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Strategies for Preventing and Treating Opioid Use Disorder and Overdose – A Literature Review

Ian M. DeGram

Abstract

The use of prescribed and illicit opioids in the United States is still a major contributing factor to overdose deaths nationwide. Two out of every three overdose deaths in 2018 were related to chronic opioid use (Division (DCD), 2018). Continual research has been conducted over the last decade in an attempt to reduce the negative impact that opioid analgesics have on public health. The Centers for Disease Control and Prevention (CDC) released updated prescription guidelines, and in 2018 Congress addressed a proposal for a multi-step plan to reduce the stigma surrounding opioid use disorder. This article addresses these policies, as well as other prescription strategies and alternative treatments used to combat the opioid crisis in the United States. In recent years, several states have observed a modest decline in the number of opioid-related overdose deaths, but most states have not experienced significant decline. Opioid use disorder (OUD) and overdose statistics today are still triple what they were twenty years ago, so the implementation of improved prescription policies and increased use of opioid alternatives for pain management should be considered in reducing the impact of opioid misuse in the United States.

Introduction

The opioid epidemic is a major socio-economic health crisis in the United States. The issue began decades ago, but the efforts of the past decade have been effective in reducing the number of people who abuse opioids, either prescribed or illicit. One patient in every four prescribed with long-term use of prescription opioids will develop an opioid addiction, and in 2016 more than 11.5 million patients prescribed opioids reported abuse in the last year (*Opioid Overdose / Drug Overdose / CDC Injury Center, 2021*). Opioid prescription peaked in 2012, when 81.3 prescriptions were written for every 100 Americans. In 2017, that number had dropped down to 58.8 prescriptions per 100 Americans, but the amount of opioid medication prescribed today is still more than 3 times greater than in 1999 (*Opioid Overdose / Drug Overdose / CDC Injury Center, 2021*). The misuse of prescription opioids has even exceeded the use of street narcotics in the U.S. (Kaye et al., 2017).

Despite the predominance of prescription opioids, illicit opioids such as fentanyl and heroin still contribute significantly to the issue. Overdose death counts from synthetic opioids such as fentanyl have multiplied by nearly 12 times since 2013, and the most recent data from the CDC show that the death counts have accelerated during the COVID-19 pandemic as well (*Opioid Overdose / Drug Overdose / CDC Injury Center, 2021*). In addition, heroin overdose-related deaths have increased by 5 times between 2010 and 2018 (*Opioid Overdose / Drug Overdose / CDC Injury Center, 2021*). The COVID-19 pandemic is likely exacerbating the issue of opioid addiction. The shelter-in-place orders and social distancing have helped to quell the spread of the coronavirus, but for addicted individuals it has limited access to resources and treatment; the pandemic may also be hiding a resurgence of opioid addiction due to the lack of reporting and lower amounts of in-person patient/physician interaction (*The Escalation of the*

Opioid Epidemic Due to COVID-19 and Resulting Lessons About Treatment Alternatives, 2020).

In fact, from June 2019 to May 2020 the number of deaths related to synthetic opioids rose 38.4%, and the majority of this increase occurred between the months of March and May of 2020, when social distancing was first implemented and people across the country were isolated from each other (*LA County Department of Public Health*, n.d.).

Despite various efforts to control the opioid crisis, it remains a predominant issue in the United States today. Opioids are prescribed primarily as analgesics for pain relief, though they are highly regulated both because of their addictive qualities and also because they induce mood-altering effects that open the door to abuse (Kaye et al., 2017). These regulations have been constantly reformed, with the most recent being the official CDC recommendations for the prescription of opioids. Alternatives to opioids are also being explored vigorously to find novel ways to treat pain. Both of these strategies will be discussed in detail below.

