Trends in Opioid Use: History, Background, and Origins of the Epidemic

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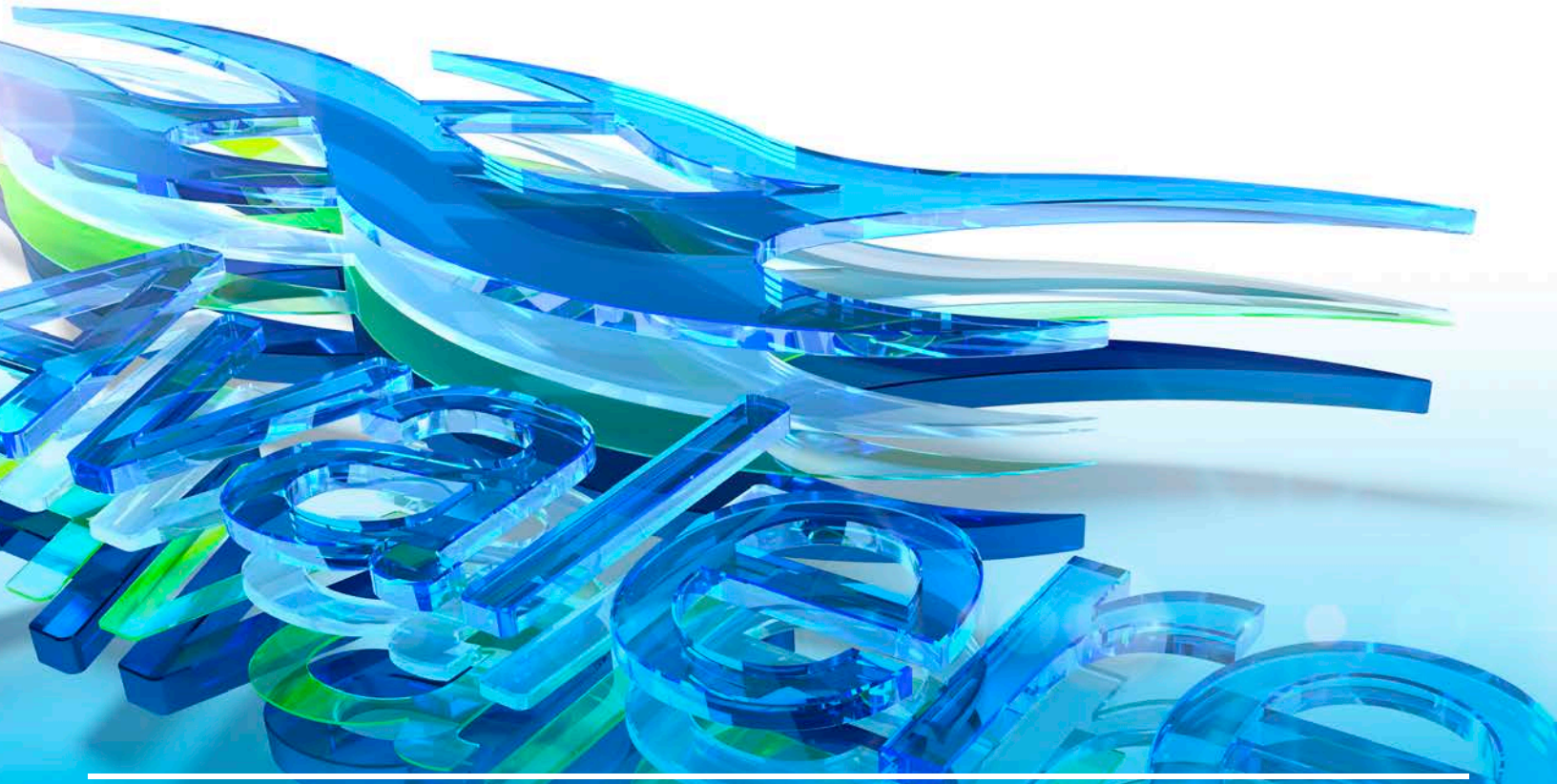

