indication (for example, after cancer patients enter remission or are cured) to prevent opioid use disorder in this patient group. Where continuation of analgesic therapy is unavoidable in the treatment of non-malignant pain, possible alternatives for opioid therapy (such as NSAIDS and antidepressants or antiepileptics) should be considered. In this indication, prolonged opioid use should be avoided at all costs, as little scientific evidence has been provided to support continued opioid use in chronic non-malignant pain [107]. Additionally, when appropriate, complementary approaches such as physical therapy, psychological support and rehabilitation programs should be considered. Not only can these non-pharmacological treatments help in alleviating chronic non-malignant pain, but can also aid patients to deal with the pain and accept

it. It has been demonstrated that multidisciplinary approach to pain management is more beneficial for a patient than a conventional one. Patients treated by such a team reported having reduced pain intensity, improved psychological well-being, quality of sleep and physical functioning [188]. Furthermore, patient empowerment in the treatment of chronic non-malignant pain will provide the necessary information to the patient so they can make an informed decision about the initiation of the opioid treatment and be alerted for possible side effects [189]. Additionally, it can aid in detecting opioid misuse when an opioid is already prescribed [190]. Unfortunately, these alternative approaches are not always reimbursed by health insurance, nor are the lengthy patient consultations that are required.

As we have shown, due to the complexity of the opioid crisis, there is not one universal cure. A combination of measures, aimed at different underlying mechanisms behind the opioid crisis, and always in concordance with all parties involved, are the best way forward.

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