Backstories on the US Opioid Epidemic. Good Intentions Gone Bad, an Industry Gone Rogue, and Watch Dogs Gone to Sleep

Richard D. deShazo, MD,a,b,c McKenzie Johnson, BS,a Ike Eriator, MD,d Kathryn Rodenmeyer, BAe

aUniversity of Mississippi Medical Center Department of Medicine, Jackson; bUniversity of Mississippi Medical Center Department of Pediatrics, Jackson; cMississippi Public Broadcasting, Jackson; dUniversity of Mississippi Medical Center Department of Anesthesiology, Jackson.

ABSTRACT

Epidemics of opioid use are old news in the United States, but an epidemic that kills over 200,000 Americans is not. A multiplicity of intertwined factors have brought us to this place. From 30,000 feet, it is the story of good intentions gone bad, a drug industry gone rogue, and government watch dog agencies gone to sleep. At ground level, it is the story of physicians unfamiliar with addictive drugs and drug addiction, new long-acting opioids deceptively marketed, cheap black tar heroin, encouragement to use opioids for chronic noncancer pain by professional organizations with conflicts of interest and without science, a culture intolerant to pain and tolerant to drug use, and the greedy response of the pharmaceutical industry and drug cartels to an expanding market opportunity. These factors are among those that have joined to form a tsunami of addiction and deaths that keeps on coming. A better understanding of them could speed the end of the present cycle of opioid abuse, perhaps prevent others, and inform future decisions about pain management.

INTRODUCTION

The current American epidemic of opioid-related deaths began in the 1990s and has resulted in over 200,000 deaths.1 The average American does not know who to blame (Figure 1).2 The only systematic review on causation suggests that the factors are multiple, intertwined, and frequently changing (Table 1).3 That review determined that physician behavior is clearly one of them. This paper reviews backstories on some factors that help inform our response as physicians.

AMERICA’S LONG TARANTELLA WITH OPIOIDS

Extracts of the poppy plant have been used for medicinal purposes since the Sumerians named it the “joy plant” 5000 years ago. By the time of the American Revolution, an alcohol-based tincture of 10% powdered opium called “laudanum” was widely prescribed in the United States and many became addicted. Morphine was isolated from opium about 50 years before it caused “Soldier’s Disease,” an epidemic of addiction during the Civil War.4 Bayer Pharmaceuticals marketed heroin in 1874 as an analgesic and claimed it was less addictive than other opioids, claims made about the new opioids to follow. During this period, opium, heroin, and cocaine were used in over-the-counter patent medicines and sold over the counter in “emergency kits” equipped with hypodermic syringes and needles (Table 2). By 1925, there were an estimated 200,000 heroin addicts in the United States.

The problem of opioid addiction led to passage of federal legislation to control it in 1906, 1909, 1914, and 1924 (Table 3). Tolerance for illicit drug use increased after young people smoked marijuana in public and Jimi Hendrix followed his psychedelic version of the national anthem with his song, “Purple Haze” at the 1969 Woodstock Music and Art Fair. By 1971, 15% of soldiers in Vietnam had become heroin addicts. In response, President Nixon declared drug addiction “public enemy number one” in 1972 and established

Funding: The Selby and Richard McRae Foundation.
Conflicts of Interest: The authors of this article declare that they have no conflicts of interest.
Authorship: All authors were actively involved in the writing of this paper.
Requests for reprints should be addressed to Richard D. deShazo, MD, University of Mississippi Medical Center, 2500 North State Street, Jackson, MS 39216.
E-mail address: rdeshazo@umc.edu

0002-9343/$ - see front matter © 2018 Elsevier Inc. All rights reserved.
federally supported methadone clinics, only to have methadone quickly become a drug of abuse. Around 1996, the confluence of a new pain movement and the pharmaceutical industry were associated with a substantial escalation of prescription opioid use, abuse, and opioid-related deaths in the United States.