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Avalere

Executive Summary

The current opioid epidemic is driven by numerous complex factors; while the rates of opioid abuse, overdose, and death are widely acknowledged today, the beginnings of the epidemic can be found as far back as 30 years ago when shifts in clinical practice planted the seed for the sharp uptick in prescription opioid use. Between the mid-1980s and 1990s, individual pharmaceutical manufacturers, scientific and clinical bodies, including the National Academy of Sciences, the Institute of Medicine, the American Pain Society (APS), and the American Academy for Pain Management (AAPM) began a push to treat pain more aggressively, culminating in widespread acceptance of "pain as the fifth vital sign" – a measure that should be assessed and managed as closely as pulse, respiration, temperature, and blood pressure.[1,2] At the same time, limited understanding of the potential for addiction of many opioid analgesics coupled with quality measures and reimbursement incentives to aggressively manage pain led to clinicians prescribing a greater number of these medications while not fully appreciating the dangers of iatrogenic addiction. In fact, it was not until 2009 that APS and AAPM updated their guidelines to warn of the potential for abuse and addiction; it would take the federal government, under the auspices of the Centers for Disease Control and Prevention (CDC) almost another decade to issue guidelines on appropriate use of opioids for chronic pain.3 However, since 2011, the volume of prescription opioids has been declining steadily and opioid abuse has largely manifested in use of heroin and illicitly manufactured fentanyl (IMF), again changing the face of the epidemic.

Numerous clinical, regulatory, and reimbursement incentives coincided to create a perfect storm, driving demand for opioids and a steady increase in the number of patients taking these medications. An effective response to this epidemic demands a comprehensive understanding of the myriad factors that led to the current crisis.

Introduction

Opioid analgesics can provide critical relief to patients with severe pain but also have the potential to be abused; while the majority of patients who are prescribed an opioid for chronic pain use them appropriately, approximately 2-4% develop an opioid use disorder (OUD).[1,2] The Centers for Disease Control and Prevention (CDC) estimates that more than 42,000 Americans died from an opioid overdose in 2016, although it is important to note that since 2010, heroin and illicitly manufactured fentanyl (IMF) have accounted for a greater share of deaths than prescription opioids.[3–5] This public health impact—coupled with an estimated $500 billion in economic losses annually due to premature death, lost productivity, and increased healthcare and criminal justice costs—has led to wide-ranging attention across a spectrum of stakeholders.[4,6] Policymakers, politicians, patients and patient advocacy groups, clinicians, law enforcement, and public health professionals, as well as the media have focused increased attention on the opioid epidemic.

In response to the growing epidemic, both the Obama and Trump Administrations took steps to combat drug addiction and the opioid crisis.[7] At the same time, federal policymakers have considered a series of bills designed to address various elements of the crisis, while individual state houses have proposed a range of legislative and regulatory solutions along with increased funding for OUD treatment and prevention.[8,9] What has received less attention, however, are the origins of the epidemic. The present-day opioid epidemic evolved over many years in local communities across the country; without understanding the multiple, complex factors that led to the widespread use and misuse of opioids, including the proliferation of illegal opioids, it will be impossible to design an effective response. This brief outlines the myriad factors that contributed to the increase in opioid use that has led to the current epidemic.

