



Government Legislation in Response to the Opioid Epidemic

Mark R. Jones¹ · Matthew B. Novitch² · Syena Sarrafpour¹ · Ken P. Ehrhardt³ · Benjamin B. Scott⁴ · Vwaire Orhurhu¹ · Omar Viswanath^{5,6} · Alan D. Kaye³ · Jatinder Gill¹ · Thomas T. Simopoulos¹

Published online: 1 May 2019

© Springer Science+Business Media, LLC, part of Springer Nature 2019

Abstract

Purpose of Review Opioid misuse and abuse in the USA has evolved into an epidemic of tragic pain and suffering, resulting in the estimated death of over 64,000 people in 2016. Governmental regulation has escalated alongside growing awareness of the epidemic's severity, both on the state and federal levels.

Recent Findings This article reviews the timeline of government interventions from the late 1990s to today, including the declaration of the opioid crisis as a national public health emergency and the resultant changes in funding and policy across myriad agencies. Aspects of the cultural climate that fuel the epidemic, and foundational change that may promote sustained success against it, are detailed within as well.

Summary As a consequence of misuse and abuse of opioids, governmental regulation has attempted to safeguard society, and clinicians should appreciate changes and expectations of prescribers.

Keywords Opioid epidemic · Addiction · Overdose · Prescription drug monitoring program · Commission on combating drug addiction · Opioid crisis · Abuse-deterrent formulations

Background

Over the past 30 years, opioid misuse and abuse in the USA has evolved into an epidemic, resulting in tragic pain and suffering. Once thought to be a benign medication, liberal prescribing of opioids, unlike any other group of medications, has led to a spectrum of opioid use disorders that manifest as

misuse, abuse, addiction, and even death. Growing rates of addiction to prescription opioids have also led to the increased use of synthetic opioids such as fentanyl and powerful street drugs such as heroin.

In the late 1990s, marketing strategies by drug companies assured doctors that new opioid formulations carried a low risk of addiction, resulting in profound increases in prescribing rates of these medications [1]. The decades to follow proved these assurances, formed without a legitimate scientific basis, incorrect. Nevertheless, opioid prescriptions continued to escalate, which led to more concerns of patient safety as parallel increases in overdoses and death were reported [2•]. In 2010 alone, there were over 16,000 deaths attributed to prescription opioid misuse and overdose [3•, 4]. The number of opioids dispensed peaked in 2012 with 62 million prescriptions dispensed [3•]. According to a 2015 study, about 1 in 4 people prescribed chronic opioids misuses these medications [5•].

This article is part of the Topical Collection on *Hot Topics in Pain and Headache*

✉ Mark R. Jones
mjones13@bidmc.harvard.edu

¹ Department of Anesthesia, Critical Care, and Pain Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Ave, Boston, MA 02215, USA

² Medical College of Wisconsin, Wausau, WI 54401, USA

³ Department of Anesthesiology, Louisiana State University Health Science Center, New Orleans, LA 70112, USA

⁴ Department of Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02215, USA

⁵ Valley Anesthesiology and Pain Consultants, University of Arizona College of Medicine-Phoenix, Phoenix, AZ, USA

⁶ Creighton University School of Medicine, Omaha, NE, USA

Overview of Opioid Addiction

Opioids provide pain relief mainly via mu receptor agonism in multiple areas of the brain. Delta and kappa opioid receptors also exist throughout the nervous system and exhibit varying

degrees of cross-reactivity, but most current opioids exert their analgesic effect through targeted mu receptor agonism [6••]. The anterior cingulate, insula, thalamus, and periaqueductal gray that contain high concentrations of the mu receptors are involved in pain perception [7••]. Brain stem mu receptors, when triggered, also decrease respiratory rate and breathing. This unfortunate side effect is the mechanism of opioid overdose that leads to death by respiratory failure. On the spinal cord, the highest concentration of mu receptors resides in the dorsal horn, which modulates responses to pain [7••]. The ventral tegmental area and nucleus accumbens regions of the brain also exhibit high concentrations of the mu opioid receptors. These centers influence reward and pleasure experiences and are most likely involved in mediating behaviors of misuse, abuse, and addiction.