**THE CONFLUENCE OF THE PAIN MOVEMENT AND PHARMA**

In 1980, a one-paragraph “Letter to the Editor” in the *New England Journal of Medicine* reported that of 11,882 hospitalized patients treated with narcotics, <1% of them became addicted. The letter was subsequently “uncritically cited” in 439 articles published in scientific journals. Meanwhile, a shared interest in better management of cancer pain led Raymond Houde, MD, Katherine Foley, MD, and Russell Portenoy, MD at Cornell University-Weill Medical College to become leaders in the American Pain Society (APS). Two of them concluded that opioid maintenance therapy for chronic noncancer pain was safe and humane. The APS became an advocacy group for opioid treatment of pain and eventually received most of its support from Purdue Pharma (Stamford, Conn), maker of the opioids MS Contin® and OxyContin®.

In 1995, the APS proposed that pain be measured as the “5th Vital Sign” and trademarked the term. That society published a consensus statement with the American Academy of Pain Medicine in 1997 and declared that there was insufficient evidence to show that addiction occurs when opioids are appropriately prescribed for the treatment of pain. In 2010, the International Association for the Study of Pain added a patient’s rights component to the pain movement when it declared that all patients were entitled access to pain management when it declared that all patients were entitled access to pain management and treatment, including opioids.

Another advocacy group, the American Pain Foundation organized e-mail campaigns to media outlets they determined to be biased against opioids for pain treatment at a time when it received 90% of its funding from the drug and device industry. Many “thought leaders” from pain societies gave Pharma-supported lectures to provider groups to encourage treatment of pain with opioids.

The APS was joined by the Veterans Affairs Medical System (VA), the Joint Commission for Accreditation of Health Organizations (now The Joint Commission [TJC]), the American Medical Association, the American Academy of Family Physicians, and patient advocacy groups in support of Pain as the 5th Vital Sign. Opioid manufacturers and pain management advocates then convinced the US Congress to declare “A Decade of Pain Control and Research” in 2000. By 2001, new TJC Pain Management Standards, used as a component of hospital accreditation and reimbursement, were implemented and required pain to be assessed and addressed in all hospitalized patients.

The commission also implemented its own pain initiative and developed educational materials for it with support from Purdue Pharma and the National Pharmaceutical Council, Inc. These included the monograph *Improving the Quality of Pain Management through Measurement and Action*, which advocated opioid use for pain and was co-branded with the logos of TJC and the National Pharmaceutical Council. A nurse developed and copyrighted the Wong Baker Facial Scale that allowed patients to grade their pain from 1-10 by choosing faces that smiled or frowned, a subjective measure that soon came to be used as an objective one. The VA mandated the measurement of Pain as the 5th Vital Sign and that it be addressed in every clinical encounter in 1999. In 2016, as opioid deaths exploded, Physicians for Responsible Opioid Prescribing petitioned TJC to stop their support of opioid use and claimed their pain standards “foster dangerous pain control practices” which “often lead to the inappropriate prescribing of opioids” and “disastrous consequences.” A 2015 opinion piece noted the physiological futility of using pain intensity to guide pain treatment and the need to return to the basics of pain management, which were already outlined in a 2010 National Institute of Health Pain Initiative. All of this eventually led to the 2011 Institute of Medicine report, *Relieving Pain in America*. About the same time, both the

---

**CLINICAL SIGNIFICANCE**

- The opioid epidemic proves that money and power can subvert the best intentions of many.
- A major research initiative to better understand the mechanisms of pain and better pain management is essential.
- A second research initiative should be undertaken to better understand why drugs of abuse are so attractive to so many.