Prescription Opioid Trends

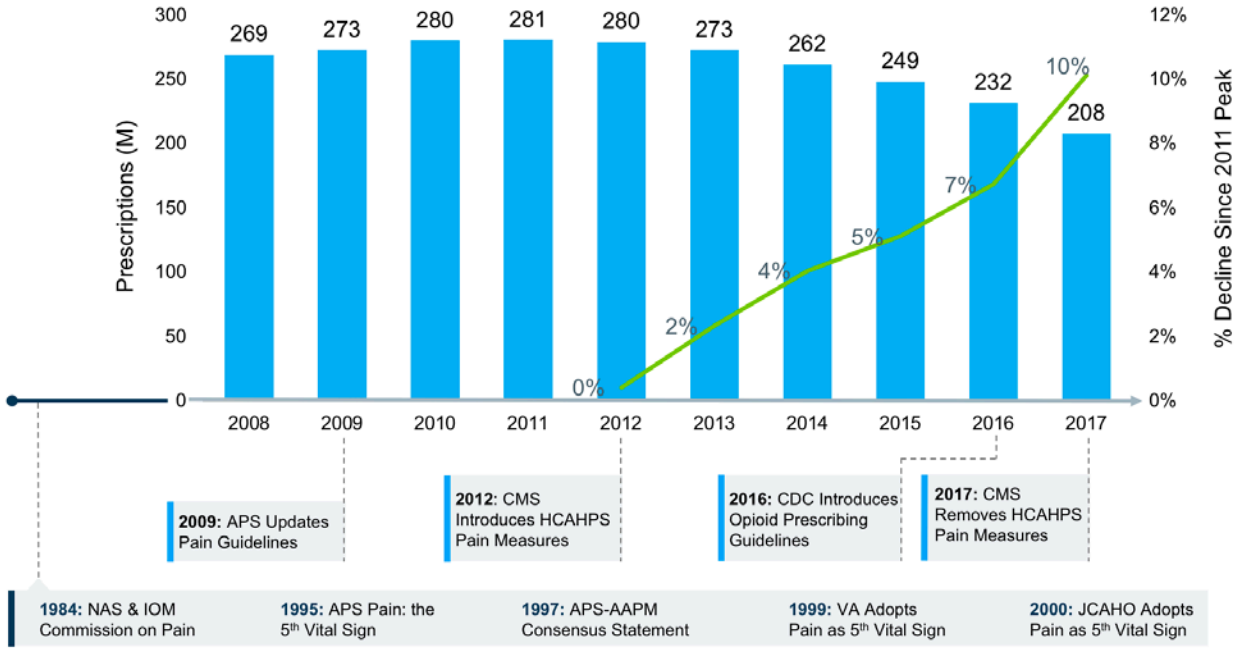
Beginning in the mid-1990s, the total volume of prescription opioids dispensed grew at a relatively steady 6% each year[1] until plateauing in 2011.[10–12] While morbidity and mortality from opioid misuse and abuse continued to increase, the volume of prescription opioids dispensed in the US has fallen steadily from its peak at the beginning of the decade (figure 1).[13] Between 2011 and 2017, the number of prescription opioids that were sold fell by 25.8%—from nearly 281 million prescriptions to just over 208 million in 2017. In each year following the peak, prescription opioids sales declined at a growing rate, falling by less than 1% over the 2011-2012 period to a 10.1% decrease between 2016 and 2017.

Despite the sharp decrease in sales and opioid use, the continued focus on prescription opioids masks the fact that the current epidemic is driven largely by use of dangerous illicit

1 [1] From 1990-2010, population grew between 9.7% - 13.2%

substances.[17] Recent research also indicates that over the past four decades, the United States has seen a remarkably steady, exponential increase in drug overdose deaths – from cocaine to methamphetamine to opioids; the current opioid epidemic is thus part of a larger, decades long substance abuse overdose trend across a wide mix of drugs.[15] The narrow focus on prescription opioids belies these population level trends and the fact that a significant number of individuals who abuse opioids have a history of prior substance abuse and may require complex interventions.[16] Additionally, the steep decline in opioid availability for chronic pain patients has left some medical experts concerned about unintended consequences and a swing back to potential under-treatment of pain, the original impetus for increased utilization.[17,18] An examination of the early years of the epidemic and the evolving attitudes towards pain management follows.

Figure 1: Annual Volume of Opioids Sold in the US and Percent Change, 2008-2017



Source: Avalere Health analysis of National Prescription Audit (NPA) data from QuintilesIMS, 2008 – 2017. Includes prescriptions dispensed by pharmacists from the following Channels: Retails Pharmacies (inclusive of Chain Pharmacies, Food Stores w/ Pharmacies, Independent Pharmacies); Mail Order and Long-Term Care facilities.
Horizontal axis corresponds to the 12-month period beginning in April of that year.