Repeated use and abuse of opioids enhances the desire for the euphoria associated with the drug, while continued use of opioids increases tolerance and drives physical dependence [7••, 8]. Exogenous opioid administration effectively shuts off endogenous opioid production; dependence on exogenous opioid then induces withdrawal when patients abruptly stop using opioids or decrease dosage [7••, 9]. Depending on the amount and frequency of opioids used, withdrawal and dependence resolve over durations varying from 1 to 14 days after cessation. Withdrawal symptoms typically include nausea, vomiting, muscle aches, and diarrhea. Chronic use of opioids often results in increasing doses of opioid in order to achieve the same amount of analgesia, a phenomenon known as tolerance, which can be observed with all types of opioids [10].

Addiction is a chronic mental illness that only occurs in a small but significant percentage of patients and does not resolve with discontinuing opioids. Addiction typically takes months of habitual use to develop and prompts functional and structural changes in the reward and inhibitory centers of the brain [7••, 11]. Patients who develop addiction to opioids suffer a high likelihood of relapse and commonly require preventive treatments [7••].

Initial National Response

It is well established that overprescribing of opioids throughout the 1990s contributed to abuse and addiction among countless patients. On recognition of the developing phenomenon, the federal government implemented laws and regulations intended to deter opioid misuse and encourage safer pain management. In 2000, the Drug Addiction Treatment Act (DATA) was signed into law under the Children's Health Act by President Bill Clinton [12]. DATA allows doctors to obtain a waiver allowing treatment of patient's addiction and dependence to opioids with Schedule III, IV, and V medications approved by the FDA. Physicians must satisfy certain conditions to be granted the waiver designated in DATA 2000.

Buprenorphine formulations specifically indicated for the treatment of opioid addiction are the only medications approved by the FDA that can be prescribed under this waiver [10]. This 2000 waiver stated a limit that a physician or physician group can only have 30 patients being treated under these circumstances [12].

In 2002, buprenorphine/naloxone (Trade Name: Suboxone) was approved by the US Food and Drug Administration as a sublingual medication that consists of buprenorphine, which is a partial mu agonist, and naloxone, an opioid antagonist [13]. This combination provides protection from abuse, as naloxone renders no effect if the medication is taken as intended, sublingually. Yet, if the medication is improperly injected IV, naloxone protects against abuse by antagonizing opioid receptors systemically and inhibiting euphoric reactions. This formulation has helped prevent abuse seen in patients prescribed buprenorphine alone [13].

In 2006, the National Drug Control Policy Reauthorization Act was passed, which increased the number of patients a physician or physician group could treat for opioid dependence under the DATA 2000 law from 30 patients to 100 patients. After qualification under DATA 2000, doctors are limited to 30 patients the first year before being authorized to treat 100 patients thereafter [14].

In 2017, the Joint Commission improved its pain management and assessment protocols for all accredited hospitals [15]. As a part of the new protocols, each hospital should create a leadership team overseeing opioid prescriptions and pain management. Pain management physicians should be available within a hospital system for consultation of complex pain conditions [15]. Patients at high risk for opioid dependence and addiction should be treated with opioid-sparing multimodal measures. All physicians prescribing opioids should have access to drug monitoring program databases [15]. Protocol also now recommends that patients take active roles in their own pain treatment plans. Before treatments begin, patients should be counseled on the realistic goals of pain management, which may lead to better patient satisfaction and pain control [15].