Opioids work biochemically in the body by binding to the G protein-coupled receptors (GPCRs) of the neurons in the central nervous system. Non-endogenous opioids, those administered clinically and not produced by the body, have been found to bind to GPCRs both on the cell surface and inside the neurons, and have additionally been found to bind different neural pathways than endogenous opioids (*How Opioid Drugs Activate Receptors*, 2018). The relief of pain and euphoric sensations of opioid use result from the binding of the opioid molecules to the neurons of the central nervous system. There may be a way to manipulate the endogenous production of opioids rather than introducing them in drug form in order to reduce the likelihood of addiction, but there is not adequate research on this topic to inform whether this would result in a decrease in opioid abuse (*How Opioid Drugs Activate Receptors*, 2018).

The primary pathologies for which opioids are prescribed are chronic cancer pain, moderate to severe chronic pain not related to cancer, post-surgical pain management and pain management related to severe trauma (*Opioid Overdose / Drug Overdose / CDC Injury Center*, 2021). Most cases of abuse result from chronic prescription rather than acute treatments. Over time, patients taking chronic opioid pain medication can develop medical tolerance, which is defined as a loss of potency in the body that results in the need for increasing amounts of drug treatment to keep pain manageable (Benyamin et al., 2008). This decrease in effectiveness and sensitivity to the opioid can result in physical dependence to the medication, and physical dependence can lead to chemical addiction (Benyamin et al., 2008). Furthermore, a syndrome known as opioid-induced hyperalgesia (OIH) can occur in long-term opioid users. This paradoxical phenomenon is characterized by an increase in pain despite continued opioid use (Brush, 2012). However, halting opioid use can still cause withdrawal symptoms in OIH patients. The exact mechanism of OIH is unknown, and it is not fully explained by the mechanisms of tolerance or physical dependence. There is a correlation between chronic opioid use and the development of increased pain rather than analgesia (Brush, 2012).

Two common risk factors for opioid prescription are uncontrolled diabetes mellitus and end-stage renal disease (ESRD), because these patients typically experience chronic pain and require pain management. In 2017, nearly 66% of patients currently on dialysis (including diabetes and ESRD patients) were prescribed opioids for pain, and 25% of patients were prescribed amounts that were greater than the CDC recommendations (Kimmel et al., 2017). Despite effectively managing their pain, there is evidence that the use of opioids for patients on dialysis actually increases their risk of hospitalization, dialysis discontinuation and death (Kimmel et al., 2017). Patients taking opioids will experience a reduction of pain in most cases,

but there are many side effects, such as physical dependence, immunosuppression, opioid-induced hyperalgesia (increased pain), constipation, urinary retention, neurological sedation and even coma or death that bring into question their use as a prescription analgesic (Benyamin et al., 2008).

There have been several new or modified ideas proposed for solving the opioid problem in the past decade. One of the more prominent is to find and implement alternative analgesics such as buprenorphine, which is slightly less addictive and is not associated with as many negative side effects (*The Escalation of the Opioid Epidemic Due to COVID-19 and Resulting Lessons About Treatment Alternatives*, n.d.). Further improvements to prescription policies and strategies have also been considered in the last decade. The CDC released an updated guideline to clinical opioid prescription in 2016. These recommendations include a) how to determine when to initiate/continue opioid treatment, b) opioid selection, dosage, duration, etc., and c) assessing risks and harms of the use of opioids (“CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016,” 2016). Expectedly, these recommendations suggest the use of nonpharmacologic or non-opioid treatment before the use of opioids, and that when opioids are used they are used at the lowest effective dose for the least amount of time possible to avoid chronic use, abuse and/or addiction (“CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016,” 2016).

This literature review aims to summarize the strategies to combat the opioid epidemic that have been proposed in the last decade. The two primary strategies are the use of alternative pain management therapies and improvements to prescription guidelines for clinicians. There are several less studied strategies that will be addressed as well, such as the possible development of a vaccine to prevent or alleviate addiction and withdrawal symptoms in patients with OUD. A

discussion of the most effective modern strategies to combat this drug crisis is necessary due to the fact that a literature review has not been published on the subject since 2014, and the effectiveness of the strategies that are currently employed have not been successful in reducing the negative impact of opioid abuse on society.

