Opioid Addiction Science and Society

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Opioid abuse and misuse have led to an epidemic which is currently spreading worldwide. Since the number of opioid overdoses is still increasing, it is becoming obvious that current rather un-systematic approaches to tackle this health problem are not effective. This review suggests that fighting the opioid epidemic requires a structured public health approach. Therefore, it is important to consider not only scientific and biomedical perspectives, but societal implications and the lived experience of groups at risk as well.

Keywords: OxyContin ; opioid abuse ; chronic pain ; patients' narrative

1. Introduction

The current coronavirus crisis has brought into sharp relief that while no one is immune to the virus, an epidemic may affect groups to different degrees. Thus, the COVID-19 pandemic has shown that socially and economically disenfranchised groups are particularly at risk in an epidemic. Dramatically, the U.S. currently seems to be in the grip not only of the COVID-19 epidemic, but also of another major crisis: the so-called opioid epidemic, which is now also spilling into many areas of the world. This paper demonstrates that in order to develop effective solutions to this crisis, a multidisciplinary approach is necessary, which links the life sciences and the humanities. For an in-depth understanding of the trends in opioid use and abuse, it is essential to understand a complex network of not only doctors, pharmaceutical companies, patients and institutions, but also society and social factors at large. This becomes even more evident, if studies indicate that on a therapeutic level, management of pain could or should effectively be combined with cognitive behavioral therapy [1][2]. For such therapeutic strategies, in turn, it may be crucial to understand not only the individual factors, but also cultural and societal factors which may lead to opioid addiction. As the American Psychological Association (APA) suggests, cognitive behavioral therapy (CBT) might contribute to strategies for coping with addiction, which are better embedded in a reconceptualization of the affected individuals [3]. While it is not surprising that the APA walks down the paved roads of dealing with addiction (like in alcohol or heroin abuse), the strategy sheds some light on the lack of preventive strategies. First, this paper combines approaches from pharmaceutical biology and the humanities in order to foster a multidisciplinary approach to combatting the opioid crisis by a more preventive approach. Second, we would like to recommend routes for further research where this multidisciplinary approach could be applied to complement the health impact assessment of opioid addiction with health needs assessment. We argue that an assessment of institutional and local measures to tackle the opioid crisis is urgently needed, in order to investigate which preventive measures might be effective and thus become a venture point for the policy making which is urgently needed to effectuate a public health approach to the opioid crisis locally, nationally and globally.

This review will first provide an overview of the opioid crisis and its inception, focusing specifically on OxyContin™ as a key example. Secondly, it will explore factors often associated with opioid overdose and analyze the necessity of opioid chronic pain management, also looking at post-surgery pain management as an entry point for opioids in the lives of patients. It will then examine the mechanisms behind an opioid addiction from the perspective of pharmaceutical biology. The discussion will subsequently lead to a patient perspective, exploring the role of patient compliance and the cultural framing of opioid addiction. In the final part of this paper, current avenues for treatment will be examined. In the conclusion, we explore the potential advantages and challenges of an interdisciplinary approach, which combines the life sciences and the humanities [4] and we suggest that without such interdisciplinarity, we may fail to grasp the current opioid crisis in all its complexity. Finally, while this article discusses the opioid crisis in the U.S. specifically, it also has worldwide implications for the use of opioid-based pain medication. What are the factors which might lead to such a global opioid epidemic? Crucially, through its interdisciplinary approach, this review thus seeks to contribute to preventing a further spread of the epidemic, both on the level of the U.S. and on the global level. A recent published report has argued that it is important to tackle the opioid crisis by “going back to its roots” [5]. Through understanding the mechanisms which led to the U.S. opioid epidemic, we may be able to stop it from flooding Europe as well. At the same time, it demonstrates that most discussions so far have failed to take cultural and social perspectives sufficiently into account. This paper, however,

argues that the “root” of the problem of the opioid crisis may not only be medical, but it may also be a cultural and a social problem. For this reason, the following discussion links the methodologies of the life sciences and the humanities in explaining the opioid epidemic in its current form. All this, however, needs to be rooted in a sound understanding of the role of pain and pain management as it is practiced *legis arte* today.