The Beginnings of an Epidemic: De-Emphasis of the Addictive Potential of Opioids

Opioid analgesics have a long history of use for the treatment of both acute and chronic pain; while their addictive potential was well known, and they were heavily regulated, in the early to mid-1980s several academic publications gave credence to the belief that newer formulations

had decreased potential for iatrogenic addiction, and use of these analgesics to treat chronic pain became more widespread. A widely cited letter to the editor published in the New England Journal of Medicine reported that less than 1% of patients receiving prescription narcotics had become addicted.[19] A second study published in 1986 concluded that narcotics "can be safely and effectively prescribed to selected patients with relatively little risk of producing the maladaptive behaviors which define opioid abuse."[13] Though FDA labelling requirements and classification as a Schedule II controlled substance sent a strong message about the addictive potential of opioids, competing priorities de-emphasized concerns over iatrogenic addiction."

Thus, in the mid-1980s and early 1990s, there was a trend in academic publications and regulatory guidance that encouraged the medical community to focus on addressing the widespread under-assessment and under-treatment of pain, with opioids as a viable option.[20,21] This paradigm shift in how the medical community viewed and managed pain resulted in a significant and steady increase in the use of natural opioids such as morphine and codeine, semi-synthetic opioids including oxycodone and hydrocodone, and synthetic opioids such as methadone, tramadol, and fentanyl. Reflecting this newfound focus on pain management, the number of different formulations and combinations of opioids available to patients increased dramatically, with the FDA issuing 263 new approvals[2] between 1997 and 2015.[22] These medications provided significant relief and improved quality of life for many patients suffering from severe pain and, coupled with clinical guidelines directing physicians to manage pain more aggressively, the incentives started aligning to lead to a steady increase in opioid use.[23–25]

Changes in Clinical Recommendations: Recognizing Pain as a Vital Sign

In 1984, the National Academy of Sciences (NAS) and Institute of Medicine (IOM) were enlisted to explore the relationship between illness and pain. In the resulting report, published in 1987, the IOM recommended that physicians implement systematic assessments using quantitative measures of pain such as a 10-point scale.[26] In response to patient needs, widespread reports of pain under-treatment, as well as evolving expert recommendations, the American Pain Society (APS) initiated a large-scale campaign beginning in 1995: "Pain, the Fifth Vital Sign."

Shortly thereafter, in 1997, APS and the American Academy of Pain Medicine (AAPM) released a consensus statement that endorsed opioids for chronic pain and warned prescribers not to allow addiction or diversion concerns to interfere with their opioid prescription patterns.[27] The recommendations released in 2005 continued to de-emphasize the risks of abuse and addiction; and it was not until the updated guidelines were released in 2009 that risks of addiction, abuse, and diversion were discussed with considerable concern.[28,29] As the 1990s ended, the practice

2 [2] This includes both New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs)

of measuring pain with a subjective 10-point scale, as recommended by the IOM, became standard protocol and the concept that pain relief was a fundamental patient right had grown into a widespread dogma, opening the doors to widespread opioid utilization.

National Policies and Regulations Promoting Opioids Use

While the medical community's understanding of pain and pain management continued to evolve, the Social Security Administration was battling considerable tension with federal courts over beneficiaries with chronic pain. In 1984, standards were put in place to define pain and the Secretary of the Department of Health and Human Services (HHS) appointed a Commission on the Evaluation of Pain. The result of this commission was the aforementioned IOM report, recommending the creation of standards to measure pain and ultimately improve pain management. Together, the evolving federal policies and professional society recommendations increased the credibility of the moral imperative and professional responsibility to treat pain. Concurrently, the APS's "Pain, The Fifth Vital Sign" campaign was magnified when the nation's largest integrated healthcare system, the Department of Veterans Affairs, designated pain as the 'fifth vital sign' and began requiring pain intensity ratings for all patients in 1999. Today, veterans have among the highest rates of OUD in the nation.[30,31]