Prescription Strategies

Historically, the primary method employed to reduce the impact of the opioid crisis is to look for new ways to improve the prescription strategies for physicians. Prescribing appropriate amounts of medication for appropriate time frames can help to reduce the prevalence of opioid use disorders. The difficulty arises in determining what the proper amount of medication should be. In order to help standardize the process for healthcare providers, the CDC released new guidelines on opioid prescription in 2016 that have become the standard recommendations followed by clinicians in the US.

The first and most obvious recommendation is that clinicians should choose to prescribe nonpharmacologic or non-opioid drug treatments for acute and chronic pain. These may include non-steroidal anti-inflammatory drugs (NSAIDs), antidepressants, lidocaine patches, psychosocial behavioral therapy and even cannabis, all of which will be discussed in detail later. If opioids are used, the clinician should discuss the risks and benefits with the patients as well as establish a recommended time period for the cessation of opioid treatment (“CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016,” 2016). The CDC recommendations that follow define the process that clinicians should work through when prescribing opioids or managing opioid treatment:

“When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids. When opioids are started, clinicians should prescribe the lowest

effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when increasing dosage to ≥ 50 morphine milligram equivalents (MME)/day, and should avoid increasing dosage to ≥ 90 MME/day or carefully justify a decision to titrate dosage to ≥ 90 MME/day. Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than seven days will rarely be needed. Clinicians should evaluate benefits and harms with patients within 1 to 4 weeks of starting opioid therapy for chronic pain or of dose escalation. Clinicians should evaluate benefits and harms of continued therapy with patients every 3 months or more frequently. If benefits do not outweigh harms of continued opioid therapy, clinicians should optimize other therapies and work with patients to taper opioids to lower dosages or to taper and discontinue opioids. Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms. Clinicians should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone when factors that increase risk for opioid overdose, such as history of overdose, history of substance use disorder, higher opioid dosages (≥ 50 MME/day), or concurrent benzodiazepine use, are present. Clinicians should review the patient's history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or dangerous combinations that put him or her at high risk for overdose. Clinicians should review PDMP data when starting opioid therapy for chronic pain and periodically during opioid therapy for chronic pain, ranging from every prescription to every 3 months. When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs. Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible. Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder." ("CDC Guideline for Prescribing Opioids for Chronic Pain — United States" 2016)

The CDC guidelines are based on a multitude of studies conducted both in the United States and around the world. The guidelines are a helpful tool for clinicians, but there are also several other predictive methods that can be utilized to assess the risks of opioid prescription and

how best to combat those risks. A predominant tool that is referenced in the 2016 CDC guidelines is prescription drug monitoring program (PDMP) data, which tracks the rate and dosage of prescriptions in a geographical area, as well as the prevalence of documented opioid use disorder patients in the same area (Strickler et al., 2020). One such PDMP is known as the Prescription Behavior Surveillance System (PBSS); PBSS and similar PDMPs are in use to track opioid prescription in almost every state (ibid.). From 2010-2016, the PBSS gathered data from 11 different states on the prescription rate, daily opioid dosage, percentage of patients with high dosages and percentage of opioid treatments with overlapping benzodiazepine prescriptions. The study found that rates in all of the aforementioned categories had declined over the six-year period, and the information gathered by PBSS from the 11 states included in the surveillance system was also consistent with national data (ibid.).

In 2017 a prescription opioid registry protocol was established based on the CDC guidelines that had been published a year earlier (Ray et al., 2017). Through the use of a retrospective cohort study, the team created a system of algorithms capable of identifying daily opioid use, MME dosages, length of use and other factors to determine a patient's likelihood of becoming a chronic opioid user (ibid.). The study found that common predictors of chronic opioid use were chronic pain, use of opioids for sedative/hypnotic purposes, psychiatric disorders and non-opioid substance use disorders (ibid.). The algorithms developed have been put to use as a resource for further research on opioid use, as well as being used clinically to assess a patient's risk of opioid use disorder (ibid.). PBSS and other PDMPs like it show that the regulation of controlled substances and various prescription strategies that have been employed to reduce the prevalence of opioid use disorder have been significantly effective. However, the prevalence of opioid use disorder in 2016 was still more than triple that of 1999, indicating that the opioid

crisis in America is far from over despite recent declines in opioid use disorder and overdose deaths (Strickler et al., 2020).