---

**Figure 1** Responses to the question, “Who is most responsible for the nation’s opioid crisis?” from a random survey of 3645 individuals by *Fortune* magazine. Adapted from Reference 3.
American Medical Association and the American Academy of Family Physicians voted to rescind their previous support of pain as the 5th Vital Sign. The actions of 3 New York City psychiatrists, the Sackler brothers, played a major role in this story. Dr. Arthur Sackler (D-1987) became a wealthy pharmaceutical marketing executive, publisher of medical trade publications, and father of direct-to-physician marketing. He and his brothers Mortimer (D-2010) and Raymond (D-2017) purchased Purdue Frederick, a New York drug manufacturer that produced an ear wax remover, a laxative, Betadine®, and a tonic that was 11% alcohol under the name Purdue Pharma. Their first new product was the long-acting morphine, MS Contin® released in 1984, followed by OxyContin®, a long-acting oxycodone. After Food and Drug Administration (FDA) approval in 1995, OxyContin® was marketed as a “less addictive opioid.” OxyContin® was launched only after the Sackler brothers deployed a carefully considered marketing plan using a 600-person sales force and a list of over 90,000 physicians judged likely to prescribe OxyContin®. Physicians received free trips to exotic locations to hear paid members of the Purdue “Speakers Bureau” give talks supporting opioid use for chronic pain, and patients received coupons for an up-to-30-day supply of OxyContin® for free. Both the unsubstantiated “Theory of Pseudo-Addiction” suggesting that drug-seeking by pain patients treated with opioids reflected undertreatment of pain, and the report of a 1% addiction rate of opioids were included in OxyContin® marketing. These same erroneous claims were spread through a multitude of over-the-counter products.

### Table 1: Some Factors Promoting Escalation of Opioid Use in the United States Around 1996

<table>
<thead>
<tr>
<th>Number</th>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A well-intentioned effort among some physician groups to better manage chronic pain</td>
</tr>
<tr>
<td>2</td>
<td>False marketing claims about addiction to new, longer-acting opioids</td>
</tr>
<tr>
<td>3</td>
<td>Lack of physician education on the use of drugs with high abuse potentials</td>
</tr>
<tr>
<td>4</td>
<td>Direct-to-physician marketing</td>
</tr>
<tr>
<td>5</td>
<td>Provider-run pill mills</td>
</tr>
<tr>
<td>6</td>
<td>Culture of drug use and abuse</td>
</tr>
<tr>
<td>7</td>
<td>Multitude of cheap, widely available drugs of abuse including black tar heroin</td>
</tr>
<tr>
<td>8</td>
<td>Over-prescription of narcotics</td>
</tr>
<tr>
<td>9</td>
<td>Expansion of Mexican drug cartels</td>
</tr>
<tr>
<td>10</td>
<td>Corporate greed</td>
</tr>
</tbody>
</table>

Adapted from Reference 3.

### Table 2: Representative Over-the-Counter Patented Medicines and Kits for Dispensing Opioids

<table>
<thead>
<tr>
<th>Product</th>
<th>Content</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mrs. Winslow’s Soothing Syrup Bangor, Maine (1849)</td>
<td>Morphine sulfate 65 mg/oz</td>
<td>Sleep aid and analgesic for children</td>
</tr>
<tr>
<td>Stickney and Poor’s Pure Paregoric Use (1905)</td>
<td>Opium 1/8 gr/ounce in 46% alcohol</td>
<td>Asthma for patients 5 days old and up</td>
</tr>
<tr>
<td>Bayer &amp; Company’s-Heroin (1890)</td>
<td>Heroin 1/24 grain per pill and in elixirs</td>
<td>Antitussive</td>
</tr>
<tr>
<td>Vapor-Oil Treatment No. 6. National Vaporizers Co. Kalamazoo, Mich. (Late 1800s)</td>
<td>Opium 35 mg/oz in alcohol</td>
<td>Asthma and “spasmodic affections”</td>
</tr>
<tr>
<td>Parke-Davis &amp; Company’s “Emergency Kit” (1894)</td>
<td>Cocaine, morphine, atropine, strychnine, and a hypodermic syringe</td>
<td>“Emergencies”</td>
</tr>
</tbody>
</table>