State-Level

State governments have implemented various policies to mitigate the opioid epidemic. Increased monitoring of controlled prescriptions via state regulations has effected significant and rapid changes in opioid prescribing. All 50 states, District of Columbia, Guam, and Puerto Rico have developed an active prescription drug monitoring program (PDMP), an electronic database which collects data related to prescribers' practices including controlled substances [16, 17]. PDMPs vary state to state; however, they allow physicians to observe a patient's prescription drug history to improve Schedule II and III level

prescribing, prevent misuse of prescription medications, and protect at-risk patients [16, 17]. These programs increase reporting and monitoring of controlled prescriptions, which helps decrease opioid prescribing patterns and control opioid misuse [16, 18]. Despite the widespread nature of the opioid epidemic, only 11 states have implemented laws regulating pain management clinics and even fewer states have laws limiting the duration of controlled substances used to treat patients [19, 20]. These “pill mill” laws represent an additional step that the states have implemented to gain control over the opioid crisis. The laws are intended to prevent divergent prescribing behaviors, including the “cash for pills” problem in which dishonest pain management clinics inappropriately dispense controlled prescription medications in exchange for cash [20, 21]. By mandating routine inspections for pain management clinics, introducing new requirements for prescribers, and imposing penalties on clinics who do not comply with regulations, state governments have lowered the number of state opioid prescribers [18, 20]. For instance, the state of Florida, widely considered the epicenter of the opioid epidemic, has seen a significant decline in overall opioid volume, prescriptions, and deaths since implementation of its pill mill law in September 2011 [21]. Over the course of 1 year since implementation of the law, there was a 1.4% reduction in opioid prescriptions and a 2.5% decrease in opioid volume [16]. This translates into a reduction of about half a million 5-mg hydrocodone pills a month [21]. Furthermore, in 2012, Florida saw a reduction in oxycodone overdose deaths by 50%, and an overall 17.7% decrease of drug overdose deaths per 100,000 people [22].

State regulations have expanded in eight states that have announced a state of emergency related to the opioid epidemic [23]. Declaring an emergency allows a state to reallocate funds and increase communication among various governmental agencies, including the law enforcement and public health sectors [19]. These states have expanded public awareness regarding the severity of the opioid epidemic and promoted accessibility to naloxone [19]. Naloxone can be a life-saving treatment and remains a focal point of many public health campaigns. Increased training, education, public advertisement, and a “no prescription” necessary have contributed to more people obtaining naloxone.

The Center for Disease Control and Prevention (CDC) also funds 29 states with over \$28 million through the Overdose Prevention in States (OPIS) [16]. Under this branch, there are primarily three programs which fund state efforts to curb the opioid epidemic. These include Prescription Drug Overdose: Prevention for States (PfS), Data-Driven Prevention Initiative (DDPI), and the Enhanced State Opioid Overdose Surveillance (ESOOS). PfS provides states with resources and supports to help them address the opioid problem. PfS seeks to maximize PDMPs for universal use by obtaining more timely information, improving reporting, and utilizing

the data more effectively to better understand the epidemic [16]. Other goals under the PfS include enhanced public insurance interventions to improve prescribing guidelines, evaluating effective and meaningful policies, and creating a rapid response project to navigate emergency interventions and responses [16]. In 2012, New York and Tennessee, among other states, required prescribers to check the state’s PDMP prior to prescribing opioids, which resulted in a 75% and 36% reduction in patients visiting multiple prescribers for the same opioid in 2013 [16]. Ohio and Kentucky also mandated that prescribers review the state’s PDMP, resulting in a morphine milligram equivalent per capita reduction in 85% and 62% of counties from 2010 to 2015 [16]. The DDPI focuses on developing more drug overdose-prevention programs and obtaining information on behaviors leading to opioid abuse and overdose [16]. The ESOOS awards the states with financial support to provide more timely and complete data on overdoses and risk factors through the State Unintentional Drug Overdose Reporting System [16]. This sub-branch aims to enhance surveillance activities, improve the utilization of surveillance information, and support medical examiners through comprehensive toxicology testing during fatal and non-fatal overdoses to provide information. ESOOS has spurred significant increases in reporting, primarily in the Midwest and Northeast, with a 109% increase in Wisconsin [24]. In addition, eight states have seen > 25% increase in ED visits for opioid overdose [24].

