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PAIN MEDICINE (GJ MEREDITH, SECTION EDITOR)

Opioid Safety: We Are Not There Yet

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Abstract Opioids are highly effective in acute pain control; however, their use for the treatment of chronic non-cancer pain is controversial. Chronic opioid use is associated with several side effects that include and are not limited to tolerance, dependence, and hyperalgesia. Opioid prescription drug overdose is at a national epidemic status in the USA. It is estimated that a prescription drug overdose death occurs every 19 min. Several national and state interventions have been implemented to address the staggering statistics of increased deaths due to opioid overdose. The recently released Center of Disease Control (CDC) practice guidelines are designed to improve physician patient communication and avoid opioid prescription drug overdose. In this chapter, we will review some of the recent guidelines for opioid prescribing and the current efforts in place to address this epidemic.

Keywords Chronic pain · Opioids · Prescription drug overdose · Opioid prescribing guidelines · Opioid safety

Introduction

Opioids are some of the most effective pain relievers known. However, evidence of the long-term benefits of opioids in treatment of chronic pain remains inconclusive, while strong evidence of potential harm is on the rise. In an effort to raise awareness to the prevalence of chronic pain, the American Pain Society ran a successful but controversial campaign in 1999. The campaign advocated for adopting pain as the fifth vital sign. Pain as a fifth vital sign was later adopted by Joint Commission of accreditation (JACHO) and the Veterans Affairs Health Care System (VAHCS). Since this endorsement, there has been an escalating rise in the number of opioid prescriptions for chronic non-cancer pain, in addition to being the standard of care for moderate to severe pain [1]. This shift in practice is clearly reflected in the dramatic increase in the sales of opioids and consequently the overdose deaths due to opioids, which has surpassed heroin and marijuana. There has also been a dramatic increase in admission to substance abuse programs. Importantly, this epidemic has also emerged in many other developed and developing countries such as Canada and Germany among others. For example, it is estimated that 1–3 % of Canadians and close to 2 million Germans abuse prescription opioids.

Despite the high demand for opioids for moderate to severe pain, opioids are only effective for short-term pain relief and have highly variable effectiveness in the long-term relief (greater than 3–6 months) of pain [2]. Thus far, there has been little progress in alternative non-invasive therapeutic strategies for chronic pain patients maintained on opioids. Rightfully so, much of the effort has been focused on improving patient compliance and prescription practices. Therefore, the approach to the current opioid abuse epidemic requires not only implementation of safer practice guidelines, but also novel therapeutic approaches. Here, we provide an overview of the magnitude of the current epidemic of prescription opioid abuse and outline the new CDC guidelines for opioid prescribing.

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Opioid Use Disorder

Opioid use disorder is defined as both opioid dependence and opioid abuse combined into one disorder according to the new Diagnostic and Statistical Manual of Mental Disorders (DSMV).

In concurrence with the dramatic increase of opioid prescriptions, the incidence of opioid use disorder has risen. It is currently a major health problem in the USA with increasing morbidity and mortality due to misuse and abuse [3, 4]. Recent reports have outlined the rise in opioid use, abuse, and overdose deaths due to prescription opioid medications [5]. Currently, more than 1300 deaths due to overdose per year involve prescription opioids. Deaths from drug overdose are now the leading cause of death among persons aged 35 to 54, surpassing motor vehicle accidents [6]. The rise in opioid related problems led the FDA to propose a risk evaluation and mitigation strategy (REMS) for all long acting and immediate release opioids. The advisory panel also urged that education for safe prescribing of opioids become mandatory for prescribing physicians [7]. A shift in clinical practice in the form of leniency in opioid prescription patterns has occurred gradually over last 20 or more years. Consequently, this has resulted in a staggering increase in number of opioid sales, prescription drug abuse overdoses, and admissions to substance abuse programs. Responding to these concerns places a burden on pain treating providers to find the right balance as they strive to properly address the patients' needs, while avoiding under prescribing or over-prescribing, and monitoring for misuse and abuse [8].

