

SCIENCE SERIES

Treating Pain: The Unintended Journey From Relief to Desperation

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ABSTRACT

Opioids have been integral to pain management since ancient times. The isolation of morphine marked a significant medical advancement in pain treatment but also revealed its addictive properties. Despite regulatory efforts, synthetic opioids like heroin emerged, leading to increased addiction. In the late twentieth century, the US Food and Drug Administration (FDA) approval of opioid painkillers gave hope to many patients with chronic non-cancer pain. However, aggressive marketing practices of pharmaceutical companies that downplayed addiction risks, coupled with increased medical prescriptions, drove widespread misuse and the opioid epidemic, impacting both patients with legitimate medical needs and those who turned to illicit sources as prescriptions ended. Synthetic opioids like fentanyl, far more potent and fast-acting than heroin, became major contributors to overdose fatalities, underscoring the need for comprehensive pain management that minimizes addiction risks while providing adequate analgesia for those suffering from chronic pain. To address the opioid epidemic and save lives, we must reinforce policies on preventing opioid misuse, introduce comprehensive educational programs for both health care providers and the public, and support those affected by addiction.

EARLY USES OF OPIOIDS

Opioids are a class of drugs whose origins can be traced back more than 3,000 years. The use of opioids began in ancient civilizations, where the opium poppy (*Papaver somniferum*, from Latin *papāver* meaning poppy, *somni* meaning sleep, and *ferre* meaning to bring) was used for its medicinal and psychoactive properties. Ancient Egyptian medical texts reference the use of opium for pain relief and to induce sleep. Similarly, the Minoans of Crete recognized the euphoric effects of opium, as evidenced by artifacts depicting the opium poppy. Greeks and Romans employed it for various ailments, including headaches and coughs.¹ In these early societies, opium was highly valued for its dual ability to alleviate pain and induce pleasure, a combination that ensured its continued use across millennia.

DEVELOPMENT OF OPIATES AND SYNTHETICS

In the early 1800s, there was a significantly expanded use of opioids with the isolation of morphine, a potent analgesic derived from opium. Morphine quickly became a staple in medical practice, particularly for pain management during the American Civil War. In this period, heroin, the acetylated form of morphine, marked the era of synthetic opioids.² It soon became evident that these opium derivatives have addictive properties, leading the United States to restrict opium imports for medical purposes only. In 1912, the United States and other nations signed the International Opium Convention, which regulated the import, manufacture, and sale of morphine.³ By the 1920s, the Heroin Act prohibited heroin's manufacture, importation, and even medical use.⁴ However, these measures did not stop opioids from being produced by design or serendipitously (Table 1). The 1970s saw the development and marketing of additional opioids, such as oxycodone and hydrocodone, intended for acute and cancer pain relief.

Table 1. Classification of Opioids by Synthetic Process⁵

Natural Compounds	Semisynthetic Compounds	Synthetic Compounds
Morphine	Diamorphine (heroin)	Pethidine
Codeine	Dihydromorphone	Fentanyl
Thebaine	Buprenorphine	Methadone
Papaverine	Oxycodone	Alfentanil
		Remifentanil
		Tapentadol

Hope for Treating Pain

At first, opioid medications were prescribed strictly for acute pain due to injury or surgery or severe pain related to cancer or terminal illnesses. Physicians were reluctant to prescribe opioids for other conditions because there was a concern for addiction. Additionally, physicians were legally constrained from prescribing opioids more liberally because of the imminent risk of investigation and potential disciplinary action by state medical boards.⁷ However, in 1986, Portenoy et al⁶ reported in their study that comprised only 38 patients

that opioid pain relievers could be safely prescribed for chronic pain on a long-term basis. The medical community ignored potential misleading study design flaws, such as the incredibly small sample size, a lack of clearly stated selection criteria, or a control group of patients on nonopioid drugs. Although some patients needed an increase in the treatment dose, the implications of developing tolerance were not fully addressed during the study. Nevertheless, this case series provided a stepping stone to the gradual expansion of opioid use in the 1980s, culminating in a 1996 consensus statement by the American Academy of Pain Medicine and the American Pain Society, which endorsed opioids for chronic noncancer pain.⁷ Somehow, thousands of years of human knowledge related to opioids and their side effects were underestimated. Many states passed Intractable Pain Acts, removing physician restrictions on prescribing opioids,⁸ bringing hope to many patients seeking relief from chronic pain.