Several other state grant programs are available for additional financial support. The Medication Assisted Treatment-Prescription Drug and Opioid Addiction (MAT-PDOA) helps states expand and enhance treatment systems to increase admissions to MAT and decrease opioid drug use following the 3-year program [25]. The program also aims to decrease the use of opioids and reduce the risk of overdose in at least two high-risk communities within the state [25]. The Opioid-State Targeted Response aims to expand prevention, treatment, and recovery support for individuals with an opioid use disorder [25]. The Strategic Prevention Framework for Prescription Drugs strives to raise awareness of the harm from sharing medications, and risks of over-prescribing to young adults [26]. Other grant programs include Strategic Prevention Framework State/Tribal Incentive Grant, Partnerships for Success, Prevent Prescription Drug/Opioid Overdose Related Deaths, and the First Responders-Comprehensive Addiction and Recovery Act Cooperative Agreement (FR-CARA).

Federal Response

The federal government has implemented several different approaches to combat the opioid crisis and has enlisted nearly every major national health organization in the fight against it [27]. The U.S. Department of Health and Human Services

(USDHHS) “5 Point Strategy” has contributed significant momentum against the current opioid epidemic. This program strives for the following:

1. Improving citizens’ access to better prevention, treatment, and recovery services
2. Acquiring better data on the opioid epidemic to better understand the crisis
3. Improve Pain Management
4. Invest in the discovery of overdose-reversing drugs
5. Increasing funding on pain and addiction research.

The USDHHS provided \$800 million in grants last year to begin tackling the first point in their plan. Notable investments include the following:

- \$44.7 million to the First Responders-Comprehensive Addiction and Recovery Act, which is a program that provides training and medication for treatment of opioid overdose.
- \$9.8 million to the Treatment of Pregnant and Postpartum Women Comprehensive Addiction and Recovery Act, which supports family-based services for pregnant and postpartum women with substance abuse disorders
- \$35 million to the Targeted Capacity Expansion Medication Assisted Treatment-Prescription Drug and Opioid Addiction program, which expands access to medication-assisted treatment for persons with an opioid use disorder seeking treatment.

The second point in the plan has been addressed by improving the understanding of the opioid crisis with public health level data and reporting, a responsibility assumed primarily by the Center for Disease Control (CDC) [28–30]. In August 2017, the CDC released the first Annual Surveillance Report of Drug-Related Risks and Outcomes in the USA, which was a collection of the latest data available on the rates of opioid prescribing, substance abuse disorder, nonfatal hospitalizations and emergency department visits, and overdose deaths related to opioids.

Improving pain management, the third point in the plan of the USDHHS, focused on ensuring that pain management therapies were focused on evidence-based methods as championed by the National Institutes of Health. The NIH funds “Centers of Excellence in Pain Education” at 11 academic institutions in the USA which act as hubs for the development, evaluation, and distribution of pain curriculum resources. In addition, the fourth point has primarily been funded by the Health Resources and Services Administration, which awarded \$17.1 million to support the treatment of opioid overdose in all 55 poison control centers in the USA. Finally, the NIH addressed their fifth and final point by nearly doubling funding for research on opioid misuse, addiction, and pain from approximately \$600 million in the fiscal year 2016 to \$1.1 billion in the fiscal year 2018.

The Trump Administration declared the opioid crisis a national public health emergency on October 26, 2017 [19, 31–33]. Subsequently, the President’s Commission on Combating Drug Addiction and the Opioid Crisis was formed and led by Governor Chris Christie. This Commission outlined a 56-point recommendation, conveyed to the President with suggestions regarding the proper steps to take by the Federal Government in 2017. The 138-page document outlined four subjects they requested the President to address:

1. Federal Funding and Programs
2. Opioid Addiction Prevention
3. Opioid Addiction Treatment, Reversal, and Recovery
4. Research and Development

The first, Federal Funding, began by urging the President to create uniform block grants which would allow more resources to be spent on lifesaving programs. Additionally, it was suggested that a coordinated system for tracking all federally funded initiatives be created with support from USDHHS and the Department of Justice, with a requirement that programs have quantifiable goals and metrics.

