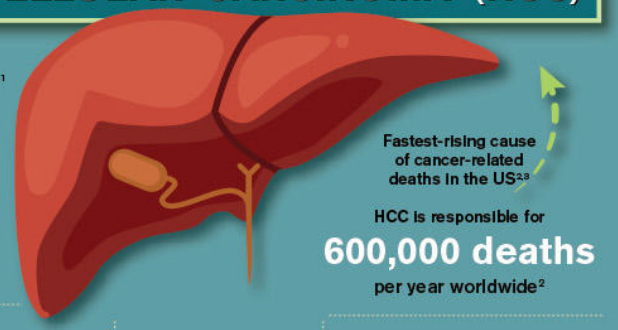
HEPATOCELLULAR CARCINOMA (HCC)



HCC is a leading cause of cancer burden globally[1]

Fastest-rising cause of cancer-related deaths in the US[2,3]

HCC is responsible for **600,000 deaths** per year worldwide[2]

>70% of patients diagnosed with HCC have disease that is not amenable to treatment with liver transplantation or locoregional therapy[4]

The switch from transarterial chemoembolization (TACE) to systemic therapy should be performed in due time[5]

Hand-foot skin reaction (HFSR) is reported with an incidence of **≥1% to 45%** in patients treated with multikinase inhibitors[6]

PLEASE JOIN US FOR A CME WEBCAST

featuring leading experts in Hepatic Oncology and Dermatology and live Q&A Sessions

Emerging Therapy Sequences in Hepatocellular Carcinoma with New Molecular Targeted Therapies: Extending Life Beyond TACE

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University Medical Center
Mainz, German

NICOLE R. LEBOEUF, MD, MPH
Director, The Program in Skin Toxicities from Anticancer Therapies
Clinical Director, Center for Cutaneous Oncology
Dana-Farber/Brigham and Women's Cancer Center
Boston, Massachusetts, USA

WEBCAST & CASE STUDY: TUESDAY, OCTOBER 9

8:00 AM – 9:30 AM AKDT	9:00 AM – 10:30 AM PDT
10:00 AM – 11:30 AM MDT	11:00 AM – 12:30 PM CDT
12:00 PM – 1:30 PM EDT	1:00 PM – 2:30 PM BRT
5:00 PM – 6:30 PM BST	6:00 PM – 7:30 PM CEST
7:00 PM – 8:30 PM EEST	9:00 PM – 10:30 PM YEKT

Webcast & Case Study 2:

REGISTER ONLINE AT

https://webinars.on24.com/HCCWebcast/2

This activity has been approved for *AMA PRA Category 1 Credit*™. Supported by an unrestricted educational grant from Bayer Pharmaceuticals.

PROGRAM OVERVIEW

HCC is one of the most common malignancies in the world and is a complex tumor that is steadily rising in incidence globally.[1,3] The majority of patients diagnosed with HCC have advanced disease,[5] and these patients, represent the highest priority for improved outcomes and healthcare provider education. The proven efficacy of systemic therapies offers the hope of prolonged survival in these patients.[5] However, the timing of transition to systemic treatment is debated and the need to effectively manage side effects must be addressed in order to improve the long-term prognosis for patients with HCC.[1-3,5]

As a part of this webcast series, topical presentations will explore HCC as discussed by the experts. Throughout the series, case study presentations will highlight these issues.

INTENDED AUDIENCE

This activity is directed toward medical oncologists, hepatologists, gastroenterologists, and interventional radiologists who treat patients with hepatocellular carcinoma. Other healthcare providers are also invited to participate.

EDUCATIONAL OBJECTIVES FOR THE WEBCAST

- Understand management strategies for intermediate and advanced disease in patients including transition from local-regional to systemic therapies
- Gain awareness of recent, global, evidence-based literature and clinical trials on systemic therapies and sequencing for HCC
- Understand management of treatment-related adverse events with focus on HFSR
- Provide learners the knowledge to help with the development and implementation of local institutional clinical pathways to optimize management of HCC

CONTINUING EDUCATION CREDIT

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of the University of Massachusetts Medical School Office of Continuing Medical Education (UMMS-OCME) and Strategically Speaking, Inc. The UMMS-OCME is accredited by the ACCME to provide continuing medical education for physicians.