The World Health Organization (WHO), together with the International Association for the Study of Pain, have recognized proper pain management as a fundamental human right [6]. Nonetheless, adequate pain management, particularly if it comes to chronic pain, has been a challenge both for doctors and for patients, who have been facing the problem of insufficient pain management for years (as the goal is to reduce pain with minimum side effects) and the ubiquitous presence of opioids with little thought on adoption, addiction and abuse in the last decade. Even after decades of research in pain management, opioids still remain the most prescribed drugs for treating postoperative pain [7][8][9]. Historically, the isolation of morphine from the opium poppy in 1805 by Friedrich W. A. Serturner was a turning point for pain management in medicine. After more than 200 years, morphine is still one of the most prescribed opioids and is used as a standard to compare the potency of other opioids [10]. However, because of its pharmacokinetic profile, scientists have tried to synthesize stronger and more effective compounds. If administered orally, morphine undergoes a significant first-pass effect, as it metabolizes through the liver to morphine-6-glucuronide, a more potent analgesic; it has a half-life of 2–3 h, requiring a new administration approximately every 4 h [11]. Following repeated use, it leads to tolerance and physical dependence [11] Therefore, scientists have searched for more potent opioids with a better bioavailability and as such the release of OxyContin™ in 1996 by Purdue Pharma in USA seemed like a promising alternative. However, even then multiple studies concluded that there is no comparable advantage in comparison to other oxycodone preparations, besides a reduced dose frequency [12]. In this light, one key questions needs to be answered: how did opioids become America’s most used and misused drugs?

2. How Did Opioids Become America’s Most Used and Misused Drugs?

The Food and Drug Administration (FDA) is responsible under the Food, Drug and Cosmetics Act to regulate the advertising and promotion of prescription and noncontrolled drugs in order to assure their truthfulness and have a positive impact on public health. The U.S., together with New Zeeland, remain the only two countries in the world which allow direct-to-consumer advertising of prescription drugs. Back in 1996, shortly after introducing OxyContin™ on the market, Purdue Pharma started a highly aggressive marketing and promotion campaign without submitting promotional videos to the FDA to be reviewed [13]. Purdue Pharma conducted multiple conferences on pain management, which were attended by over 5000 physicians, pharmacists and nurses, who were then recruited as Purdue’s speakers [13]. Not only did Purdue Pharma target primary care physicians, but they also offered branded promotional items to healthcare professionals and various coupons for OxyContin™ for new patients [13]. During the same time pain was described as “the fifth vital sign” and the problem of more than seldom undertreated pain attracted the attention of healthcare providers, who then decided to improve the treatment guidelines of pain management [14][15]. This led to a more liberal use of opioids in the treatment of pain. Purdue promoted the use of Oxycontin™ in non-cancer-related pain and assured that the risk of addiction was low due to its formulation as a controlled-release tablet. With the intent to improve pain management and patient outcomes, doctors started overprescribing strong opioids, creating a slippery slope. By 2005, through the liberalization of prescription opioids, nationwide there was an increase in opioid prescriptions and drug abuse [16][17]. Oxycodone became the most abused prescribed opioid in the USA and led to more deaths than heroin [18]. In 2010, Purdue Pharma released an abuse-deterrent formulation (ADF) for oxycodone, making it harder to crush or dissolve, and in 2013 the FDA decided the prior formulation should be removed from the market for safety reasons. Several studies have examined the efficacy of the abuse-deterrent formulation and have concluded that it is associated with a decline in the abuse of oxycodone [19][20][21][22]. However, one study, which also included patients misusing prescription opioids or heroin, highlighted the limited effectiveness of the abuse-deterrent formulation, as the level of residual abuse has remained stable despite the new formulation [19]. Although the ADF has reduced the abuse of oxycodone, the active compounds in these formulations preserve their euphoric effects and strong side effects, including overdose potential. As such, the search for new analgesics continued and a new approach targeted the peripheral opioid receptors using hydrophilic substances and polyglycerol-based nanocarriers; this strategy has shown promising results [23]. Other strategies include increasing endogenous opioid mechanisms, use of allosteric modulators, bivalent ligands and bivalent signaling [23].