At the same time, payers began to take notice and encouraged providers to aggressively screen and manage pain to meet quality guidelines.[32] By 2000, the Joint Commission (formerly known as JCAHO) took the recommendations of the 1987 Institute of Medicine (IOM) report and announced their own standards for pain management, also officially recognizing pain as the fifth vital sign and encouraged clinicians to improve diagnosis and management of pain.[33,34] These standards cemented the concept that patients have a right to pain relief and drove further uptake of opioid analgesics.[35]

Furthermore, the Federation of Medical Boards issued Model Guidelines in 1998 which provided support for physicians to increase the volume of opioid prescriptions and contributed to the successful introduction of the following language into most state medical practice acts: "no disciplinary action will be taken against a practitioner based solely on the quantity and/or frequency of opioid prescribed."[36] These actions and statements largely absolved physicians of the consequences of opioid overuse and created a community-wide justification for increased opioid utilization that culminated in a soaring number of prescriptions. The severance of responsibility for opioid overuse along with right to pain treatment served as an integral part of the philosophical changes regarding pain treatment which continued to blossom in the early to mid-1990s.

Quality Measures and Reimbursement Tied to Pain Management

The changing attitude towards pain management reflected in the shifts in national policies and clinical guidelines were also mirrored in updated quality measures and reimbursement practices that further incentivized aggressive management of pain, largely through the use of opioid analgesics. In addition to their joint consensus statement, APS-AAPM released Quality Improvement Guidelines in 1995 emphasizing the under-treatment of pain and the need to increase availability and convenience for analgesic prescriptions.[37] Just as in their clinical guidelines, the Quality Improvement Guidelines noted the need to urge patients to communicate their pain, with no caution or mention of abuse.

More significantly, in the mid-2000s, the Hospital Quality Alliance (HQA), in conjunction with the Agency for Healthcare Research and Quality (AHRQ) developed the Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS), a survey that is administered to patients when they are discharged from the hospital.[38] The HCAHPS survey consists of 27 questions, including 2 questions specifically on pain management. While participation in the HCAHPS program was initially voluntary, in 2012 the Centers for Medicare & Medicaid Services (CMS) tied hospital reimbursement and payment in the Medicare program to performance on several quality measures, 30% of which was based on HCAHPS score.[39] Thus, providers were incentivized through additional reimbursement and bonus payments to aggressively manage patients' pain, further driving up opioid utilization.