### Table 3: Representative Federal Legislation to Control Opioid Use in the United States

<table>
<thead>
<tr>
<th>Date</th>
<th>Title</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1906</td>
<td>Pure Food and Drug Act</td>
<td>Requires patent medicines with opiates to be labeled as “dangerous or addictive”</td>
</tr>
<tr>
<td>1909</td>
<td>Smoking Opium Exclusion Act</td>
<td>Criminalizes the importation, possession, or smoking of opium</td>
</tr>
<tr>
<td>1914</td>
<td>Harrison Narcotic Tax Act</td>
<td>Creates registry of all who produce, import, manufacture, dispense, or give away any product of the poppy or coca leaf. Singles out addiction as a moral not a medical issue. Limits prescriptions for small amounts of narcotics to doctors</td>
</tr>
<tr>
<td>1926</td>
<td>Heroin Act</td>
<td>Makes production and possession of heroin illegal</td>
</tr>
<tr>
<td>1919-1933</td>
<td>21st Amendment to the US Constitution</td>
<td>Period of Prohibition via Comprehensive Drug Abuse Prevention Act (Title II)</td>
</tr>
<tr>
<td>1970</td>
<td>Controlled Substances Act</td>
<td>Regulates manufacture and distribution of narcotics. Establishes 5 narcotics schedules. Marijuana becomes a controlled substance</td>
</tr>
<tr>
<td>1973</td>
<td>US Reorganization Plan No. 2 of 1973</td>
<td>Reorganizes federal drug law enforcement and establishes the Drug Enforcement Agency (DEA) in the Department of Justice</td>
</tr>
<tr>
<td>1974</td>
<td>Narcotic Addict Treatment Act</td>
<td>Allows physicians to register to provide narcotics to addicts for “maintenance treatment” and establishes the National Institute of Drug Addiction (NIDA)</td>
</tr>
<tr>
<td>2016</td>
<td>Comprehensive Addiction and Recovery Act of 2016 (CARA)</td>
<td>Authorizes $181 million dollars for prevention and treatment of the opioid epidemic</td>
</tr>
</tbody>
</table>
included in a publication of opioid use for pain management by the Federation of State Medical Bonds (FSMB) sponsored by Purdue Pharma.24 In 2007, Purdue paid $630 million dollars to settle FDA claims for false marketing of OxyContin®, and several company officials paid an additional $34 million in fines (Table 4). More FDA investigation continued and opioid makers and distributors looked for relief.

The Pain Policy Study Group composed of social science faculty at the University of Wisconsin, Madison received $2.5 million dollars in grants from the pharmaceutical industry, including $1.6 million dollars from Purdue Pharma in the process of its work on opioids-prescribing policies.22 In 2002, the Pain Policy Study Group reported a 10-year collaboration with the FSMB to “update and clarify state medical board policies on the use of opioid analgesics to treat pain.” Their report was used to develop Model Guidelines for the FSMB to address “prescribing of opioid analgesics for pain and physicians fears of regulatory scrutiny”25 (Table 5). In 2003, Purdue provided $100,000 for the printing of 300,000 widely distributed copies of the FSMB Model Guidelines, which were highly supportive of opioid use for chronic pain and used to develop opioid-prescribing policies by most state boards.22 The Guidelines were developed in the absence of high-quality scientific studies and reflected the opinions of the pain management community who collaborated on their formation.19

THE FAILURES IN OVERSIGHT OF OPIOID MANUFACTURE, DISTRIBUTION, PRESCRIBING, DIVERSION, AND IMPORTATION

The Controlled Substance Act of 1970 relaxed the antiopioid portions of the Harrison Narcotics Act of 1914 and recognized that opioids had legitimate medical purposes (Table 3).23 It established the US Drug Enforcement Agency (DEA) to set production quotas and to monitor and control diversion and excessive production of narcotics.24 In response to the pain movement, the DEA joined with 21 health care organizations in 2001 to call for improved approaches to ensure that prescription opioids were available for medical use and prevented from diversion.25 Surprisingly, for a drug enforcement agency, they noted that pain was undertreated and that opioids were the most effective treatment for many patients. Between 1996 and 2007, the DEA approved increases in US production of the opioids hydrocodone fourfold, fentanyl 10-fold, and hydromorphone four and a half-fold, but sanctioned <0.1% of physicians for narcotic-prescribing violations from 1999 to 2003.26,27