Even though great advancements have been made in the practice of surgery, as techniques have become more precise and less invasive [24] in order to improve the outcomes, opioids are still the first choice for postoperative pain management [25][26]. In the attempt to improve recovery and quality of life, as well as reduce hospital stays, physicians started prescribing more opioids, so that up to 80% of patients in the USA receive strong opioids after a surgical procedure.

Due to increased morbidity associated with opioid overdose, various studies have started analyzing the factors influencing the opioid prescribing patterns in opioid-naive patients. Opioid-naive patients are defined as patients with no prescription for any opioids in the last 6 to 12 months prior to their first opioid prescription and with no history of substance abuse [27]. The trends in opioid prescriptions in opioid-naive patients after low-risk surgical procedures (*e.g.*, carpal tunnel release) have been analyzed for a time period from 2004 to 2012. The study evaluated the proportion of patients filling an opioid prescription (especially oxycodone/acetaminophen or hydrocodone/acetaminophen) within 7 days after a procedure. Seventy percent of them filled an opioid prescription within a week. Additionally, there was an increase in opioid dose of 18% for all procedures. A more complex investigation associated the characteristics of the initial opioid use with pain etiology. The most common indications for opioid prescription are chronic non-cancer pain, surgery, trauma and burns. The authors concluded that patients initiated with tramadol, long-acting opioids or doses over 90 morphine milligram equivalents were more likely to continue opioid use [28] Additionally, multiple studies have characterized the duration of the prescription and high opioid dose as strong predictors of the likelihood of long-term use [27][28][29][30]. Other risk factors are continued use of other medicines (benzodiazepines, muscle relaxants), history of alcohol, tobacco or drug abuse, lower socioeconomic status and psychiatric disorders [31][32] which will, unfortunately, most likely increase as a consequence of the ongoing COVID-19 pandemic and the related anxiety and social deprivation. As numbers of opioid overdose deaths continue to grow in the U.S., Centers for Disease Control and Prevention (CDC) discovered that in 63% of cases there is also another drug involved. Both alcohol and CNS depressants are known to cause respiratory depression, therefore mixing them can have fatal effects. A recent study gathered data from the last 20 years and confirmed that co-involvement of alcohol or benzodiazepines in opioid overdose deaths (OOD) is common and the prevalence rate is increasing for alcohol from 12.4% (1999) to 14.7% (2017) and for benzodiazepines from 8.7% (1999) to 21.0% (2017), more and more replacing the former culturally accepted (but now increasingly unacceptable drug), alcohol, with a “medication”. Alcohol is still more commonly used by men [33], while benzodiazepines are more frequently used by women [33]. The proportions of co-involved alcohol and benzodiazepines vary depending on the opioid subtype (prescription opioid vs. illicitly manufactured), as illicitly manufactured fentanyl has been responsible for almost half of the opioid overdose deaths since 2015 [33]. These results should be considered by physicians when prescribing both opioids and benzodiazepines and should be integrated in public health communication since many patients, at first, seem to not be fully informed of potential risks. The prescription rates of benzodiazepines have also increased substantially in the last decades, as they have become the most prescribed sedatives [34]. In 2016, the CDC published a guideline with recommendations for prescribing opioids for chronic pain with the intent to improve the effectiveness of treatment and reduce adverse events and risks. In the guidelines, CDC recommends starting an opioid therapy for chronic pain only if the benefits outweigh the risks and the therapy should be combined with nonopioid (NSAIDs, anticonvulsants and antidepressants) and nonpharmacologic therapy (CBT, exercise therapy). Clinicians should determine realistic goals, discuss the risks with the patients and only continue therapy if significant improvement appears. Additionally, opioid therapy for chronic pain should start with the lowest effective dose and immediate-release opioids are preferred to extended-release. Thus, an evaluation of the therapy benefits should be done within the first 4 weeks after starting the treatment and then every three months, which is in many Western countries the threshold for developing chronic pain. Generally, the CDC recommends avoiding the concurrent prescription of opioids and benzodiazepines, as the risks are higher than the benefits. Last but not least, a patient’s medical history should be reviewed, and urine drug tests should be done annually, in the case of long-term treatment. If there are any risk factors involved, clinicians must establish strategies to minimize the risks [35]. To improve the knowledge of healthcare providers, avoid overprescribing opioids and help them apply these guidelines, the CDC now offers different interactive online training programs targeting professional groups.