Part of the issue is that the United States is overly fond of post-surgical opioid therapy when compared to the rest of the developed world. “Studies from the USA and Canada suggest that up to 1 in 10 patients become persistent opioid users after surgery,” (Fiore et al., 2019). Additionally, 42-71% of opioids prescribed after surgery will likely go unused and were therefore unnecessary to prescribe for the patient in the first place (ibid.). These unaccounted for medications can also find their way into illicit use on the streets. The use of opioid analgesic treatments post-operatively is common in North America and much less so in Europe and Asia; similarly, post-surgical pain relief outcomes are more positive in Europe and Asia than in North America (ibid.). The prevalence of opioid prescription is greater in North America when compared to the rest of the world, but pain management appears to be slightly more favorable in countries where opioids are used less frequently. Countries in Europe and Asia use non-opioid pharmacologic analgesics such as NSAIDs, antidepressants and other non-opioid therapies at higher rates than the US and Canada, and thus they experience less opioid-related addiction and overdose than North American countries.

A study conducted in 2018 examined two cohorts of patients who had undergone abdominal or gynecological surgery and received pain management therapy in the United States. The first cohort received an average dosage of opioids, while the second cohort was prescribed using an ultra-restrictive opioid prescription protocol (UROPP), greatly reducing the opioid dosage for the second cohort (Mark et al., 2018). When comparing the two cohorts, the study found no statistically significant difference in pain scores or post-surgical complications,

suggesting that the use of a larger opioid prescription is not associated with greater pain relief (ibid.).

Creating strictly clinical prescription guidelines has been moderately effective. However, there is an element of social stigma to the issue of substance use disorders that can prevent clinicians from accurately assessing their patient's risk of chronic opioid use. One method that has been proposed to mitigate the stigma surrounding the issue is to carefully choose terminology during the patient-provider interaction when assessing risks and benefits (Lyden & Binswanger, 2019). For example, the use of the terms "abuser", "addict" or "substance abuse" incur a negative connotation about the patient – the patient may often perceive their opioid use disorder to be their fault rather than a clinical condition requiring treatment (ibid.). Lyden and Binswanger propose the use of phrases such as "a patient with opioid use disorder" instead, to address the issue as a medical problem rather than a patient problem (ibid.). The CDC addressed the need to reduce the stigma surrounding the opioid crisis as well in their 2018 guideline for evidence-based strategies on preventing opioid overdose (*Evidence-Based Strategies for Preventing Opioid Overdose: What's Working in the United States, 2018*, n.d.). The use of state legislation that have come to be known as "911 Good Samaritan Laws" has been recommended by the CDC to protect individuals who experience or witness an overdose from legal obligation (ibid.). Often those calling EMS are illicit drug users themselves, and calling 911 can lead to their arrest; therefore, Good Samaritan Laws offer protection for these witnesses so that they are not hindered from calling for medical assistance when someone near them overdoses (ibid.). Another method proposed to reduce the stigma surrounding opioid use, as well as to reduce the number of overdose deaths related to opioids in America, is to make naloxone distribution to chronic opioid-users commonplace and affordable (ibid.). Naloxone, commonly known as

Narcan, is a drug that is delivered in response to opioid overdose that binds to opioid receptors and negates the effects of whatever opioid is in the patient's system. The CDC's goal is to send patients prescribed chronic opioids or diagnosed with opioid use disorder home with their own naloxone doses so that they or bystanders near them can deliver a potentially life-saving dose (ibid.). The mass distribution of these self-Narcan doses, similar in theory to carrying an Epi-pen, could help to normalize treatment for opioid use disorder and allow patients to more openly approach healthcare professionals with opioid-related health problems.