The University of Massachusetts Medical School designates this live activity for a maximum of ***1.5 AMA PRA Category 1 Credits***™. Physicians should claim on the credit commensurate with the extent of their participation in the activity.

DISCLOSURE POLICY

It is the policy of the University of Massachusetts Medical School to ensure fair balance, independence, objectivity, and scientific rigor in all activities. All faculty participating in CME activities sponsored by the University of Massachusetts Medical School are required to present evidence-based data, identify and reference any mention of off-label product use, and disclose all relevant financial relationships with those supporting the activity or others whose products or services are discussed. Faculty disclosures will be provided as part of the educational activity.

FEE INFORMATION AND DISCLOSURE

There is no fee for this educational activity, which is supported by an unrestricted educational grant from Bayer Pharmaceuticals.

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QUESTIONS?

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Commentary

The Opioid Epidemic in the United States—Overview, Origins, and Potential Solutions

Greg H. Jones, BS[1]; Eduardo Bruera, MD[2]; Salahadin Abdi, MD, PhD[3]; and Hagop M. Kantarjian, MD[1,*]

OVERVIEW AND EVOLUTION OF THE OPIOID EPIDEMIC IN THE UNITED STATES

Drug overdose is now the leading cause of accidental death in the United States: it caused approximately 65,000 deaths in 2016, a 21% increase from the previous year.[1] From 1999 to 2008, mortality from drug overdoses quadrupled, as did opiate prescriptions. During the same period, admissions for the treatment of substance use disorder increased 6-fold.[2] The opioid class of drugs includes prescription pain relievers such as oxycodone, hydrocodone, codeine, morphine, and fentanyl in addition to illicit substances such as heroin. Although numbers vary widely, it is estimated that 20% to 30% of patients who are prescribed opioids for chronic noncancer pain misuse them, and 8% to 12% progress to develop opioid use disorder.[3]

Despite representing only 5% of the global population, Americans consume 80% of the world's oxycodone and 90% of the world's hydrocodone.[4] This trend peaked in 2012 when approximately 259 million prescriptions were written for opioids, more than enough to provide 1 bottle for every adult in America.[5] Although prescription rates have fallen nearly 20% since 2012, rates of overdose from nonprescription opioids continue to increase rapidly (Fig. 1).[6,7]

Approximately 115 Americans die every day from opioid overdoses, and this surpasses the death toll of the September 11 attack on a monthly basis. The White House Council of Economic Advisers estimated that the opioid epidemic cost the United States $504 billion in 2015, which represents 2.8% of the nation's total gross domestic product.[1]

Despite these striking trends, during the last 25 years, the drug manufacturers that have contributed to the epidemic have paid only $35 billion in fraud settlements out of $711 billion in worldwide net revenue from opioids.[8] Such fines are negligible in comparison with the profits that they derive from questionable and often illegal marketing practices.

ORIGINS AND STATUS

The Trigger

The misrepresentation of 1 study largely laid the groundwork for the marketing practices that spawned the opioid epidemic in the United States. In 1980, the *New England Journal of Medicine* (*NEJM*) published a letter from a Boston University Medical Center physician, Dr. Hershel Jick, who studied more than 11,000 patients receiving opioids in the inpatient setting. He concluded that "despite widespread use of narcotic drugs in hospitals, the development of addiction is rare in medical patients with no history of addiction."[9] As described in a 2017 article in the *Atlantic*, publications such as *Time Magazine* and *Scientific American* characterized this letter as an "extensive study" that portrayed "the exaggerated fear that patients would become addicted to opioids" as "basically unwarranted."[10] The *NEJM* letter rapidly became a landmark study: it was cited 608 times between 1980 and 2017, with a significantly increased citing frequency after the introduction of OxyContin (extended-release oxycodone HCl) in 1995. Seventy percent of the citations used the letter as evidence that addiction was rare among patients treated with opioids. More than 80% did not mention that patients from the original study were exclusively hospitalized while receiving the medication.[11] The misinterpretations and inaccurate citations contributed to the propagation of understating the dangers of opioid addiction.