Slow Federal Response Exacerbated a Growing Epidemic

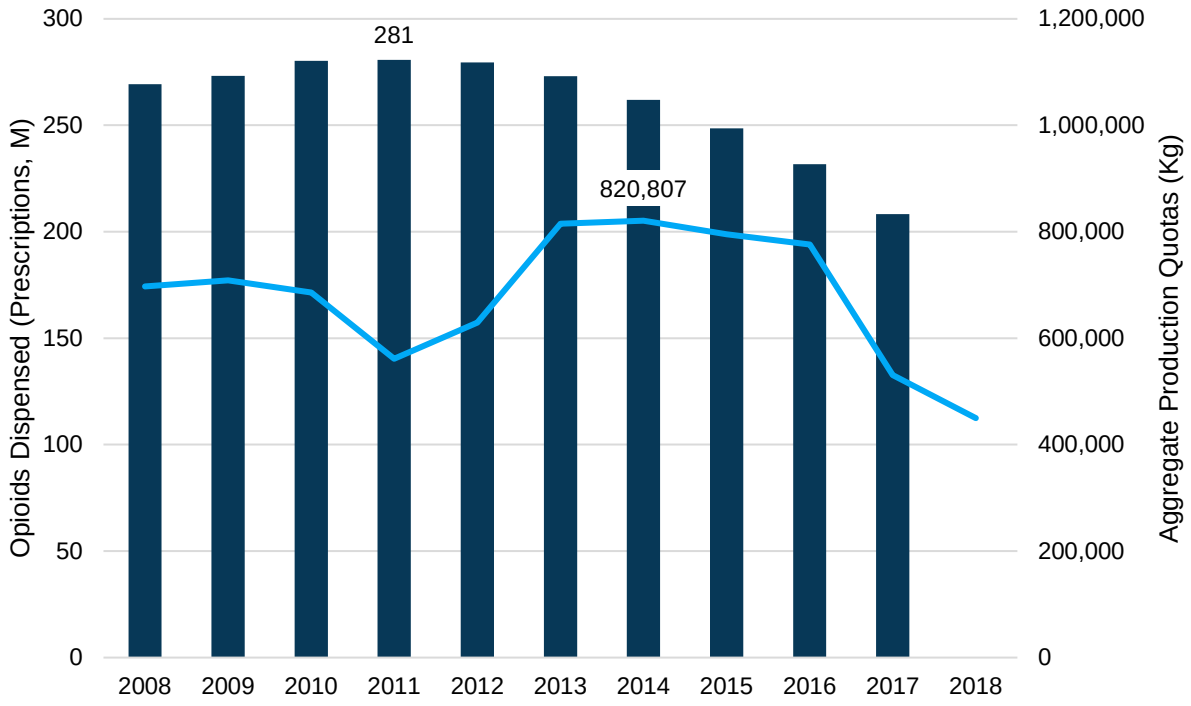
The multiple antecedent factors that led to the sharp and continued increase in the use of opioid analgesics resulted in a widespread opioid epidemic that continues to affect nearly every state and community in the nation. An initial de-emphasis of the potential for iatrogenic addiction coupled with a coordinated push by multiple stakeholders to manage pain more aggressively sowed the beginnings of the epidemic, but a slow, under-resourced, and uncoordinated response caused the epidemic to rage.

Although drug overdose deaths in the US increased 3-fold between 1999 and 2016, the CDC did not develop guidelines for prescribing opioids for chronic pain until 2016, and HHS did not declare a public health emergency until another year later.[3,1 37] And, as noted earlier, it took the APS more than a decade to reverse their original recommendation strongly endorsing the use of opioids for pain management and introducing the idea that opioid analgesics should be used with caution. In response to concern that the pain management question in the HCAHPS survey

was putting “financial pressure on clinicians …to overprescribe medications,” CMS removed the pain management questions in 2017.[42]

Figure 2: Annual Sales and Aggregate Production Quotas for Opioids in the US

In addition to the retrenchment of guidelines, recommendations, and financial incentives, the federal government has the ability to regulate the supply of opioids. The US Drug Enforcement Administration (DEA) regulates the supply of Schedule I and II controlled substances by using



Source: Avalere Health analysis of the DEA’s Aggregate Production Quote History For Selected Substances data, 2008 – 2018. Last updated on November 15, 2017. Accessed online: https://www.deadiversion.usdoj.gov/quotas/quota_history.pdf
In May of 2018, Commissioner Gottlieb of the U.S. Food & Drug Administration (FDA) called for an independent audit of IQVIA’s opioids NSP data—a different data source than that used by Avalere in this analysis but from the same vendor. The FDA found that IQVIA utilized faulty conversion factors in determining the amount of fentanyl contained in certain prescription products. The FDA assessed that the error inflated fentanyl sales data over at least the prior five years. After uncovering the issue with fentanyl, the FDA found similar issues with oxymorphone and hydrocodone. https://www.fda.gov/Drugs/DrugSafety/ucm607823.htm

Aggregate Production Quotas (APQs) in order to “reduce or eliminate diversion from legitimate channels of trade” while also providing sufficient, uninterrupted quantities of controlled substances for medical purposes. The DEA sets these quotas taking into consideration specific factors including disposal rates, inventory levels, and projected demand while balancing production sufficient for legitimate medical purposes against “production of excessive amount[s] of these potentially harmful substances”.[43] In its APQ history summary, the DEA publicizes the APQs for select substances, including 27 different opioids. Above, figure 2 overlays the DEA’s APQs for opioids onto the volume of opioid sales.*

3 * In both the prescription sales and APQ data, the products included have changed over the past decade. Certain products have been withdrawn from the market and others are no longer prescribed by physicians; other products may also have been introduced.