The second, Addiction Prevention, targeted the Department of Education (DOE) and suggested it collaborate with states on student assessment programs such as Screening, Brief Intervention and Referral to Treatment (SBIRT—a program that uses a screening tool by trained staff to identify at-risk youth who may need treatment). Additionally, it was suggested that a wide-reaching, national multi-platform media campaign addressing the hazards of substance use, the danger of opioids, and stigma be created. The USDHHS recommended the coordinated development of a national curriculum and standard of care for opioid prescribers, with an updated set of guidelines for prescription pain medications as established by an expert committee composed of multidisciplinary specialties.

The Prescription Drug Monitoring (PDMP) Act was a large portion of this recommendation. The PDMP mandates that States receiving grant funds comply with PDMP requirements, including data sharing. This Act directs the DOJ to fund the establishment and maintenance of a data-sharing hub. Mandated PDMP checks by federal agencies were suggested, and adding this requirement to the Emergency Medical Treatment and Labor Act was also discussed. Finally, it was recommended that the PDMP be integrated into electronic health records, such that providers could easier access and thereby identify patients at risk for opioid-related adverse events. This portion of the document also covered supply reduction and enforcement strategies, which generally meant harsher penalties for those convicted of drug trafficking, as well as counteracting the forces that render opioid-alternative treatment options cost-prohibitive for hospitals and doctors, particularly those options for treating immediate

post-operative pain. Recommendations supporting an alternative to opioid-based treatment methods bled into the opioid addiction treatment, reversal, and recovery portion of the document, which essentially highlighted the USDHHS five-point plan alongside similar recommendations for preventing opioid addiction.

Lastly, discussions on research and development concluded that federal agencies, including HHS (National Institutes of Health, CDC, CMS, FDA, and the Substance Abuse and Mental Health Services Administration), DOJ, the Department of Defense (DOD), and others engage in a comprehensive review of existing research programs and establish goals for pain management and addiction research. A fast-track review process for any new evidence-based technology supporting substance abuse disease prevention and treatment was also established. Finally, the Commission recommended that the FDA establish strict guidelines for post-market surveillance related to diversion, addiction, and other adverse consequences of controlled substances [34].

Policies from previous administrations also remain active, including the Obama administration's Comprehensive Addiction and Recovery Act (CARA), the 21 Century Cures Act, the INTERDICTION Act, and numerous acts implemented by the Substance Abuse and Mental Health Services Administration (SAMHSA) [27, 30, 35].

CARA was signed into law by the Obama administration in 2016 and established a comprehensive strategy to enhance grant programs that expand prevention and education efforts while promoting treatment and recovery. The provisions of CARA include the following:

1. Expanding prevention and educational efforts aimed at teens, parents, and the aging population to prevent the abuse of illicit substances
2. Expanding the availability of naloxone to law enforcement agencies and first responders
3. Expanding resources to treat incarcerated individuals suffering from addiction disorders
4. Expanding disposal sites for unwanted prescription medications
5. Strengthen prescription drug monitoring programs to help states monitor and track prescription drug diversion and help at-risk individual's access services.

The 21 Century Cures Act was signed into law on December 13, 2016, and was designed to accelerate medical product development and bridge new innovations and advances with patients who need them faster and more efficiently. Although this did not particularly target the opioid epidemic, it created the ability to speed the development and review of novel medical products with a potential to affect the opioid epidemic, similarly to the recommendations Governor Christie made as a part of his President's Commission. The

Cures Act authorized \$500 million over 9 years to help FDA cover the cost of implementing the law.

Finally, the INTERDICTION (International Narcotics Trafficking Emergency Response by Detecting Incoming Contraband with Technology Act) was placed into law June 2018. INTERDICTION requires U.S. Customs and Border Protection (CBP) to increase the number of chemical screening devices available to CBP officers in order to detect fentanyl, other synthetic opioids, and other narcotics and psychoactive substances illegally imported into the USA. This includes substances imported through the mail or by express consignment operator or carrier. The value of the grant to the CBP was \$9 million.