Continually updating the recommended prescription strategies is the primary method that the government employs to combat the opioid epidemic. The CDC guidelines are the national gold standard that clinicians can draw guidance from when treating their patients. These guidelines are based on extensive data that are gathered with the use of PDMPs and recent studies on the use of opioids in pain analgesia. One of the new recommendations in the last decade has been to focus more on reducing the stigma around opioid use via community educational programs and Good Samaritan Laws. In recent years it has been shown that European and Asian countries that do not struggle as prominently with opioid misuse are also not prescribing opioids as frequently as North American countries. The increased use of alternative medications and therapies in these countries is one of the reasons why this disparity exists, and the next section will explore what alternatives are available so that providers can avoid prescribing opioids altogether.

Alternative Strategies

The opioid crisis is a complex problem, so a simple solution will not alleviate the public health issues of opioid abuse and addiction. Various prescription strategies have been shown to have a positive effect on the prevalence of opioid related health issues and death, but we still

have a long way to go before opioid use is no longer a public health problem. The second most employed method for reducing the effects of opioid use in the United States is the use of non-opioid alternative medications and treatments. Alternatives that are present today may very well be more effective for a variety of non-cancer chronic pain patients. In fact, there is very little evidence that opioid prescription is significantly effective at reducing gastrointestinal pain (Szigethy et al., 2018). The effectiveness of opioid treatment has largely been studied in the treatment of musculoskeletal pathologies and cancer patients, so the extrapolation to all pain control is difficult to make (ibid.). For many patients, this means that the opioid medication they are prescribed to treat their pain may not be the most effective drug therapy.

There are numerous non-opioid pharmacological treatments for acute and chronic pain. Part of the 2016 CDC prescription guidelines included a section on non-opioid pain medication, specifically for non-cancer chronic pain therapy. The aforementioned step-wise recommendations state that non-opioid drugs should be recommended first, the most common of which are acetaminophen and ibuprofen (*Opioid Overdose / Drug Overdose / CDC Injury Center, 2021*). These are the least effective medications for pain management, but if pain can be controlled using them then it should. A large portion of the chronic pain that patients experience is a result of inflammation, so non-steroidal anti-inflammatory drugs (NSAIDs) are also recommended for inflammatory pain (ibid.). Pain associated with neuropathy can be treated effectively with Gabapentin or tricyclic antidepressants, and fibromyalgia-associated pain can be controlled using pregabalin and/or serotonin/norepinephrine reuptake inhibitors (SNRIs) as well (ibid.). Specific tetracyclic antidepressants (TCAs) or SNRIs may be used as a pharmacological therapy for generalized chronic pain and have been shown to be effective in non-musculoskeletal and non-cancer chronic pain (Szigethy et al., 2018). Antipsychotic medications in low doses and

anticonvulsant medication have also been shown to be effective at controlling pain in patients with inflammatory bowel disease (IBD) and other gastrointestinal pathologies (ibid.). There are numerous pharmacological treatments available for pain management that do not incur the risk of opioid addiction, and these medications are recommended first. Their use should be further implemented so that the prescription of opioids can be reduced.

There are several other less-established pharmacological drug therapies available that may act as a replacement for opioids. More recently, the use of cannabis for pain management therapy has been taken under serious consideration, specifically for cancer patients (Bennett et al., 2017). Cannabidiol (CBD) has been found to reduce inflammation, seizures and muscle spasm, making it a prime candidate for most pain management (ibid.). In fact, the legalization of marijuana for medicinal purposes is correlated with a reduction in the number of opioid overdoses, indicating that the legalization of this drug could act in a multi-faceted manner to reduce the impact of the opioid crisis (ibid.).