Adverse Effects of Long-Term Opioid Use

Long-term treatment with opioids can be complicated by numerous and dangerous side effects development of tolerance, dependency, addiction, abnormal pain sensitivity, hormonal changes, and immune modulation [9]. Thus, whereas opioids were initially considered a solution for chronic pain, they have been shown to further exacerbate the problem [10]. A more cautious approach towards escalating doses of opioids is now being advised as new evidence suggests that prolonged high dose opioid is neither safe nor effective [9].

Emerging evidence reveals a more complex and wide range of side effects associated with long-term opioid use that are often overlooked. In addition to tolerance, there is also an increase in pain perception due to neuronal plasticity at the spinal dorsal horn level or more central in the rostroventral medulla (Fig. 1) and hippocampus [11]. Opioids in animal and humans have also been found to widely affect neuroendocrine functions. In a review by Vuong et al., most of the studies that the authors found seemed to highlight the acute changes in the neuroendocrine function, despite chronic changes being more relevant. Opioids were found to increase growth hormone and decrease luteinizing hormone, leading to hypogonadism and weight gain [12]. The immune suppression effects of opioids have been known since 1890, when morphine was shown to decrease the resistance to bacterial infection in guinea pigs [13]. Immune cells express classic and novel opioid receptors, which are believed to be the site of the non-proliferative action of opioids [14, 15], and long-term opioids have been shown to compromise optimal function of the immune response system. The clinical effects of opioids on the immune system are of particular concern in immune-compromised patients such as HIV infected patients and the elderly [16]. Opioids also increase the risk of pneumonia in older adults; the odds of developing pneumonia were found to be 1.38 in elderly opioid users (95% confidence interval (CI) = 1.08–1.76) versus non-opioid users. Despite the risk being highest in the first 14 days of opioid use, there was an increased risk of pneumonia with long-acting opioids had a higher odds ratio (OR) (3.43 (95% CI = 1.44–8.21) versus non-opioid users, as for short-acting opioids, OR was 1.27 (95% CI = 0.98–1.64) versus non-opioid users. In the same population the risk of pneumonia was not seen with other similar drugs such as benzodiazepines [17].

Chronic Exposure to Opioids Increase Pain and Neuronal Plasticity

In order to develop innovative treatment strategies for chronic pain, mechanistic understanding of the underlying pathology is paramount. A critical determinant of the pathophysiology of chronic pain is the maladaptive inflammatory response, which mediates and propagates chronic pain long after the initial insult subsides. At the spinal cord level macrophages and lymphocytes have been shown to invade the dorsal root ganglia (DRG) after acute injury in rodents.[27] Macrophages and lymphocytes are essential for initial healing; however, problems arise when their presence persist at the DRG after healing. These cells secrete pro-inflammatory cytokines that generate spontaneous impulses in sensory nerves. Continuous and spontaneous firings of sensory nerves lead to the generation or progression of acute pain into chronic neuropathic pain [18]. Pro-inflammatory cytokines play a significant role in peripheral and central sensitization causing increased severity and duration of pain [19].

The chronic administration of opioids increases levels of circulating inflammatory cytokines interleukin 1B (IL1B), interleukin 6 (IL6), and tumor necrosis factor (TNF), all of which lead to hyperalgesia and increased pain [20]. Unfortunately, the chronic use of anti-inflammatory drugs to counteract this response is suboptimal and is associated with a marked increase in adverse effects including gastrointestinal, renal, and cardiovascular complications, resulting in a