The week of September 20, 2018, the U.S. Department of Health and Human Services awarded over \$1 billion in opioid-specific grants to help combat the crisis ravaging our country. The awards reinforced the HHS five-point strategy as previously discussed, which was launched last year and enhanced this week. New data unveiled recently by HHS suggests that efforts are now yielding progress at the national level [35].

What's Missing?

The opioid epidemic persists despite the numerous state and federal interventions outlined above. The social, economic, and medicolegal complexities underlying the epidemic render it difficult to single-handedly address all related factors with a single law or intervention. Among the most difficult to address are the root causes of opioid misuse, which include social inequalities, income disparity, and lack of educational and work opportunities [28]. People, particularly young adults, are subject to higher risk of opioid abuse due to a variety of factors, including more frequent residence in lower-income neighborhoods and/or rural areas, and a lack of a supportive network [36]. Jobs in lower socioeconomic strata are often more physically demanding, and over time can lead to chronic pain [28]. The resultant combination of high rates of dissatisfaction and chronic pain engenders a climate in which opioids are more likely to be abused [28]. Certain programs can be created to develop improved life satisfaction and mitigate hardships by increasing employment and educational opportunities. The government can implement more social policy programs to promote socially resilient and supportive environments. The opioid epidemic will not be solved solely by mandating laws and regulations related to opioid prescribing. By increasing primary prevention and rebuilding vulnerable communities, states can simultaneously alleviate the isolation and hopelessness wrought by the epidemic while decreasing the over-reliance on opioids among populations in underprivileged socioeconomic areas [28].

A more recent act interferes with the ability to regulate questionable packages entering the USA. The Drug Enforcement Administration (DEA), which functions in part to deter illegal drug manufacturing and distribution, is hampered by the Ensuring Patient Access and Effective Drug Enforcement Act of 2016, which was originally designed to guarantee opioids to patients for legitimate use [37]. This law also changed criteria to seize large suspicious shipments and made it more difficult for the DEA to withhold suspicious shipments into the USA [32].

There are countless other interventions the government can focus on to improve understanding and curb the opioid crisis. Education surrounding proper management of acute and chronic pain must begin in medical school. Adequate pain management curricula and instruction on regulations for responsible opioid prescribing, in guidance with the Federation of State Medical Boards, is a feasible approach for medical schools. In addition, Continued Medical Education (CME) should be required for prescribers with an emphasis on non-opioid pain management options. Only 12 states currently require CME on controlled substance prescribing and pain management for all physicians [37]. Hospitals can develop opioid mitigation programs structured as an inpatient setting. Patient satisfaction ratings, reports to medical boards, and legal action by patients should no longer be used to coerce physicians into prescribing opioids. Physicians need more support and less harassment from organizations in their quest to treat pain and obviate opioids. Furthermore, tertiary care centers should organize opioid addiction and recovery programs, which can provide facilitated access and availability of resources to treat opioid dependence. The final missing link is to ensure patient access to non-opioid therapies that are frequently denied by third-party payers, even though many have been approved by the FDA.

Conclusion

The current opioid epidemic resulted from decades of misguided efforts by multiple industries to balance adequate and essential treatment of pain against the misuse and abuse of opioid medications. The damage inflicted upon our society has reached proportions that no one agency may hope to dampen on its own. State and Federal government interventions, along with coordinated policy changes by medical associations, insurance, and regulatory agencies, are required for any palpable change to take effect. The country-wide reaction to the epidemic has begun to reflect the enormity of the issue, as evidenced by President Trump's declaration of the opioid crisis as a national public health emergency. Ground-level culture shifts must take place as well, however, if new policies and regulations are to bring about sustainable change.

Compliance with Ethics Standard

Conflict of Interest Mark R. Jones, Matthew B. Novitch, Syena Sarrafpour, Ken P. Ehrhardt, Benjamin B. Scott, Vwaire Orhurhu, Omar Viswanath, Alan D. Kaye, Jatinder Gill, and Thomas T. Simopoulos declare no conflict of interest. Dr. Kaye is a speaker for Depomed, Inc. and Merck, Inc.