The sharp decline observed in APQs from 2010 to 2011 can be largely attributed to the US Food and Drug Administration's announcement in November 2010 against the continued prescribing of the Propoxyphene, which had comprised roughly 13.4% of APQs for opioids.[44] Analysis of the DEA's APQ data shows a 3-year lag from peak prescription opioid sales in 2011 to peak opioid APQs in 2014. Although both sales and production quota trends show persistent declines since their respective peaks, it was not until 2016 that the APQ data suggest a strong federal response as evidenced by the sharp 31.6% decline.

While the DEA, like many stakeholders, was trying to balance the need for opioid medications based on rising prescription levels against the risk of illegitimate use, it seems federal authorities' response in using all available tools to combat the opioid epidemic trailed behind market realities. Between 1993 and 2015, the production quotas for opioids increased 39-fold.[45] What is clear from the data, however, is that by 2014, both federal policy and healthcare market forces were aligned to cause a sharp contraction in the amount of prescription opioids available to US consumers. This decrease in prescription opioid availability, though, is not mirrored in the epidemiological data on OUD prevalence and overdose mortality, as a significant percentage of opioid overdose deaths are now due to heroin and IMF.[13]

Discussion

A thorough understanding of the multiple drivers of the opioid epidemic is the first step in designing a truly comprehensive and effective response. The epidemic is the result of numerous factors, actions, and missed opportunities across multiple stakeholders—from professional societies, the federal government, biopharmaceutical companies, payers, and clinicians. Likewise responding to the epidemic will require coordination across all of these many disparate groups. The fractured healthcare and monitoring system dampened stakeholders' ability to first detect nascent opioid abuse and overuse until it became an epidemic and continues to bedevil the ability to provide an effective response. The continued focus on prescription opioids belies the reality of the current epidemic that is largely driven by illicit substance use.

Today, there are numerous bills that have passed or are under consideration at the state level to limit the amount of opioids that can be prescribed; these include initiatives to allow partial fills of opioid prescriptions, script limits (including days-supply limits and limits on the morphine milligram equivalent that can be prescribed), prescription drug monitoring programs (PDMP), e-prescribing, mandated clinician training or continuing medical education requirements around opioid prescribing and substance abuse, more strict licensure of pain clinics and drug take-back programs, among the hundreds of different bills and policy proposals that are in various stages of adoption. In 2018, there were 216 bills in 41 states addressing some aspect of the opioid epidemic.

Coupled with these legislative initiatives, the federal government has also turned an eye toward regulations and guidelines to tamp down opioid abuse. The CDC has issued updated guidelines

on opioid prescribing and continues to provide training and educational resources to providers on how to safely manage patients with chronic pain.[41] The DEA also drastically decreased opioid production quotas by 25% in 2017 and in April 2018 issued a proposed rule that would update the factors used to determine APQs to include the extent to which a substance is diverted and consideration of data on both legitimate and illegitimate use.[46] In 2018, the DEA announced further reductions aligned with President Trump's goal to "cut nationwide opioid prescription fills by one-third within three years."[43] Finally, in October 2018, Congress passed the Substance Use Disorder Prevention that Promotes Opioid Recovery and Treatment (SUPPORT) for Patients and Communities Act, a comprehensive bill that contains provisions to treat and prevent opioid misuse.[47]

With additional funding for and a focus on both treatment and prevention, these initiatives are a step in the right direction to a truly comprehensive, coordinated response. However, many of these initiatives target prescription opioids, which have been declining steadily in volume since their peak in 2011, while failing to address the illicit opioids that have become a significant driver of mortality and morbidity. Addressing the epidemic requires a broad focus on both prescription and illicit opioids that may not be addressed by initiatives such as additional PDMP programs and fill limits. Critically examining the true drivers of the opioid epidemic, from reimbursement practices to clinical guidelines to patient and clinician attitudes towards pain care is critical to understanding how to best respond to this public health crisis.

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