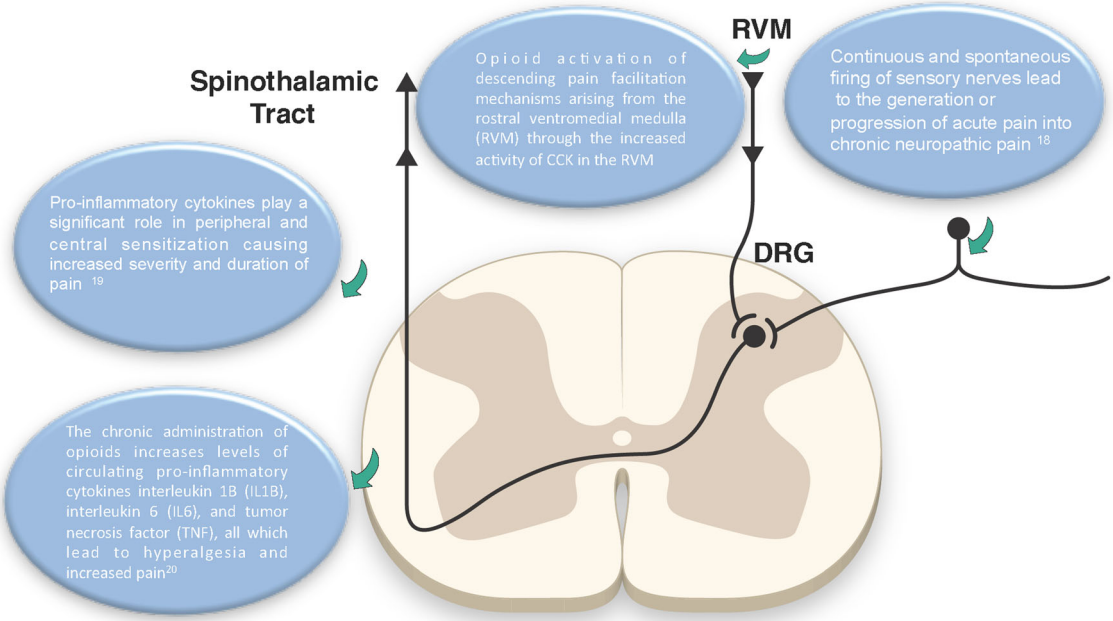

Fig. 1 Role of opioids in the development of central sensitization. Schematic of the effect of opioids on mechanisms of pain conduction and perception. Opioids enhance spontaneous firing of the peripheral nerves and facilitate the descending facilitatory pathways from the rostroventral medulla (*RVM*). In addition, opioids increase levels of circulating inflammatory mediators resulting in central sensitization. *DRG* dorsal root ganglia, *RVM* rostroventral medulla, *CCK* cholecystokinin

significant increase in morbidity and mortality. Therefore, there is a significant disconnect between the escalating use of opioids for treatment of chronic pain and the toxic effects of opioids upon inflammatory processes prolonging the pain.

Efforts in Place to Promote Safe Opioid Prescribing Practices and Use

In response to the growing epidemic of opioid prescription epidemic, several efforts have been made across multiple levels including state and federal guidelines. Although many of these regulatory efforts have met resistance because they complicate opioid prescription and increase the burden on pain management specialists, these efforts are long overdue and are just the beginning. The medical community needs a paradigm shift so as not to be unnecessarily dependent on opioids and consider them a panacea. In 2012, the FDA approved a risk evaluation and mitigation strategy (REMS) for extended release (ER) and long-acting (LA) opioid medications. The REMS program has been in effect since 2007 and was not originally designed to specifically target a certain class of drugs. The inclusion of opioids in the REMS program in 2012 reflected increased awareness and concern of the federal government about the opioid prescription epidemic, especially with regards to long-acting and extended release opioids. The most important part of this plan was to enhance the education of the prescribers, requiring over 20 opioid manufacturers to provide educational programs on appropriate use of these drugs. Patient education on the use of opioids and potential adverse effects was also included in the program. The program also included partnering with the US Drug Enforcement Administration (DEA) as well as law enforcement, and state-based databases to prevent unlawful dissemination of prescription opioids.