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 major importance

1. Promotion and Marketing of OxyContin. Commercial triumph, public health tragedy. *Am J Public Health*. 2009;99(2):221–7.
2. Jones MR, Viswanath O, Peck J, Kaye AD, Gill JS, Simopoulos TT. A brief history of the opioid epidemic and strategies for pain medicine. *Pain Ther*. 2018;7(1):13–21. **Provides an overview of the evolution of opioid use into the epidemic of today.**
3. Dart RC, Surratt HL, Cicero TJ, Parrino MW, Severtson SG, Bucher-Bartelson B, et al. Trends in opioid analgesic abuse and mortality in the United States. *N Engl J Med*. 2015;372(3):241–8. **Traces the development of opioid use into the current proportions.**
4. National Vital Statistics System. Multiple cause of death file. Atlanta: Centers for Disease Control and Prevention; 2012.
5. Vowles KE, McEntee ML, Julnes PS, Frohe T, Ney JP, van der Goes DN. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. *Pain*. 2015;156(4):569–576. **Discusses the causes and prevalence of opioid use disorder in patients suffering from chronic pain.**
6. MR J, Kaye AD, Kaye AJ, Urman RD. The emerging therapeutic roles of κ -opioid agonists. *J Opioid Manag*. 2016;12(2):101–7. **A useful insight into recent research concerning opioid medications.**
7. Volkow ND, McLellan AT. Opioid abuse in chronic pain—misconceptions and mitigation strategies. *N Engl J Med*. 2016;374(13):1253–63. **Discusses the pertinent characteristics and patterns of patients with chronic pain and proposes strategies for interventions.**
8. Ewan EE, Martin TJ. Analgesics as reinforcers with chronic pain: evidence from operant studies. *Neurosci Lett*. 2013;557:60–4.
9. Williams JT, Christie MJ, Manzoni O. Cellular and synaptic adaptations mediating opioid dependence. *Physiol Rev*. 2001;81:299–343.
10. Buntin-Mushock C, Phillip L, Moriyama K, Palmer PP. Age-dependent opioid escalation in chronic pain patients. *Anesth Analg*. 2005;100:1740–5.
11. Volkow ND, Morales M. The brain on drugs: from reward to addiction. *Cell*. 2015;162:712–25.
12. Center for Substance Abuse Treatment. Clinical guidelines for the use of buprenorphine in the treatment of opioid addiction. Rockville (MD): Substance Abuse and Mental Health Services Administration (US); 2004.
13. Schaeffer T. Abuse-deterrent formulations, an evolving technology against the abuse and misuse of opioid analgesics. *J Med Toxicol*. 2012;8(4):400–7.