OPIOID HYPE

The aggressive marketing of opioid painkillers to health care providers and patients began with the US FDA approval of oxycontin produced by Purdue Pharma LP in 1995.^{9,10} The company downplayed the addictive nature of opioids, promoting them as safe and effective for chronic pain management, repetitively citing 2 reputable medical journals. Porter et al¹¹ in the *New England Journal of Medicine* revealed minimal addiction in 11,882 opioid-treated patients, and Perry et al¹² in *Pain* showed no addiction among 10,000 burn patients experiencing acute pain but failed to address the addiction risk when opioids were used long-term for chronic pain.

Purdue Pharma LP executed a well-planned, aggressive campaign strategy, funding over 20,000 pain-related educational programs and providing financial support for organizations like the American Pain Society, the American Academy of Pain Medicine, the Federation of State Medical Boards, the Joint Commission, pain patient groups, and other organizations,¹³ which subsequently advocated for more aggressive pain management. In 1995, the president of the American Pain Society introduced pain as “the fifth vital sign,” urging health care professionals to assess pain with the same importance as other vital signs and to use opioids for chronic pain.¹⁴ Shortly after, the Veterans Affairs health system and the Joint Commission (the entity that accredits hospitals and health care organizations) adopted the concept of chronic pain opioid relievers. The American Pain Society and the American Academy of Pain Medicine issued a consensus statement endorsing opioid use for chronic pain,⁷ claiming that addiction risk was low, respiratory depression was brief, and concerns about drug abuse should not limit

prescribing. These combined efforts significantly influenced the widespread acceptance of opioids, causing the rate of opioid use to accelerate rapidly.¹⁵

In the years that followed, pharmaceutical companies adopted Purdue Pharma LP's strategy, investing heavily in influencing prescribing practices through extensive marketing efforts to clinicians and patients, with annual spending exceeding \$25 billion in recent years.¹⁶ Over the past 2 decades, nearly all major pharmaceutical companies have faced settlements for off-label promotions, largely because of violations of the False Claims Act (Table 2). In particular, aggressive downplaying of drug risks and the promotion of unapproved uses have been well documented in opioid-related settlements.¹⁷ Despite public scrutiny and legal actions, pharmaceutical companies continued to market heavily to clinicians, totaling nearly \$2 billion annually.¹⁸ Recent court cases have questioned the enforcement of the Food, Drug, and Cosmetic Act's requirements for demonstrating safety and efficacy in off-label promotions.

Opioid Crisis

Labeling pain as the “fifth vital sign”¹⁴ led to a substantial increase in pain surveillance during hospital stays. Consequently, the use of opioids rose rapidly. Despite later revisions and the eventual removal of these guidelines in 2009 because of the evident concerns about excessive treatment,²⁰ the crisis has continued to escalate. The result was a dramatic increase in opioid painkiller prescriptions at unprecedented rates, from 76 million in 1991 to 217 million in 2012 and a decrease to 207 million in 2013.²¹ This surge in prescribing led to widespread misuse and addiction. Although approximately 10% of individuals prescribed opioids develop an addiction, the significant rise in opioid prescriptions has led to greater exposure.²² Patients who initially received opioids for legitimate medical reasons often found themselves dependent on the drugs. When their prescriptions ran out, many turned to illicit sources with more potent and cheaper agents, such as heroin and fentanyl. Although prescription opioids initially drove the crisis, by 2015, deaths from prescribed opioids had plateaued, yet fatalities from illicit synthetics continued to escalate.²³