By the time this REMS program was announced in 2012, most states already had setup state prescription databases to track opioids prescriptions. In fact, the National Alliance for State Drug Laws (NAMSDL) was established in 1993, with the primary goal of "creating a model code of laws to help states effectively address alcohol and other drug abuse." While NAMSDL casts a wide net over alcohol and drug abuse in general, it also is charged with drafting model state drug laws, policies, and regulations. The NAMSDL also oversees prescription drug monitoring programs through individual state prescription databases.

More recently, the CDC conducted a review based on available evidence on effectiveness and risks of opioids, which included observational studies and randomized clinical trials. This review, that evaluated any long-term benefit of opioids in chronic pain (more than 1 year of use), found strong evidence that opioid use was associated with a significant increase in morbidity and mortality. As a result, in 2016, the CDC released 12 recommendations, the most prominent being that non-opioids pain medications are now the first line of therapy for chronic pain. Additional recommendations included establishing treatment goals with the patients, the use of lowest effective dose, plans for assessing benefits, complications,

and dependence, as well as management of opioid use disorders when they arise [21•].

(http://www.cdc.gov/drugoverdose/prescribing/guideline.html).

Finally, the National Institute of Health (NIH), through the National Institute on Drug Abuse (NIDA) is charged with advancing science of drug abuse and addiction. Recognizing the paucity of studies to address the current opioid abuse epidemic, NIDA has systematically increased funding for research focused on opioid abuse. Importantly, NIDA started an initiative on "Prescription Opioid Use and Abuse in the Treatment of Pain," which is designed to increase funding for projects focusing on various aspects of opioid addictions such as neurobiology, genetics, screening, prevention, and treatment. Moreover, NIDA is actively funding projects that explore new classes of pain medications as an alternative to opioids.

Alternative Treatment Options Instead of Long-Term Opioid Prescriptions

Due to the rise of opioid misuse, abuse, dependence, and overdose, it is important to investigate other treatment options. Not only could new treatment options limit the opioid prescription epidemic, but could also potentially be more efficacious in both the short term, long term, and improve the overall patient's quality of life across both physical and psychological measures [22, 23•]. Recent studies have tested other treatment options and have reported encouraging results [22, 23•, 24]. An interdisciplinary group-based therapy approach was tested among chronic pain patients with suicidal ideation, because suicide rates among chronic pain patients is at least double the rate of the normal population [23•]. The treatment strategy included twice a week therapy meetings, exercise 4 days a week, group discussions, and relaxation training. The researchers reported that interdisciplinary group-based therapy approach reduced suicidal ideation as well as reported pain scores [23•]. Building on the recent emphasis on mental health in regards to chronic pain, many alternative treatments are psychological in nature and vary by modality. These include mindfulness, acceptance and commitment therapy (ACT), and cognitive behavioral therapy (CBT), and all have been investigated as therapeutic modalities for treating chronic pain. The literature suggests all have been a component of a successful treatment program [22, 24, 25]. All three emphasize and teach volitional control of pain perception and other emotions of distress, and each study explored the efficacy of one of those three therapeutic modalities and reported lower self-reported pain, decreased depression, anxiety, and disability [22, 24, 25].

In addition, alternative pharmacological approaches have also been studied. Because chronic pain is frequently comorbid with depression, researchers have studied psychotropics including antidepressants, anticonvulsants, and other analgesics [26]. Several studies have investigated the efficacy of tricyclics (TCAs) antidepressants and tetratrycyclics (TeTCAs) in the treatment of various chronic pain conditions and reported that these medications effectively reduced symptoms of chronic pain [26–29]. Researchers have also studied other types of antidepressants including serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) and have found decreased symptoms of chronic pain similar to those of the TCAs and TeTCAs [26, 30, 31]. Taken together, the literature suggests that other forms of medications and therapeutic modalities may be effective in treating chronic pain either alone or in conjunction with more traditional forms of analgesics, circumventing the need to long-term opioid treatment. Finally, the search for newer classes of analgesics has been ongoing for decades, and although no new drugs have reached the clinic yet, several promising new molecules have been recently discovered. For example, in a recent *Nature* article, investigators used computational docking to identify a new compound PZM21which had significantly superior analgesic properties, without apparent respiratory depression or opioid-like reinforcing activity [32••]. This and other similar lines of research hold significant promise for finding opioid alternatives, without the side effects, and importantly, without opioid-like dependence.