The Drug Industry Seizes the Opportunity

Around this time, large manufacturers such as Purdue Pharma, Johnson & Johnson, and Endo Pharmaceuticals began funding nonprofit groups involved in the medicine of pain management, such as the American Pain Society. The

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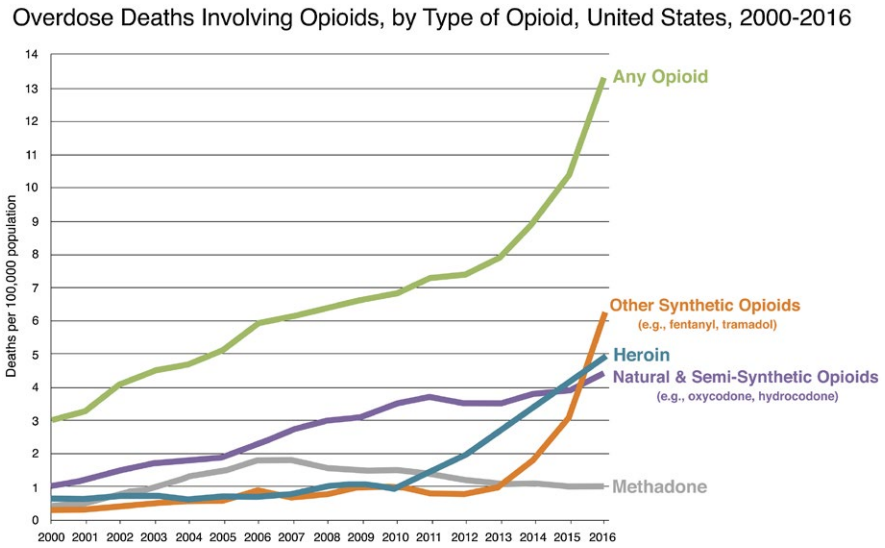

Figure 1. Overdose deaths involving opioids by type of opioid in the United States, 2000-2016. Reprinted from the Centers for Disease Control and Prevention Web site.[7]

leadership of the organization drew attention to the growing recognition in the medical community that many individuals with chronic pain were being treated inadequately. In part by issuing a 1996 consensus statement titled *The Use of Opioids for the Treatment of Chronic Pain*, some of the thought leaders advocated for the use of pain as a "fifth vital sign."[12]

Capitalizing on this sentiment, Purdue Pharma helped to fund a "pain management education program" organized by the Joint Commission. The Joint Commission proceeded to publish a Purdue Pharma–sponsored guide, which stated that "some clinicians have inaccurate and exaggerated concerns [about risks of addiction] … This attitude prevails despite the fact there is no evidence that addiction is a significant issue when persons are given opioids for pain control." Eventually, the Joint Commission would adopt pain as the fifth vital sign and establish a 1 to 10 rating system for patients to convey their subjective pain level. The National Cancer Center Network also published cancer pain guidelines that included escalating opioid pain treatment according to pain intensity on a scale of 0 to 10.[13,14]

In 2004, the Federation of American Medical Boards joined the movement by encouraging state medical societies to enact physician punishments for undertreatment of pain. This policy was drafted by several individuals with ties to narcotics manufacturers. Some were members of an industry speakers' bureau and later became company executives. In addition to nearly $2 million in funding from the pharmaceutical companies since 1997, a federation-published book outlining this punitive opioid policy was subsidized by manufacturers, including Purdue Pharma and Endo Pharmaceuticals.[12]

Purdue Pharma

Between 1996 and 2002, Purdue Pharma funded more than 20,000 pain-related educational programs and exerted enormous influence over physician prescription habits nationwide.[13] In 1998, the company followed the growing trend of inaccurate citations of Jick's 1980 letter to the *NEJM* and developed what turned out to be a misleading advertising campaign. Although the original *NEJM* letter reported on the use of opioids only in the hospital setting, with no follow-up regarding outpatient use, Purdue Pharma turned the results into a blanket statement and claimed that the risk of addiction associated with prescription opioids was "much less than 1%."[15] This erroneous portrayal apparently became a landmark justification to aggressively market OxyContin. Jick would later condemn this tactic, stating, "I'm essentially mortified that that letter to the editor was used as an excuse to do what these drug companies did."[16]