Topical medications have also been recommended for use in chronic pain management. Lidocaine patches for use in neuropathic or musculoskeletal pain, topical NSAIDs and capsaicin cream for use in neuropathic, musculoskeletal and even gastrointestinal pain have all been recommended by the CDC as non-opioid alternatives (*Opioid Overdose / Drug Overdose / CDC Injury Center, 2021*). These medications have the benefit of causing minimal side effects compared to other opioid and non-opioid therapy and are convenient to administer (LaPietra & Motov, 2019). Another topical treatment has experienced recent increased use for myofascial pain: trigger point injections (ibid.). Many chronic musculoskeletal pain patients experience their symptoms because of Myofascial Pain Syndrome (MPS), so trigger point injections may be more effective than opioid therapy to manage pain (ibid.). A trigger point injection involves the

insertion of a needle into a trigger point, which is a small, tight band of skeletal muscle that is painful to movement and touch. These tender areas are often the result of chronic strain or skeletal muscle disorders (ibid.).

Pharmacological treatments are not the only potential alternative to opioid pain management therapy. In light of the coronavirus pandemic, researchers Marcelina Jasmine Silva, DO, and Zakary Kelly, MBA at the *American Journal of Managed Care* have found that the social distancing protocols put in place to help control the pandemic have exacerbated the issue of opioid abuse (*The Escalation of the Opioid Epidemic Due to COVID-19 and Resulting Lessons About Treatment Alternatives*, n.d.). The researchers have made the proposal that if social distancing has negatively impacted the opioid crisis, then doing the opposite should positively impact opioid use (ibid.). Health education, the formation of relationships between patient and physician, stress reduction and physical human connection may all be measurable factors that can be employed in the future to help combat the opioid crisis (ibid.).

Furthermore, psychosocial behavioral therapy has started to be employed as a non-pharmacological alternative (Szigethy et al., 2018). There has been recent growth in the literature addressing the use of therapy and mindfulness training showing that there is potential for treating chronic pain without the use of strong opioid medication (ibid.). Cognitive and psychological intervention has primarily been proposed as one factor in a comprehensive treatment plan that would likely still involve non-opioid pharmacological treatment, but there is a positive association between behavioral therapy and reduced pain in chronic pain patients (ibid.). Vital to the successfulness of a psychosocial behavioral approach is a strong and positive relationship between patient and provider, so that patients can understand the benefits and consequences of a long-term chronic pain treatment with minimal stress (ibid.).

The options for non-opioid pain management grow every year as new research is published on the topic. However, in 2018 Congress was presented with a 3-pronged comprehensive approach to implement some of these new ideas into public health policy (Manchikanti et al., 2018). The first proverbial prong of this proposal involves an aggressive public health education campaign tailored to providers, patients and the general public about the intricacies and issues surrounding the opioid crisis (ibid.). This educational campaign would specifically inform on illicit drugs such as heroin and fentanyl that currently run rampant on the streets of the US. It also involves education of patients currently prescribed opioid medications and general education on the side effects of opioids, particularly when they are used in tandem with benzodiazepines (ibid.). The use of opioids and benzodiazepines together is not recommended by the CDC guidelines because both are sedative drug therapies that depress the nervous system. When patients overdose on either benzodiazepines or opioids, it is often because the sedative nature of the drug has depressed the patient's breathing to the point of inducing hypoxia, or a systemic lack of oxygen (*Benzodiazepines and Opioids / National Institute on Drug Abuse (NIDA)*, n.d.).

The second prong of this proposal involves the implementation of a "National All Schedules Prescription Electronic Reporting Act (NASPER)" program to facilitate ease of access in the documentation of opioid prescription (Manchikanti et al., 2018). This also involves making non-opioid pain management options more advertised and readily available, so that physicians do not feel pressured to give patients opioids. Many providers have reported feeling administrative pressure to prescribe opioids in order to keep patient satisfaction numbers high (Bennett et al., 2017). The third and final aspect of the 2018 proposal focuses on increasing the prevalence of buprenorphine for use in treating patients who are at risk for or have already

developed opioid use disorder (Manchikanti et al., 2018). Buprenorphine, along with methadone and naltrexone, are the three medications that are FDA approved for treatment in opioid use disorder (OUD) patients (*A Shot Against Opioids*, 2020). However, this proposal suggests the reduction in classification of buprenorphine and the removal of methadone from the list of approved medications, as methadone has been found to contribute to over 3,000 deaths every year, and buprenorphine has been found to have a less negative influence on patient health (Manchikanti et al., 2018). These suggestions would be taken into account and added onto the current 2016 CDC guidelines for opioid prescription in the healthcare setting if the proposal were to be approved.