In recent years, fentanyl and its potent synthetic analogs have become major contributors to the opioid crisis. From 2010 to 2016, fatalities linked to fentanyl and other synthetic opioids increased nearly 6-fold, climbing from 3,007 to over 19,413 deaths.²⁴ Currently, synthetic opioids contribute to twice as many overdose fatalities as prescription opioids. Fentanyl is 50 times stronger than heroin because of its high affinity for opioid receptors and rapid onset of action. Its low production costs make it an attractive option for mixing with heroin, methamphetamine, cocaine, and illegally man-

Table 2. Pharmaceutical Companies Marketing Opioid Products in the United States, 2004-2020

Company Name	Opioids, Brand Name (Generic)	Named in Opioid Litigation
BioDelivery Sciences International	Belbuca (buprenorphine) Bunavail (buprenorphine/naloxone) Onsolis (fentanyl)	2018
Collegium Pharmaceuticals	Xtampza (oxycodone) Nucynta (tapentadol)	2018
Daiichi Sankyo	Roxybond (oxycodone)	2015
Depomed	Roxybond (oxycodone) Lazanda (fentanyl) Nucynta (tapentadol)	2017
Egalet US	Oxaydo (oxycodone) Arymo (morphine)	2019
Endo Pharmaceuticals	Belbuca (buprenorphine) Percocet (oxycodone/acetaminophen) Opana (oxycodone)	2014
Galena Biopharma	Belbuca (buprenorphine) Percocet (oxycodone/acetaminophen) Opana (oxycodone)	2017
Insys Therapeutics	Subsys (fentanyl)	2013
Johnson & Johnson	Duragesic (fentanyl) Nucynta (tapentadol)	2014
Mallinckrodt Pharmaceuticals	Exalgo (hydromorphone) Roxicodone (oxycodone) products	2017
Mylan	Ultiva (remifentanyl)	2017
Pernix Therapeutics Holdings	Zutriprio (hydrocodone/chlorpheniramine pseudoephedrine) Rezira (hydrocodone/pseudoephedrine) Vituz (hydrocodone/chlorpheniramine) Zohydro (hydrocodone)	2018
Pfizer	Troxyca (oxycodone/naltrexone)	2018
Purdue Pharma	Oxycontin (oxycodone)	2004
Teva Pharmaceuticals	Actiq (fentanyl) Fentora (fentanyl) Vantrela (hydrocodone)	2014
The Medicines Company	Ionsys (fentanyl)	2019
Zogenix	Zohydro (hydrocodone)	2018

Adapted from Uppal et al.¹⁹

ufactured prescription opioids to increase their potency. Importantly, many heroin users unknowingly consume fentanyl, increasing the likelihood of a fatal interaction. Two milligrams of illicit fentanyl can be lethal, depending on a person's body size, tolerance, and past usage. Analysis has found that 42% of counterfeit pills contain from 0.02 mg to 5.1 mg of fentanyl per tablet.²⁵ Fentanyl enters the brain very rapidly and causes a “rush” of euphoria, pain relief, and sedation, along with lasting respiratory depression and combined effects when mixed with other drugs.²⁶

As if fentanyl was not enough, xylazine appears to be the next emerging threat.^{27,28} Its nonopioid compound is used as a sedative, anesthetic, muscle relaxant, and tranquilizer

for animals, but it is not FDA approved for use in humans. As a strong synthetic $\alpha 2$ -adrenergic agonist, xylazine causes severe central nervous system depressant effects. It has increasingly been found mixed with fentanyl to extend its effects. However, in many cases, users are not aware that xylazine is in their drugs. Although xylazine has long been in the street opioid supply in the US territory of Puerto Rico, it only emerged in Philadelphia in the late 2000s.²⁹ Alarming, overdose deaths involving xylazine rose nearly 20-fold between 2015 and 2020 in all major US regions.³⁰

