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# Fentanyl: Heroin Yielding to a Deadlier Street Cousin

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## Abstract

Over the last two and a half decades, the use and distribution of opioids has dramatically increased. As a result, rates of abuse, addiction, and death associated with opioids such as OxyContin and synthetic opioids like fentanyl, have consequently increased. Eventually dubbed, "The Opioid Epidemic" this crisis was first identified when economist Angus Deaton and his wife, Anne Case, found an increase in rates of morbidity and mortality in the Centers for Disease Control and Prevention (CDC) data among middle-aged white non-Hispanic Americans (Case and Deaton). This opioid epidemic has profound, medical, legal, and ethical implications. Medically, questions are raised about the proper use of opioids when managing acute and chronic pain, post-operative pain, or pain from terminal conditions like advanced stage cancer, and how to treat the long-term effects of opioid abuse. The legal implications include whether to treat or incarcerate addicts and abusers, whether physicians are obtaining informed consent from their patients and treating with the appropriate standard of care, and whether pharmaceutical companies should be held liable after misleading the FDA, physicians, and the public about the addictive nature of some opioids. Ethical issues arise from the prescribing practices of some physicians and whether the risk of abuse and addiction outweighs the benefit of pain relief in addition to the social, political, and economic effects of the epidemic on broader society. As of 2016, the opioid epidemic has only grown worse with just under 50,000 of 64,000 overdose deaths relating to opioids (Katz). The proposed solutions to these problems in the "culture of medicine" include implementing treatment over incarceration, expanding medication-assisted therapies and the use of naloxone, establishing safe-injection sites, re-educating physicians on the proper use of opioids, and holding pharmaceutical companies responsible.

## INTRODUCTION

During the last two and a half decades, prescription and distribution of opioids has drastically increased. Opioids are a family of drugs that are either synthesized from opium and the poppy plant or synthetically manufactured. They include drugs like oxycodone extended release (OxyContin), hydrocodone, codeine, morphine, heroin, and fentanyl. Fentanyl is often used illicitly to cut down heroin, producing a dangerously potent form of the drug known as "China White" or "Apache" (NIDA, Fentanyl). Fentanyl was synthesized in 1960 by Paul Janssen and the Janssen Company in Belgium to treat cases of extreme pain. It was first used intravenously in Europe in 1963 and the United States in 1968. However, new developments in the last twenty years have led to breakthroughs in how fentanyl is administered, such as through transdermal patches. Consequently, the drug has grown in popularity among physicians looking to treat pain (Stanley).

Opioids are powerful painkillers that have high risks

of dependence and abuse, and can be lethal if taken in large quantities (NIDA, Opioids). Fentanyl, specifically, is a synthetic opioid that has been growing in popularity for both medical and illicit uses. An added benefit to synthetic opioids is the elimination of the need to grow a poppy plant and further refine opium, saving both time and money. As a Schedule II drug, fentanyl is a controlled substance used to treat patients in severe pain, or with high tolerance to opioids. Due to fentanyl's and other opioids' addictive nature, the resulting abuse of both prescription and illicit forms has become an epidemic in the United States. When looking to assign blame, the general populace typically turns to the stereotypical drug dealer. However, deeper exploration into the issue reveals that heroin is not the sole problem. With an increase of prescription opioid abuse, we begin to see that physicians and pharmaceutical companies are responsible, due to over-prescription, irresponsible prescribing practices, and aggressive and misleading marketing; subsequently these parties should be held accountable. Therefore, the purpose of this paper is to

examine the medical, legal, and ethical issues and implications surrounding this epidemic and posing potential solutions to this public health crisis. Due to the enormous breadth of this project, we hope to provide a glimpse into the various bioethical issues that will, in turn, require exhaustive examination in their own right. Unfortunately, we will only be able to skim the surface on many of these issues.

In 2015, Princeton economist Angus Deaton and his wife Anne Case, published their report “Rising morbidity and mortality in midlife among white non-Hispanic Americans in the 21st century.” Conducted between 1999 and 2013, the report found that the mortality and morbidity rate from CDC data for white non-Hispanic American men and women had increased. Between 1970 and 1998, the United States experienced a gradual decline in the mortality rate for middle aged (45-54) men and women, on par with other high-income countries. However, in 1998, there was a noticed uptick in rates of mortality and morbidity among white non-Hispanic, middle-aged Americans. During the same period, mortality and morbidity rates for the elderly continued to decline as in previous years. During this increase in mortality and morbidity, middle-aged white Americans saw a decrease in self-reported physical and mental health, an increase in reports of pain and discomfort, and an increase in difficulty with day to day living. It is worth noting that other ethnic groups did not experience this same increase in mortality and morbidity. This uptick among middle-aged whites does not appear in CDC reports as they do not account for age and ethnicity. The increase in mortality and morbidity coincided with a growing availability and distribution of opioid analgesics in the late 1990’s. Considering increased reports of pain at the same time, it is unclear which came first, the increase in reports of pain or the increase in opioid availability and distribution (Case and Deaton). It is worth considering that during this time where a greater emphasis was put on pain management, the Veterans Health Administration launched a campaign based off the slogan, “Pain as the 5th vital sign.” The hope was to increase efforts by physicians to control symptoms of acute and chronic pain in patients. However, a study found that after this initiative, no significant improvement was made in the quality of care given. Rather, this campaign likely contributed to the increase of opioids prescribed in the late 1990’s and early 2000’s (Mularski, White-Chu and Overbay). While this campaign’s intentions were wholesome, it ultimately backfired, contributing to a greater problem.