Since opioids are frequently prescribed after both minor and major surgeries, scientists have wanted to determine how often after a surgical procedure patients become chronic opioid users and which associated risk factors (alcohol, tobacco, depression) can influence the outcome [36][37]. Although chronic opioid use is common after surgery, the rates were low [36][37][38]. A report from 2016 analyzed the risk of chronic opioid use in opioid-naive patients after having 1 of the 11 most common surgical procedures, compared to nonsurgical patients. Excluding the first 90 days post-surgery, surgical patients were considered chronic opioid users if during the first-year post-surgery, they had a supply of opioids for over 120 days or filled over 10 prescriptions. In the case of the nonsurgical patients, a “surgery date” was assigned randomly, and chronic users were defined by using the same criteria. Even though two of the surgical procedures are often associated with pain (total knee arthroplasty, total hip arthroplasty), the authors suggest different pre- and postoperative techniques for pain management. The study confirmed the risk of chronic opioid use during the postoperative period and also highlighted the potential of different risk factors (history of drug or alcohol abuse, use of antidepressants and benzodiazepines) in the patient outcomes. These findings were also confirmed by other authors, who observed that the risk of chronic opioid use in opioid-naive patients following a minor or major surgical procedure is increased, and it is especially associated with other risk factors (alcohol and drug abuse, use of benzodiazepines, antidepressants) and preoperative pain disorders (arthritis, back pain) [37]. These data describe the influence of psychiatric conditions in chronic

opioid use. To increase awareness regarding the risk of chronic opioid use, a new analysis focused on both opioid-naïve and opioid non-naïve patients receiving opioids in the perioperative period. For both group of patients, it was confirmed that, if patients received over 450 Morphine Milligram Equivalent (MME)and a high amount of opioid medication, they were more likely to become chronic opioid users [38]. Additionally, various guidelines were proposed with the purpose of reducing opioid prescriptions following surgical procedures. The first study describes that from 85% of patients who received an opioid prescription at discharge on postoperative day 1, only 38% of the prescribed opioids were taken. The number of opioid pills taken the day before discharge were correlated with the number of opioid pills taken afterwards. As such, the guideline proposes the following: no opioid prescription if the patient does not need any opioids the day prior discharge; if the patient takes 1–3 opioid pills, then they receive an opioid prescription for 15 pills and if the patients require more than 4 opioid pills, they obtain a prescription for 30 opioid pills [39]. Additionally, the same group prepared another guideline for surgeons to decrease postoperative opioid prescriptions. Surgeons were recommended to prescribe NSAIDs or acetaminophen as first choice therapy. As such, the number of opioid pills decreased by over 50% and 85% of patients received acetaminophen or a NSAID and did not require opioids afterwards [40]. These studies demonstrate that although appropriate postoperative pain management remains a complex matter, surgeons often overprescribe opioids.