In 2016, The Washington Post reported that the Ensuring Patient Access and Effective Drug Enforcement Act (H.R. 4709) was “the crowning achievement of a multi-faceted campaign of the drug industry to weaken DEA enforcement activities against drug distribution companies that were supplying corrupt physicians and pharmacists who peddled narcotics on the black market.”27 The industry had contributed $1.5 million dollars to the campaigns of 23 lawmakers who sponsored H.R. 4709, including $100,000 to Representative Tom Marino. Marino withdrew from President Trump’s nomination as DEA director in 2017 after his conflict of interest was exposed.28 The DEA also closed its Special Operations Unit that covertly collected internal phone records used to monitor drug traffic after congressional criticism.29 In the fall of 2017, the acting head of the DEA resigned.

The FDA, charged with ensuring drug safety, efficacy, marketing, and labeling, was also affected by pain treatment advocacy. In the 1990s, the FDA implemented an “Enriched Enrollment Protocol” to speed approval process for pain medication. The Initiative on Method, Measurement and Pain Assessment in Clinical Trials, a group funded by the pharmaceutical industry, helped develop the protocol.30 This protocol resulted in decreased drug failure rates in clinical trials for narcotics and was criticized for increasing the risks of undetected side effects in new drugs.31

The FDA is also responsible for ensuring that the information supplied in drug advertising and promotion is accurate, balanced, and truthful, but is understaffed in that effort.31 The FDA review of the original FDA New Drug Application for OxyContin® missed the implications of a disclosure that crushing tablets immediately released 68% of the oxycodone and thus promoted it to become a drug of abuse; it also missed the disingenuous original manufacturer’s label stating that addiction to it was “very rare.”31 The 2004 label revision of OxyContin® cautioned patients not to chew or bite the tablet, which further clued abusers to crush it for illicit use. When OxyContin® was reformulated to make it more difficult to abuse in 2010, many OxyContin® addicts switched to black tar heroin.31 By then, the Sackler brothers’ corporate worth was $14 billion dollars. Between 2009 and 2010, 50% of patients admitted to hospitals for medical conditions received

---

**Table 4** Pharmaceutical Companies and Distributors Settlements With the US Department of Justice as of 2017 for Complicity in the Opioid Epidemic

<table>
<thead>
<tr>
<th>Company</th>
<th>Amount</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purdue Pharma</td>
<td>$630 M</td>
<td>2007</td>
</tr>
<tr>
<td>AmeriSource Bergen</td>
<td>$13.2 M</td>
<td>2008</td>
</tr>
<tr>
<td>Cardinal Health</td>
<td>$44 M</td>
<td>2017</td>
</tr>
<tr>
<td>McKesson</td>
<td>$150 M</td>
<td>2017</td>
</tr>
</tbody>
</table>

Adapted from Reference 19.

---

**Table 5** Purpose of the Federation of State Medical Boards (FSMB) Model Guidelines for Use of Controlled Substances for the Treatment of Pain (1998)*

1. Promote safe and effective pain relief, including the use of opioid analgesics
2. Ensure that physicians will not be sanctioned for prescribing such medications for legitimate medical purposes
3. Stress the need to safeguard against medication diversion and abuse

*From Reference 22
narcotics, and huge volumes of oxycodone and other opioids were produced, distributed, used, diverted, and abused. Opioid addiction and deaths, especially from heroin, continued to skyrocket.