Mechanism of Addiction

To comprehend the high addictive potential of opioids, it is essential to examine their effects on the human body. Although each opioid has a unique chemical structure, they all function by binding to native opioid receptors in the brain. Normally, the body's endorphins mitigate pain signals. Opioids, however, bind much more robustly and decrease the ability of pain-transmitting neurons to excite for a longer period.³¹ Additionally, when opioids bind to these receptors, they indirectly trigger the release of dopamine, a neurotransmitter associated with pleasure and euphoria. Concurrently, opioids suppress the release of noradrenaline, which normally promotes wakefulness, respiration, digestion, and blood pressure.³² At therapeutic levels, the reduction in noradrenaline caused by opioids can lead to constipation.³³ Higher doses can dangerously lower heart and breathing rates, potentially causing loss of consciousness or even death.³⁴

Over time, the body builds tolerance to opioids by reducing the number of opioid receptors or making the receptors less responsive. To achieve the same dopamine release and mood effects, individuals need to consume progressively larger doses, leading to physical dependence – addiction.³⁵ When a person who is physically dependent on opioids abruptly stops taking them, withdrawal symptoms such as muscle aches, stomach pains, fever, and vomiting occur. Although temporary, opioid withdrawal can cause severe illness for days or even weeks.³⁶ Individuals addicted to opioids often continue using the drugs not to experience a high but to avoid withdrawal sickness. Withdrawal can result in lost wages or an inability to care for oneself. If individuals relapse after a period of abstinence, they are at high risk for overdose because the previously tolerated dose can now be lethal.³⁷

ONGOING IMPACT OF THE OPIOID CRISIS ON COMMUNITIES AND VICTIMS

In June 2024, the Supreme Court overturned an \$8 billion controversial bankruptcy settlement with Purdue Pharma, intended to fund addiction treatment and public health ini-

tatives related to the opioid epidemic all over the country. A key issue was a provision that would have protected the Sackler family, Purdue Pharma's owners, from future lawsuits without fully disclosing all their assets. The court ruled that this legal strategy exceeded the boundaries of the bankruptcy code. Sadly, the decision followed Purdue Pharma's 2007 legal troubles, in which the company paid a \$600 million fine for misleading marketing practices. The settlement proposed \$6 billion from the Sacklers in exchange for protection from future civil liability. Critics argued this would allow the Sacklers to avoid past and future accountability, especially after transferring \$11 billion in profits into private accounts, shielding their wealth from creditors and victims. In addition, they had planned to dissolve and reform the company as Knoa Pharma, a new entity that would focus on producing opioid addiction treatments and overdose reversal medications while continuing to manufacture opioids.

As Purdue Pharma's legal battles unfold, broader efforts to address the opioid crisis have also been advancing, with other major pharmaceutical companies reaching significant settlements to resolve their roles in the epidemic. The 3 largest pharmaceutical distributors, McKesson, Cardinal Health, and AmerisourceBergen, and manufacturer Janssen Pharmaceuticals, Inc., and its parent company Johnson & Johnson (collectively, "J&J") reached nationwide settlements to resolve all opioid litigation brought by states and local political subdivisions in 2021. These national settlements have been finalized, and payments have already begun. The distributors started paying \$21 billion over 18 years, and J&J is paying an additional \$5 billion. In 2022, agreements were reached with 3 pharmacy chains: CVS to pay \$4.90 billion over 10 years, Walgreens to pay \$5.52 billion over 15 years, and Walmart to pay \$2.74 billion in 2023, and all payments were to be made within 6 years. Two additional manufacturers settled—Allergan agreed to pay \$2.02 billion over 7 years, and Teva agreed to pay \$3.34 billion over 13 years and to provide cash in lieu of product, as each state may elect.³⁸

Although funds to states and local governments have begun to be distributed, attention is now focused on ensuring that these resources are effectively used to combat the ongoing public health crisis. Investments in addiction treatment, overdose reversal medications, and other public health measures remain critical, with over 100,000 Americans dying annually from opioid overdoses. The opioid crisis has left significant lessons regarding the dangers of overpromoting and overprescribing medications without fully understanding their long-term consequences. As new weight-loss drugs gain popularity, the medical community and the public must remain informed, evaluating these treatments beyond the initial hype. Only time will

reveal whether the lessons from the opioid tragedy will help prevent history from repeating itself.

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