In the last decades opioid therapy has been frequently prescribed for chronic pain and as an undesired outcome the number of opioid overdoses has increased. A randomized clinical trial supported the efficacy of short-term (12 weeks) opioid therapy in treating chronic pain. However, their efficiency was not higher compared to nonopioid therapy. Regarding benefits of long-term opioid therapy, evidence still remain insufficient. Thus, various studies have concluded that higher doses of opioids are often associated with an increased risk of harm, opioid abuse and overdose [41][42][43][44]. Although the risks are well known, reducing the dose was easier said than done for patients, who had already taken high doses of opioids for a longer period. A study from 2014 evaluated, using high-dose chronic opioid users, if the recognized benefits and harms can be used as predictors of high-dose use after one year. A majority of patients (74%) reported at least one side effect and many of them reported concerns and problems associated with opioid use. Even though almost half of the patients expressed the wish to reduce or stop opioid therapy, 80% of them continued to use high doses after one year [45]. Other studies confirmed that despite the fact that chronic patients report multiple side effects and problems related to high doses of opioids, the rates of opioid reduction were still low [46]. These results reinforce how difficult it is for chronic opioid users to reduce doses even though it could improve their quality of life. Although a decrease in opioid prescribing already started in 2012 after the CDC guidelines were published, opioid prescriptions decreased at a higher rate [47]. On the other hand, this was also associated with increased illicit opioid use (heroin and illicitly manufactured fentanyl) and overdose deaths [48], as people already dependent on the opioid therapy suddenly stopped receiving their medication. A retrospective cohort study determined that patients, who had treatment discontinued and those whose doses were increased were more likely to use heroin and illicit fentanyl [49]. All in all, the available data confirm the complexity of the opioid problem and that the abrupt reduction in opioid prescriptions can produce more harm than good. Hence, it is an ethical postulate that clinicians should carefully evaluate and discuss with the patients the best measures that should be taken to reduce or cease opioid therapy without negatively affecting the quality of life. To help safely reduce opioid doses in chronic patients, various risk mitigation initiatives have been started. These initiatives have proven to be very efficient, as both high-risk patients (those with history of mental or substance use disorder) as well as low-risk patients managed to reduce their daily doses of opioids [50]. Beyond clinical practice and behavioral factors, opioid addiction is also deeply rooted in pharmacological and neurobiological mechanisms.

Although the opioid crisis has mainly affected the U.S. and Canada, a report showed that opioid prescription rates have nearly doubled in Europe during the past two decades and there are approximately 1.3 million high-risk opioid users, and the countries with the highest consumption of opioids are Germany, the UK, France, Spain, Italy and the Netherlands [51]. In comparison to the U.S., the number of opioid-related overdose deaths and hospitalizations is still low, and while in the U.S. most overdose deaths are caused by fentanyl and other synthetic opioids, in Europe heroin is attributed to most fatal overdoses [51]. Additionally, in Europe the Access To Opioid Medication in Europe (ATOME) project has provided information about opioid medication in legal, societal and policy contexts in order to help to implement various European policies [52].

A recent review has analyzed the trends in opioid prescription practices in Germany, as the country is the second largest opioid consumer in Europe, and although opioids are mostly being prescribed to treat chronic, non-cancer pain, the study concluded that currently there are no signs of an opioid epidemic [53]. New studies provide information on a national level regarding the impact of opioid misuse in different European countries such as France, the Netherlands and the UK.

As the number of opioid prescriptions has drastically increased during the past two decades, an investigation from the Netherlands reported that proxies for opioid misuse augmented, the number of opioid prescriptions, substitution therapies and opioid-related deaths doubled and opioid-related hospital admissions tripled [54]. An analysis from France from 2004

to 2017 described a significant increase in oxycodone use (+1950%), opioid-related hospitalization (+167%, 2000–2017) and opioid overdose deaths (+146%, 2000–2015) [55]. Furthermore, in the UK, the number of opioid prescriptions quadrupled, and from 1993 to 2017 opioid overdose deaths rose drastically [54]. All three studies highlight the importance of safe opioid prescribing guidelines and adequate monitoring of opioid use in the respective countries.