The use of opioids to treat chronic pain in the United States has existed for quite some time. However, new research has brought to light the fact that opioids may not be as effective as previously thought. Given the high risk of addiction, non-opioid analgesics are beginning to see more use in clinical settings. Pharmacologic treatments that have been in use for acute pain such as ibuprofen, NSAIDs, antidepressants, SNRIs, cannabis and anti-psychotics have seen more use in chronic pain in an attempt to reduce opioid prescription. Topical treatments such as lidocaine patches and trigger point injections have also shown promise. Non-pharmacological treatments such as psychosocial behavioral therapy and face-to-face support groups have also been theorized to alleviate the risk of and complications associated with opioid use disorders. Finally, the U.S. Congress proposed a 3-step plan designed to implement these various alternative treatments effectively throughout the U.S. healthcare system. Countries that use opioid alternatives more frequently also report lower numbers of opioid use disorder and overdose, so if the proposal is approved it will likely have a positive impact on the opioid epidemic in the United States.

Discussion

The opioid epidemic has been an issue for decades, and it continues to plague the American healthcare system, and to a lesser extent worldwide public health, to this day. In 2018, two out of every three overdose deaths in the United States were opioid related (Division (DCD), 2018). The most recent drug overdose statistics from the CDC reveal that a majority of states have seen no significant change from 2018-2019 in the number of opioid-related overdose deaths. However, seven states reported a decrease in opioid-related overdose deaths (ibid.). Of the seven states that saw a significant decrease in deaths, the average percent decrease was 17.5%; Oklahoma had the greatest decrease in overdose deaths, reporting a 20.9% decrease in deaths from 2018 to 2019 (ibid.). This means that nationally the statistics are improving, but most states are individually remaining stagnant in their number of opioid deaths. Updated prescription strategies and alternative treatments for chronic pain need to be implemented to a greater extent if improvements are to be seen across the board.

The use of opioid alternatives and the search for more effective prescription strategies are not the only two methods of reducing the number of opioid-related deaths in the United States. Patients who are diagnosed with opioid use disorder have several options available to them. The primary treatment for patients with opioid use disorder is one of three FDA-approved medications: methadone, naltrexone and buprenorphine (*A Shot Against Opioids*, 2020). These medications help to alleviate the symptoms of addiction and withdrawal while the physician tries to wean the patient off of their opioid prescription (ibid.). A different medication known as naloxone (or Narcan) is a single dose emergency treatment to counteract the effects of an opioid overdose. In 2018, the registered prescriptions for Narcan doubled (Division (DCD), 2018). Because the number of opioid-related overdose deaths have steadily decreased in recent years,

the similar rise in Narcan prescription suggests a correlation between the two. Despite this suggested correlation, it is not known whether the increase in Narcan prescription could have caused the decrease in overdose deaths. It is also possible that the use of sociopolitical campaigns to reduce stigma surrounding opioid use could also lead to greater distribution of life-saving Narcan doses in the community. Either way, the evidence seems to suggest that the proportion of patients being treated for OUD is increasing while the number of opioid-related deaths is decreasing.