Mexico is the largest source of the heroin used in the United States (Figure 2). The increasing demand for heroin that developed in the early 1970s resulted in the emergence of a new breed of Mexican drug cartels (Figure 3). They grew poppies where they lived, produced high-quality, less expensive black tar heroin, and packaged and smuggled it in small quantities to trusted family members serving as distributors throughout the United States. Heroin was delivered in balloons held in the mouths of distributors or their clients so evidence of the sale could be swallowed if police or thieves appeared.

Fentanyl, an opioid 80 times more potent than heroin, was brought to market in the United States as Duragesic® by Janssen Pharmaceuticals, now owned by Johnson & Johnson, Inc. (New Brunswick, NJ). In the early 1990s, drug dealers began mixing fentanyl with heroin to produce a greater high. After 350 related deaths occurred between 2005 and 2007 in Cook County, Illinois, the combination came to be noted as “Drop Dead.” By 2016, half of overdose deaths in Illinois were fentanyl-related. When overproduction of fentanyl by the US companies was finally curtailed, chemists in China produced fentanyl in large quantities and developed countless derivatives made available to heroin producers in Mexico and drug users in the United States by mail and otherwise. By 2016, carfentanil, initially used to tranquilize elephants and 100 times more potent than fentanyl, was a frequent cause of drug overdoses in Ohio, New York, Pennsylvania, Florida, and neighboring states.

**THE PLAINTIFFS BAR TO THE RESCUE**
The failure to control the scourge of America’s present opioid epidemic has many similarities to America’s long fight to limit tobacco use, another drug protected by the money and power of an industry. It was not until the 1964 report of Surgeon General Luther L. Terry, MD that science broke through the dissonance of the tobacco industry’s attempts to hide the facts about its deleterious effects on health. Efforts of federal health agencies and the US Congress to stem the tide of tobacco-related disease were blocked. The best the US Congress could do was to pass 2 acts that required health warnings on cigarettes and banned tobacco advertising in broadcasting.

The 42-year-old Democratic Attorney General of Mississippi, Mike Moore, filed the first successful law suit against “Big Tobacco” in 1994 to recover state Medicaid costs for the treatment of tobacco-related disease. The success of that suit and similar ones by other states led to the capitulation of the 4 major tobacco manufacturers and the largest corporate legal settlement in US history in 1997. Among other accomplishments, the Tobacco Master Settlement of 1998 generated an award worth over 200 billion dollars that continues to fund smoking cessation and prevention programs for all 50 states.

Subsequent to the settlements paid by opioid manufacturers and distributors to federal regulatory agencies to settle charges by federal agencies (Table 4), additional suits were filed between 2008 and 2017 on behalf of individuals addicted while taking opioids “as directed” on the manufacturer’s label. But like Big Tobacco, Big Pharma considered product litigation the cost of doing business. By 2012, enough opioids were dispensed in Ohio to provide 68 pills each for every resident. The Ohio and Mississippi attorneys general selected Mike Moore to lead their litigation to recover state expenditures for opioid addiction. Moore filed suit in May of 2017 against Purdue Pharma, Endo Pharma, Johnson & Johnson’s Janssen Pharmaceuticals, Teva Pharmaceutical Industries, and Allergan Pharma. A gathering army of state and local jurisdictions have followed. Just as tobacco manufacturers had done, the drug companies have responded with a public campaign to deny culpability.
LESSONS LEARNED

The lessons learned from this opioid epidemic are many. For organized medicine, the principal one seems old. That is, making medical treatment recommendations, policies, and decisions without solid scientific data is dangerous for all concerned. Those who are most comfortable doing so are likely to have conflicts of interest, ethical issues, and greed. The opioid epidemic has now been declared a “national emergency,” when many of the questions about the biology of pain, the treatment of acute and chronic pain, and the treatment of opioid addiction remain unanswered. 38 The course of the epidemic to date reflects our ignorance of the neurobiology of the brain’s reward system and the need for investment in basic and clinical research to understand why drugs of abuse are so attractive to so many. The National Academies have proposed a way forward. 39 We should follow their suggestions.

References