Conclusion

Opioid use disorder is an epidemic of unprecedented proportion in the USA. The impact of opioid use disorder is far reaching and finding solutions have now become a matter of pressing national priority. Although numerous regulatory measures have already been implemented, the answer to this epidemic lies primarily in evidence-based medicine, much of which is currently lacking in this field. The hope is that with increased awareness and funding, new solutions will arise in the near future. However, this calls for further diligence investigating and or utilizing other treatment approaches, as well as more research into pharmacological developments. Until then, both patients and physicians have to adapt to the new opioid-restricting regulations and adopt alternative strategies to minimize the burden of opioid use disorder and other maladaptive outcomes related to both short-term and long-term opioid use.

Compliance with Ethical Standards

Conflict of Interest Ingrid Kepinski, Emily Melikman, and Enas Kandil declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Nicholson B. Responsible prescribing of opioids for the management of chronic pain. Drugs. 2003;63:17–32.
2. Trescot AM, Datta S, Lee M, Hansen H. Opioid pharmacology. Pain Physician. 2008;11:S133–53.
3. Compton WM, Volkow ND. Abuse of prescription drugs and the risk of addiction. Drug Alcohol Depend. 2006;83(Suppl 1):S4–7.
4. Compton WM, Volkow ND. Major increases in opioid analgesic abuse in the United States: concerns and strategies. Drug Alcohol Depend. 2006;81:103–7.
5. Bohnert AS, Valenstein M, Bair MJ, Ganoczy D, McCarthy JF, Ilgen MA, et al. Association between opioid prescribing patterns and opioid overdose-related deaths. JAMA. 2011;305:1315–21.
6. WARNER M., CHEN L. H., MAKUC D. M. Increase in fatal poisonings involving opioid analgesics in the United States, 1999–2006. NCHS Data Brief 2009: 1–8.
7. Okie S. A flood of opioids, a rising tide of deaths. N Engl J Med. 2010;363:1981–5.
8. Dobscha SK, Corson K, Flores JA, Tansill EC, Gerrity MS. Veterans affairs primary care clinicians' attitudes toward chronic pain and correlates of opioid prescribing rates. Pain Med. 2008;9:564–71.
9. Ballantyne JC, Mao J. Opioid therapy for chronic pain. N Engl J Med. 2003;349:1943–53.
10. Eriksen J. Opioids in chronic non-malignant pain. Eur J Pain. 2001;5:231–2.
11. Grunkemeier DM, Cassara JE, Dalton CB, Drossman DA. The narcotic bowel syndrome: clinical features, pathophysiology, and management. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2007;5:1126–39 quiz 1121-1122.
12. Vuong C, Van Uum SH, O'Dell LE, Lutfy K, Friedman TC. The effects of opioids and opioid analogs on animal and human endocrine systems. Endocr Rev. 2010;31:98–132.
13. Benyamin R, Trescot AM, Datta S, Buenaventura R, Adlaka R, Sehgal N, et al. Opioid complications and side effects. Pain Physician. 2008;11:S105–20.
14. Roy S, Loh HH. Effects of opioids on the immune system. Neurochem Res. 1996;21:1375–86.
15. Wick MJ, Minnerath SR, Roy S, Ramakrishnan S, Loh HH. Differential expression of opioid receptor genes in human lymphoid cell lines and peripheral blood lymphocytes. J Neuroimmunol. 1996;64:29–36.
16. Sacerdote P, Franchi S, Panerai AE. Non-analgesic effects of opioids: mechanisms and potential clinical relevance of opioid-induced immunodepression. Curr Pharm Des. 2012;18:6034–42.
17. Dublin S, Walker RL, Jackson ML, Nelson JC, Weiss NS, Von Korff M, et al. Use of opioids or benzodiazepines and risk of pneumonia in older adults: a population-based case-control study. J Am Geriatr Soc. 2011;59:1899–907.