However, the fact still stands that in 2019 nearly 10.1 million Americans reported opioid misuse, and 760,000 people have died since 1999 from the use of opioid analgesics (Division (DCD), 2018). Despite recent improvements, the use of opioids is still a public health crisis in the United States, so the implementation of novel strategies to prevent or treat opioid use disorder is being researched. To create a new method for treatment of patients with OUD, the National Institute of Health established the Helping to End Addiction Long-term (HEAL) Initiative in 2018, which focuses primarily on research for a vaccine that could treat opioid use disorder (*A Shot Against Opioids*, 2020). The benefits to a vaccine are two-fold. Firstly, a vaccine against opioid addiction would theoretically act by binding to the target opioid so that it could not act on the brain's pain centers. Working in much the same way that viral vaccines do, the proposed opioid vaccine would help the body to build up an immunity to the target opioid, so that the immune system would destroy the opioid before it could affect the body (ibid.). Secondly, the building up of passive immunity would allow for the administration of alternative pain medication during the treatment for OUD, because the passive immunity would lead to the inactivation of opioids in the body (ibid.). Normally, the treatment of pain with a combination of opioids and other analgesics can cause adverse side effects such as depressed neurological

activity, constipation, hypoxia and cognitive impairment (for example, the aforementioned side effects of concurrent benzodiazepine and opioid use), but the inactivated opioid molecules will no longer exhibit these negative drug interactions. This means that patients who are being taken off of their opioid pain medication would likely have a less painful recovery process because they would be able to utilize one of the many alternatives to opioids without having to worry about drug interactions. Current research on the vaccine employs an oxycodone-targeting vaccine to test for human efficacy and vaccine lifespan. If human trials are successful, the HEAL Initiative team is also leading research for a human fentanyl and heroin vaccination (ibid.). Fentanyl and heroin constitute a large portion of the illicit opioid use that contributes to overall opioid-related death, so vaccinations against fentanyl and heroin addiction could vastly lessen the rate of death in the United States and worldwide (ibid.).

Conclusion

This literature review summarizes the current research and methods in practice in the healthcare system to combat the opioid crisis. The CDC guidelines recommend the use of opioid alternatives wherever possible, and when opioids are prescribed, the CDC gives specific recommendations for dosage, prescription length and exceptions to the rule. For the last few decades, these two methods have been more or less the primary response to the opioid problem. However, newer prescription strategies that emphasize understanding, education and destigmatization have gained traction in the last several years. Likewise, new alternative analgesic treatments, both pharmacological and non-pharmacological, have been proposed within the last decade that show promise of being competitive with the pain management capabilities of opioids, but with less addictive side effects. Pain management is the primary goal when prescribing opioids, and several alternative methods discussed in the literature of this review

show promise. Finally, the recent research surrounding a vaccine for patients with OUD is a newer approach to help catalyze the reduction in opioid-related deaths. This new approach could help to break the social stigma surrounding illicit opioid use so that physicians can treat patients and prescribe them appropriate medications or pain management therapies. Ultimately, the goal of opioid research moving forward should be to discover ways to eliminate opioid use from the healthcare system entirely. Research into treatments that break the cycle of addiction for OUD patients show promise, as do the alternative analgesic therapies that have been introduced in the last decade. Current statistics have shown that the healthcare system is making slow progress toward opioid-free pain relief, but much research is still needed before the opioid crisis can be averted.

Abbreviation Index

Term	Abbreviation	Term	Abbreviation
Centers for Disease Control and Prevention	CDC	Ultra-Restrictive Opioid Prescription Protocol	UROPP
Opioid Use Disorder	OUD	Serotonin/Norepinephrine Reuptake Inhibitors	SNRIs
G-Protein Coupled Receptors	GPCRs	Tetracyclic Antidepressants	TCAs
Opioid-Induced Hyperalgesia	OIH	Inflammatory Bowel Disease	IBD
End Stage Renal Disease	ESRD	Cannabidiol	CBD
Non-Steroidal Anti-Inflammatory Drugs	NSAIDs	Myofascial Pain Syndrome	MPS
Extended Release/Long-Acting Opioids	ER/LAs	National All Schedules Prescription Electronic Reporting Act	NASPER
Morphine Milligram Equivalents per day	MME/day	Federal Drug Administration	FDA
Prescription Drug Monitoring Program	PDMP	Helping to End Addiction Long-term Initiative	HEAL

Prescription Behavior Surveillance System	PBSS		
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