In 1996, Purdue Pharma entered into an indemnity agreement with Abbott, one of the largest pharmaceutical sales companies in America. In exchange for Purdue Pharma agreeing to pay all potential litigation costs from future sales, Abbott matched Purdue Pharma's OxyContin sales force and dedicated 300 sales representatives to its self-proclaimed opioid crusade. These individuals engaged in a plethora of questionable marketing

strategies centered on minimizing the risk of addiction associated with their product.[17]

Through this partnership, OxyContin sales grew from $48 million in 1996 to more than $1 billion in 2000. In 2001, Purdue Pharma spent $200 million on marketing OxyContin. By 2002, sales exceeded $1.5 billion. Despite double-blind randomized trials showing no clinical advantage in efficacy or safety in comparison with other analogous opioid preparations, by 2013, OxyContin represented approximately 30% of the opioid painkiller market. With increased sales came increased abuse and addiction. By 2004, OxyContin was the leading drug of abuse in the United States.[13]

On May 10, 2007, Purdue Pharma (along with 3 company executives) pleaded guilty to criminal charges of misrepresenting the risks of addiction of OxyContin and was forced to pay $634 million in penalties,[13] a small fraction of the nearly $35 billion in sales over the last 2 decades.[18]

Global Outreach

Because of reforms in prescription practices, OxyContin sales have fallen nearly 40% since 2010. To offset this loss, the Sackler family (owners of Purdue Pharma) has pivoted toward penetrating developing global markets. Its network of international companies, known collectively as Mundipharma, has expanded to Asia, Latin America, the Middle East, and Africa, and it now has a presence in 122 new markets outside the United States. Rapidly modernizing countries are expected to spend more than $20 billion on pain medication by 2020. Mundipharma representatives abroad have continued Purdue Pharma's marketing tradition, downplaying the risks of prescription opioid addiction in their respective countries. Sharon Walsh, who runs the University of Kentucky's Center on Drug and Alcohol Research, labeled these tactics as "exactly the same thing they were teaching U.S. physicians when they launched OxyContin in this country."[18]

With respect to influencing the prescription practices that instigated the opioid epidemic, Andrew Kolodny, the codirector of the Opioid Policy Research Collaborative at Brandeis University, noted that Purdue Pharma bore the lion's share of the blame.[19] However, similar marketing practices from manufacturers of more potent opioids have since contributed to the next wave of the public health crisis.

Expansion of Fentanyl Use and Increased Mortality

Insys Therapeutics, an Arizona-based manufacturer, derives virtually all of its revenue from Subsys fentanyl, an opioid sublingual spray with 100-fold greater potency than morphine. Although it is exclusively indicated for patients suffering from breakthrough cancer pain, a 2014 analysis found that only 1% of Subsys prescriptions were written by oncologists.[20]

In 2017, Arizona's attorney general filed a lawsuit against Insys Therapeutics, alleging that it "paid doctors 'sham speaker fees' in exchange for writing prescriptions, all in order to increase the sales of Subsys, without regard for the health and safety of patients." Insys Therapeutics also circumvented the prior authorization process for many of these prescriptions by setting up a call center where employees were instructed to mislead insurance companies by suggesting that they were calling from physicians' offices and providing false patient data. In late 2017, the company's founder, John Kapoor, was arrested and charged under the Racketeer Influenced and Corrupt Organizations (RICO) Act with conspiracy to commit wire fraud and violation of the Anti-Kickback Law in relation to his efforts to increase the distribution of Subsys.[21] Two individuals involved in this investigation have already pleaded guilty to violating this statute, and 1 Rhode Island physician is currently serving a 4-year prison sentence for taking payments from Insys Therapeutics.[20] Regarding these practices, Oregon Assistant Attorney General David Hart stated, "I've been investigating drug cases for about 15 years now, and the conduct that we saw in this case was among the most unconscionable that I've seen."[22]

Similarly, in 2008, Cephalon Pharmaceuticals agreed to pay $425 million to resolve claims regarding off-label marketing of 3 drugs, including Actiq, a fentanyl-based lollipop. Although approved only for use by cancer patients no longer having relief from morphine, Cephalon Pharmaceuticals allegedly promoted the use of the lollipop for other conditions, including migraines, sickle cell pain crises, musculoskeletal injuries, and anticipation of wound dressing changes.[23]