18. Hu P, McLachlan EM. Macrophage and lymphocyte invasion of dorsal root ganglia after peripheral nerve lesions in the rat. Neuroscience. 2002;112:23–38.
19. Sommer C, Kress M. Recent findings on how proinflammatory cytokines cause pain: peripheral mechanisms in inflammatory and neuropathic hyperalgesia. Neurosci Lett. 2004;361:184–7.
20. Liang D, Shi X, Qiao Y, Angst MS, Yeomans DC, Clark JD. Chronic morphine administration enhances nociceptive sensitivity and local cytokine production after incision. Mol Pain. 2008;4:7.
21.• Centers for Disease C., Prevention Public Health Service U. S. D. O. H, Human S. Guideline for prescribing opioids for chronic pain. Journal of pain & palliative care pharmacotherapy. 2016;30:138–40 **The CDC release of guidelines for opioids prescription for chronic represented an important step in standardization of opioid prescption practice, and has already started to impact clinical practice in the US**.
22. McCracken LM, Vowles KE. Acceptance and commitment therapy and mindfulness for chronic pain: model, process, and progress. The American psychologist. 2014;69:178–87.
23.• Kowal J, Wilson KG, Henderson PR, McWilliams LA. Change in suicidal ideation after interdisciplinary treatment of chronic pain. Clin J Pain. 2014;30:463–71 **Interdisciplenary treatment of chronic pain has been shown in several studies such as this to be an important component of chronic pain management. It is impirtant to note here though that these strategies should be part of an integrative approach, and should not be seen as a replacement for phamracological or interventional approaches**.
24. Buhrman M, Skoglund A, Husell J, Bergstrom K, Gordh T, Hursti T, et al. Guided internet-delivered acceptance and commitment therapy for chronic pain patients: a randomized controlled trial. Behav Res Ther. 2013;51:307–15.
25. Turner JA, Holtzman S, Mancl L. Mediators, moderators, and predictors of therapeutic change in cognitive-behavioral therapy for chronic pain. Pain. 2007;127:276–86.
26. Mika J, Zychowska M, Makuch W, Rojewska E, Przewlocka B. Neuronal and immunological basis of action of antidepressants in chronic pain clinical and experimental studies. Pharmacol Rep. 2013;65:1611–21.
27. Rasmussen PV, Jensen TS, Sindrup SH, Bach FW. TDM-based imipramine treatment in neuropathic pain. Ther Drug Monit. 2004;26:352–60.
28. Onishi H, Yamamoto W, Wada M, Nishida T, Wada M, Sunagawa Y, et al. Detection and treatment of akathisia in advanced cancer patients during adjuvant analgesic therapy with tricyclic antidepressants: case reports and review of the literature. Palliative & supportive care. 2007;5:411–4.
29. Watson CP, Chipman M, Reed K, Evans RJ, Birkett N. Amitriptyline versus maprotiline in postherpetic neuralgia: a randomized, double-blind, crossover trial. Pain. 1992;48:29–36.
30. Mazza M, Mazza O, Pazzaglia C, Padua L, Mazza S. Escitalopram 20 mg versus duloxetine 60 mg for the treatment of chronic low back pain. Expert Opin Pharmacother. 2010;11:1049–52.
31. Mattia C, Paoletti F, Coluzzi F, Boanelli A. New antidepressants in the treatment of neuropathic pain. A review. Minerva Anestesiol. 2002;68:105–14.
32.•• Manglik A, Lin H, Aryal DK, McCorvy JD, Dengler D, Corder G, et al. Structure-based discovery of opioid analgesics with reduced side effects. Nature. 2016;537:185–90 **In this recent report published in Nature, the authors describe an exciting discovery of new opioid analgesic with a favorable side effect profile using cutting edge bioinformatics and structural studies**.