14. H.R. 6344 – 109 Congress: Office of National Drug Control Policy Act of 2006.
15. Byrne, Katie, editor. *Comprehensive accreditation manual: CAMH for hospitals effective January 1, 2018*. Joint Commission, 2018.
16. Opioid Overdose: State information. Center for disease control and prevention, 23 Oct. 2017, <https://www.cdc.gov/drugoverdose/states/index.html>.
17. Prescription drug monitoring programs (PDMPs). Federation of State Medical Boards. April 2018. <https://fas.org/sgp/crs/misc/R42593.pdf>.
18. Finley EP, Garcia A, Rosen K, McGeary D, Pugh MJ, Potter JS. Evaluating the impact of prescription drug monitoring program implementation: a scoping review. *BMC Health Serv Res*. 2017;17:420.
19. Rutkow L, Vernick JS. Emergency legal authority and the opioid crisis. *N Engl J Med*. 2017 Dec 28;377(26):2512–4. <https://doi.org/10.1056/NEJMp1710862>.
20. Rutkow L, Vernick JS, Alexander GC. More states should regulate pain management clinics to promote public health. *Am J Public Health*. 2017;107:240–3.
21. Rutkow L, Chang H, Daubresse M, Webster D, Stuart EA, Alexander GC. Effect of Florida’s prescription drug monitoring program and pill mill laws on opioid prescribing and use. *JAMA Intern Med*. 2015;175(10):1642–9.
22. Centers for Disease Control and Prevention (CDC). Drug overdose deaths: Florida, 2003–2009. *MMWR Morb Mortal Wkly Rep*. 2011;60(26):869–72.
23. “Emergency declarations in eight states to address the opioid epidemic.” *Association of state and territorial health officials*, 11 Jan. 2018, <http://www.astho.org/StatePublicHealth/Emergency-Declarations-in-Eight-States-to-Address-the-Opioid-Epidemic/01-11-18/>.
24. “Emergency department data show rapid increases in opioid overdoses.” Centers for Disease Control and Prevention (CDC). March 6, 2018. <https://www.cdc.gov/media/releases/2018/p0306-vs-opioids-overdoses.html>
25. “State grant programs.” *Substance abuse and mental health services administrations*, 30 Jan. 2018, <https://www.samhsa.gov/programs-campaigns/medication-assisted-treatment/training-materials-resources/state-grant-programs>.
26. “Strategic prevention framework for prescription drugs.” *Substance abuse and mental health services administrations*, 03/29/2016, <https://www.samhsa.gov/grants/grant-announcements/sp-16-006>.
27. Christie, C., Baker, C., Cooper, R., Kennedy, P., Madras, B., & Bondi, P. (2017). On combating drug addiction and the opioid crisis.
28. Dasgupta N, Beletsky L, Ciccarone D. Opioid crisis: no easy fix to its social and economic determinants. *Am J Public Health*. 2018 Feb;108(2):182–6. <https://doi.org/10.2105/AJPH.2017.304187>.
29. Dowell D, Zhang K, Noonan RK, Hockenberry JM. Mandatory provider review and pain clinic laws reduce the amounts of opioids prescribed and overdose death rates. *Health Affairs (Project Hope)*. 2016;35(10):1876–83. <https://doi.org/10.1377/hlthaff.2016.0448>.
30. Kanouse AB, Compton P. The epidemic of prescription opioid abuse, the subsequent rising prevalence of heroin use, and the federal response. *J Pain Palliat Care Pharmacother*. 2015;29(2):102–14. <https://doi.org/10.3109/15360288.2015.1037521>.
31. Kinnard EN, Philbin MM, Beletsky L. Government actions to curb the opioid epidemic. *JAMA*. 2018 Apr 17;319(15):1619–20. <https://doi.org/10.1001/jama.2018.0741>.
32. Kolodny A, Frieden TR. Ten steps the federal government should take now to reverse the opioid addiction epidemic. *J Am Med Assoc*. 2017;318(16):1537–8. <https://doi.org/10.1001/jama.2017.14567>.
33. Soelberg CD, Brown RE, Du Vivier D, Meyer JE, Ramachandran BK. The US opioid crisis: current federal and state legal issues. *Anesth Analg*. 2017;125(5):1675–81. <https://doi.org/10.1213/ANE.0000000000002403>.
34. Stayner RS, Copenhaver DJ. Opioids, pain management and the law. *Curr Opin Anaesthesiol*. 2012;25(5):566–71. <https://doi.org/10.1097/ACO.0b013e328357a24a>.
35. HHS awards over \$1 billion to combat the opioid crisis | [HHS.gov](https://www.hhs.gov/about/news/2018/09/19/hhs-awards-over-1-billion-combat-opioid-crisis.html) [Internet]. [cited 2018 Sep 24]. Available from: <https://www.hhs.gov/about/news/2018/09/19/hhs-awards-over-1-billion-combat-opioid-crisis.html>
36. Keyes KM, Cerda M, Brady JE, Havens JR, Galea S. Understanding the rural-urban differences in nonmedical prescription opioid use and abuse in the United States. *Am J Public Health*. 2014;104:e52–9. <https://doi.org/10.2105/AJPH.2013.301709>.
37. Ensuring patient access and effective drug enforcement act of 2016. *Pub L No. 114-145*, 130 Stat 353.

Publisher’s Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.