Between 2013 and 2016, fentanyl overdoses increased 540% and surpassed common opioid and heroin overdoses. During that same timeframe, annual drug overdose deaths rose more than 22%, from 52,000 to 64,000, with drug overdoses killing Americans at a rate faster than the peak fatality rates of car crashes, the human immunodeficiency virus (HIV) epidemic, or gunshot wounds. Even though deaths from prescription opioids are finally starting to decline, the rate of fentanyl overdose deaths is accelerating, with fentanyl accounting

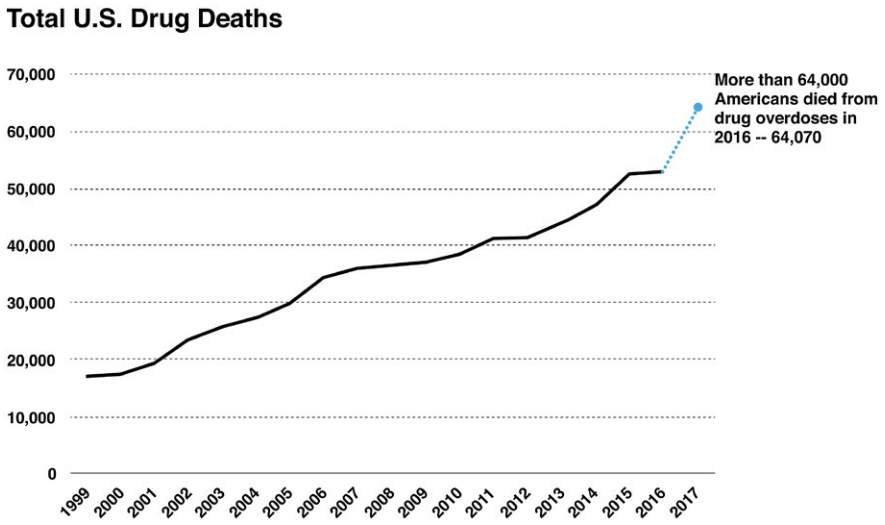

Figure 2. Total US drug deaths. Reprinted from the National Institute on Drug Abuse Web site.[24]

for "nearly all the increases in drug overdose deaths from 2015 to 2016" (Fig. 2).[24–26]

Heroin and other prescription opioids have a raw opium base, which must be cultivated and harvested. On the other hand, fentanyl is completely synthetic and can be manufactured from relatively inexpensive substrates. This explains why the majority of fentanyl seized in the United States today originates from laboratories in China and is smuggled through Mexico.[27] China has recently outlawed the clandestine production of fentanyl and its derivatives. However, this has done little to slow the efforts of Mexican cartels, which are currently flooding US markets with fentanyl from other sources.[28] Fentanyl also requires larger doses of naloxone, the common opioid antagonist used by first responders to reverse overdoses from heroin and other prescription opioids, and this contributes to the comparatively high rate of overdose mortality.[25]

The Drug Industry Proposes Financially Self-Rewarding Solutions

Just as the pharmaceutical industry prioritized profit generation over national well-being in marketing opioids, it also proposed solutions with similar motives. In the past 2 years, the pharmaceutical companies have made discreet yet concerted efforts to advocate for legislation requiring the Food and Drug Administration (FDA) to mandate the use of yet unproven abuse deterrent formulations (ADFs) of opioid painkillers, which make the pills themselves harder to crush or dissolve.[29]

Although making painkillers harder to abuse may seem like a logical solution, in reality, tampering with medication to facilitate its use via injection, smoking, intranasal snorting, or other nonoral routes is not a factor in most opioid-related deaths.[30] In addition, manufacturers are permitted to continue prior marketing strategies for ADFs under the guise of a safer product. This may ultimately result in overprescribing by physicians. The *Clinical Journal of Pain* released survey results showing that nearly half of the responding US physicians incorrectly believed that ADFs were less addictive than conventional formulations.[31]