3. What Are the Mechanisms Behind Opioid Addiction?

In order to better understand how the use of opioids affects the brain, leading to tolerance and dependence in chronic users, it is best to first take a look at their mechanism of action. The opioid receptor family includes μ- (mu), δ- (delta) and κ- (kappa) receptors and the more recently discovered nociception/orphanin FQ receptor, all belonging to the G-protein-coupled receptor class. Plus, depending on the produced response, opioids can classically be categorized as full agonists (morphine, oxycodone, methadone), partial agonists (buprenorphine, tramadol, nalbuphine) or antagonists (naloxone, naltrexone). However, recent developments have identified new classes: mixed MOR/DOR agonists, MOR/NOR agonists (cebranopadol), as well as biased agonists (oliceridine, PZM21, mitragynine pseudoindoxyl, SR-17018) [56]. The concept of biased signaling seemed to be a promising therapeutic strategy, as the arrestin pathway promotes side effects, while G-protein signaling induces analgesic effects. However, preclinical and clinical trials have demonstrated that biased agonists cause the same side effects as opioids. On a cellular level, an opioid agonist binds to the G-protein-coupled receptor causing the α subunit to replace guanosine diphosphate (GDP) (inactive form) with intracellular guanosine triphosphate (GTP) (active form) and, hence, inhibits the adenylyl cyclase. This leads to a reduced production of cyclic adenosine monophosphate (cAMP) production. Plus, the α-GTP complex also interacts with the ion channels, producing hyperpolarization of the cells by activating the K^+ channels and decreasing neurotransmitter release by inhibiting Ca^{2+} channels [57].

Different kinases phosphorylate the opioid receptors and promote arrestin recruitment leading to receptor desensitization and internalization. Arrestin, as a scaffolding protein, can be involved in both recycling and recovery of dephosphorylated opioid receptors or degradation by lysosomes.

Additionally, the activation of the opioid receptors can cause different effects, besides analgesia, depending on the location of the receptor. Activation of μ-opioid receptors produces analgesia, respiratory depression, sedation, reduced gastric motility, nausea, vomiting and miosis. The binding of agonists to δ-opioid receptors leads to spinal and supraspinal analgesia and reduced gastric motility, and the activation of κ-opioid receptors causes spinal analgesia, dysphoria and diuresis [57]. Due to their lipophilicity, opioids can pass through the blood–brain barrier and enter the central nervous system (CNS). In the brain, opioids attach to the μ-opioid receptors and cause the analgesic effect. In this manner, opioids also activate other brain processes like the mesolimbic reward system which signals the ventral tegmental area (VTA) to release dopamine and stimulate dopamine 1 (D_1) receptors in the nucleus accumbens (NAc). The fast release of dopamine activates the reward processes, causing feelings of pleasure. Opioids are not the only drugs that increase dopamine levels in the NAc. Other substances of abuse achieve similar effects through various mechanisms. Cocaine blocks dopamine transporters and inhibits the removal of dopamine from the synaptic space, leading to enhanced dopamine levels. Alcohol increases the levels of γ-aminobutyric acid (GABA) neurotransmitter in the brain, which leads to accumulation of dopamine in the VTA [58]. Additionally, another study has associated a maximum drug reward with quickly increased dopamine levels and the binding of dopamine to both D_1 and D_2 receptors. Through brain imaging of humans, it was observed that the brain reward mechanism is activated by drugs, if dopamine increases over a short period of time (<10 min), while the slow release of dopamine over a longer period of time (1 h) did not [59]. A continued consumption of these substances of abuse (opioids, cocaine) triggers the constant release of dopamine in the NAc, which leads to the craving of the drug. Nevertheless, the mesolimbic rewards system is also regulated by endogenous opioids. The endogenous opioid system influences hedonic responses and the modifications occurring with repeated drug abuse and activates κ-receptors, blocking dopamine release in NAc. Chronic drug abuse alters the physiological functions of the brain and triggers systems to restore the natural balance in the brain. As such, repeated and excessive release of dopamine in the NAc eventually leads to the activation of auto-receptors to inhibit dopamine release, causing dysphoria and drug withdrawal symptoms [60]. Through these adaptive mechanisms, chronic opioid users develop tolerance, so that in order to obtain the same effect they need to increase the dose. Tolerance develops differently for the various effects of opioids, faster for the analgesic and euphoric effect and slower for the gastrointestinal effect. The pharmacological mechanisms involved in opioid tolerance are complex and yet to be entirely explained, but desensitization and internalization of the μ-opioid receptor seems to be one of the primary causes [61]. Long-term opioid treatment leads to dependence, as such if people stop taking the drug they experience symptoms of withdrawal and hyperalgesia (increased

pain sensation); however some people also develop an opioid addiction, characterized by a compulsive urge to take the drug, even though there is no medical requirement [62]. As a consequence, opioid addiction can often lead to drug overdose.

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