This solution also conveniently represents a multibillion-dollar sales opportunity for manufacturers. Not only do these new formulations provide decades of extended patent exclusivity, they potentially allow brand name manufacturers to eliminate all low-cost generic competitors. This is not simply a theoretical threat. In 2010, Purdue Pharma released its new ADF version of OxyContin, which was harder to crush and dissolve. In 2013, when the original formulation's patent was set to expire, the FDA refused to approve any new applications for generic versions of the old, non-ADF formulation.[32]

Mandating the use of ADFs could result in up to a 20-fold increase in opioid costs, which would place an extreme burden on the US health care system.[33] In 2016, ADFs represented less than 5% of domestic opioid prescriptions but generated more than $2.4 billion in sales, almost one-quarter of the entire US market.[29]

Despite the staggering potential for increased health care costs, policymakers continue to advocate for more pharmaceutical industry–friendly legislation. Forty-nine of 100 bills introduced in 2015 and 2016 contained nearly identical language requiring insurance companies to cover ADFs. Several sponsors of the bills have openly admitted that they received wording for the legislation from pharmaceutical lobbyists.[29]

Not only has the FDA yet to conclude that ADFs have any real-world impact on outcome measures such as overdose deaths,[34] evidence suggests that ADFs are causing a shift to the usage of alternative opioids and other unintended consequences. Studies published in *JAMA Psychiatry*[35] and the *Canadian Medical Association Journal*[36] found that the introduction of ADFs led to a reduction in OxyContin use but may have contributed to a rise in heroin abuse and ultimately had no net effect on the overall opioid overdose rate. The *Canadian Medical Association Journal* authors noted that "regulations requiring tamper resistance will likely do little to address the opioid epidemic and may serve merely to line the pockets of drug companies while diverting the policy-makers' attention away from more meaningful and effective interventions."

In addition, ADFs have been shown to cause unintended harm even when patients do not switch to alternatives such as heroin. In 2015, Endo Pharmaceuticals released its new ADF version of Opana ER, and this resulted in outbreaks of HIV and hepatitis C because of needle sharing among users injecting the new formulation. In June 2017, the FDA requested that Endo Pharmaceuticals remove Opana ER from the market.[37]

As of 2016, 5 states have adopted laws requiring insurance companies to cover ADFs, with similar laws being proposed in 15 other states.[38]

POTENTIAL SOLUTIONS

Shifting Public Policy to Address the Changing Landscape

After peaking in 2012, opioid prescriptions have declined 18% overall. Despite this, total opioid overdose deaths are increasing rapidly, in large part because of a shift toward nonprescription opioids. In 2015, heroin overtook prescription painkillers and caused 15,500 deaths. During the same period, the rate of overdose deaths from fentanyl and its derivatives doubled to more than 19,000. Most of these deaths are caused by illegal pills or powder, which is often used as an adulterant in heroin and other illicit drugs.[1] In 2016, prescription opioids accounted for only 40% of total opioid overdose deaths.[39]

The dire nature and rapid evolution of the opioid epidemic necessitate radical policy shifts away from conventional methods. With more than 40 years of evidence, the failed war on drugs has shown that using law enforcement as a first-line solution for drug epidemics does not yield desirable results. In addition to very limited success in curbing overall usage, 1 full year of incarceration costs taxpayers roughly $24,000, whereas 1 year of methadone treatment costs $4700. Conservative estimates show that for every dollar spent on addiction treatment, there is a $12 return on investment through reduced health care and criminal justice costs.[40]

In this regard, Portugal can be viewed as an example of the success that can be achieved by approaching this problem primarily through the health care system. In the 1990s, 1% of Portugal's entire population was addicted to heroin. This was known at that time as one of the worst drug epidemics in the world.[41] In 2001, Portugal created a national policy making substance abuse a public health issue necessitating treatment rather than a criminal act resulting in imprisonment. After just 10 years, Portugal's drug-death rate dropped by nearly 80%, and it is now 5 times lower than the European Union average. Its drug-related HIV infection rate also dropped by 95%. Since 2001, the overall rate of drug usage has declined in many subsets of the population, especially those between the ages of 15 and 24 years (the group most at risk of initiating drug use).[42] Enacting strategies based on this model could prove beneficial in addressing the epidemic in the United States, especially because of the marked shift toward illicit opioid usage in recent years.

Improving Treatments and Access

Today in America, a large gap exists between drug addiction and treatment, with only 1 of 10 individuals who suffer from addiction receiving specialized treatment.[43] The Trump administration has pledged to bolster opioid addiction research and treatment with an additional $13 billion dollars in funding over the next 2 years. However, efforts to roll back the progress of the Affordable Care Act may result in an overall reduction in treatment access.[44] Expanding health care coverage to more Americans is a necessary preamble to closing this gap.

Increased funding for treatment programs and expansion of overall health care coverage may partially ameliorate this problem. However, even with increased access, conventional therapies such as methadone and buprenorphine/naloxone do not work for all patients, with

approximately 50% suffering a relapse after treatment.[45] Novel molecular targets for the kappa-opioid receptor and serotonin modulators, in addition to vaccines that recruit the body's own immune system to prevent opioid entry into the central nervous system, provide promising new avenues of investigation.[46]

The Role of Physicians

The director of the Centers for Disease Control and Prevention, Tom Frieden, has recently labeled the opioid epidemic as doctor-driven. However, some surveys suggest that many physicians across a wide range of specialties feel pressure to overprescribe opioids because of the linkage of reimbursements to patient satisfaction with pain control.[47] Because of this, the American Medical Association and the American Academy of Family Physicians have voted to drop pain scores as a fifth vital sign.[48] Advocating for the Joint Commission and the Centers for Medicare and Medicaid Services to echo these sentiments could alleviate some of the perceived pressure on physicians.

In 2014, an analysis of a database of nearly 3 million patients showed that 73% of those undergoing inpatient treatment with intravenous analgesics received exclusively opioids.[49] In 2016, the Centers for Disease Control and Prevention finally advocated for the preferential use of nonopioid therapies as a first option for treating chronic noncancer pain.[50] Clinicians should further this directive by promoting a multimodal, nonopioid platform as a standard of care for chronic noncancer pain management and should limit the length of opioid prescriptions for acute pain whenever possible.

Improved medical education about the multidimensional nature of chronic pain expression will reduce the oversimplified 0 to 10 guided treatment. Universal screening for substance use disorder risk and more frequent follow-up and monitoring of patients at increased risk or with documented aberrant behaviors can be easily implemented in the clinical setting.[51–53]

Novel Approaches to Pain Management

Because untreated chronic pain originally provided a lead-in to this epidemic, creating alternative modalities for chronic pain management is an integral part of solving this crisis. As previously stated, in addition to the potential financial conflict of the drug companies, promoting the use of ADFs does not appear to be a viable long-term solution for treating chronic pain. Instead, research should be directed toward inherently nonaddictive modalities. Compounds known as biased agonists showed significant promise in recently completed phase 2 trials.[46] By preferentially activating the analgesic signaling pathway controlled by the mu-opioid receptor, they provide pain relief without causing significant respiratory depression or addictive reward reinforcement (both of which appear to be modulated by a different, second messenger system of the same receptor). Other nonopioid pharmacological approaches such as sodium and calcium channel blockers and cannabinoids may also lead to novel therapeutic options.[46]

Furthermore, the use of gene therapies and neurostimulators (transcranial magnetic and direct current stimulation, peripheral stimulation, spinal cord and deep brain stimulation, and MC5-A scrambler therapy) are alternative nonpharmacological options in select cases. The use of interventional pain procedures should also be considered whenever possible.[46,54] At present, there is limited evidence for the possible value of many of the interventional procedures for pain. More robust research is needed in this area.

The ability to reliably modulate chronic pain with cannabinoids is yet unproven; however, they may reduce overall opioid mortality independently of their analgesic efficacy. Although a causal link has yet to be established, states that enact medical cannabis laws have a 25% reduction in opioid overdose mortality. This association strengthens each year after implementation.[55] Investigations regarding the efficacy of cannabis in treating pain and reducing opioid usage are currently hampered by its schedule I status, but these initial results warrant further inquiry.

The scourge of opioid addiction is a national emergency. It is imperative that public and private entities collaborate to find solutions to prevent needless deaths. We believe that our proposals are a sound beginning.

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CONFLICT OF INTEREST DISCLOSURES

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