When treating pain, it is important to consider the type of pain that is being treated. Pain experts state that there are 5 categories of pain: nociceptive pain, neuropathic pain, incidental pain, acute pain, and chronic pain. Nociceptive pain can be divided into two subcategories, somatic and visceral pain. Somatic pain is generated by nociceptors in the cutaneous deeper tissues, such as in the musculoskeletal system. This pain is characterized as “gnawing, cramping, and throbbing pain.” Visceral pain is generated from nociceptors in the cardiovascular, gastrointestinal, genitourinary, and respiratory systems. This pain is characterized by “deep aching, squeezing, and pressured” pain. However, visceral pain may often spread to cutaneous sites as it is poorly localized. The second category of pain is neuropathic pain. This pain is generated when nerve roots are agitated by a condition such as disease, and takes the form of “constant, burning, shooting, or stabbing” pain. Incidental pain is caused by associated pain and most commonly reported in patients with cancer. However, this pain can also be due to factors such as positioning and constipation. Acute pain is pain that does, or is expected to last for a short period of time, usually less than a month. This category of pain is associated with other physiological effects such as anxiety and hyperactivity of the sympathetic nervous system. The final category of pain is chronic pain. Chronic pain broadly defined as lasting for greater than one month beyond the resolution of acute tissue damage, pain persisting for long than three months, or pain that from tissue injury that is expected to progress. Due to factors such as lawsuits or patient satisfaction scores, inadequate treatment of pain is an issue that many physicians fear, especially regarding patients in the end-stages of life (Clark). To keep up with the demand of pain treatment, physicians have turned to powerful drugs like opioids in the hope that they meet the needs of the patients.

In 2016, the CDC published guidelines for physicians prescribing opioid painkillers for chronic pain treatment outside of conditions relating to cancer, palliative, and end-of-life care, and will be discussed later in this paper. These guidelines address when it is appropriate to begin or continue treatment with opioids, which opioids ought to be selected, dosage, duration, discontinuation, and risk/benefit assessment. Roughly 1 in 5 patients presenting with non-cancer pain, both acute and chronic, received a prescription of opioids. In 2012, 259 million prescriptions were filled – enough for each adult in the United States to have a bottle. The rate at which opioids are prescribed varies between states, with no medical basis in the

discrepancy. This highlights the confusion among physicians regarding opioid prescription practices. Moreover, ethnic minorities, women, the elderly, and those with cognitive impairments are at highest risk for inadequate pain management (The Centers for Disease Control and Prevention). Going back to Case's and Deaton's findings regarding how middle-aged white Americans have been hit hardest by this epidemic, we must ask ourselves if there is also a racial or age-based bias when physicians prescribe these drugs (Case and Deaton). Current guidelines focus on dosage and harm reduction strategies, and are critically lacking in our current understanding of opioid drugs. The new guidelines outlined by the CDC aim to provide safe and consistent prescribing practices that minimize risks and maximize benefits to the patient (The Centers for Disease Control and Prevention). Careful consideration ought to be given by physicians prescribing opioids as these drugs have high potential for abuse and dependency with potentially lethal consequences. These consequences are evidenced through startling figures on the rising death toll due to overdose-related deaths in the last decade and a half.

Between 1999 and 2011, the number of deaths causally related to opioids nearly quadrupled from 1.4 deaths per 100,000 to 5.4 deaths per 100,000 (Li Hui Chen, Holly Hedegaard and Margaret Wagner). From 1999 to 2006, there was a steady 18% increase of opioid related deaths each year. Although the rate slowed to a 3% increase of deaths per year from 2006 to 2011, the increasing trend continued toward the climactic year 2014 where 28,647 of the 47,055 (60.9%) drug related deaths were caused by opioids (Rose A. Rudd, Puja Seth and Felicta David). The year 2014 saw more drug related deaths than any to that date with roughly 6 in 10 overdoses directly resulting from opioids. The year 2014 also stands out due to the drastic increase in overdoses specifically related to heroin and fentanyl.

The economic impact of the opioid epidemic is overwhelming with \$55 billion spent annually on healthcare and social costs related to prescription opioid abuse. Emergency departments and in-patient care units spend \$20 billion dollars each year to treat opioid overdoses. To put into perspective just how problematic the use and abuse of opioids has become, on an average day in the United States, about 650,000 opioid prescriptions are filled, 3,900 people participate in recreational use of prescription opioids, 600 people begin to use heroin, and about 78 die from overdoses caused by both illicit and prescription forms (The Opioid

Epidemic: By the Numbers). When tax payer money fails to cover the cost of uninsured patients, hospitals and physicians bear the financial burden. Costs associated with the epidemic are only growing as local and state municipalities struggle to allocate resources to mitigate these problems.

As stated earlier, one specific synthetic opioid that has been causing a significant amount of problems in the past decade is fentanyl. Up to one hundred times more potent than morphine, fentanyl is known for its exceptionally potent pain alleviation and euphoric effects. Coupled with those effects is a high risk of abuse, addiction and overdose. Available orally, intravenously, and in a transdermal patch in prescribed forms, the drug can also be snorted and smoked when used illicitly. Fentanyl is typically used for treating pain in end-stage cancer patients or in those with high tolerance to other opioids, but has recently begun to see a spike in abuse. This was poignantly highlighted when the drug was linked to the deaths of notable musicians Tom Petty and Prince. Moreover, 2015 saw a 65% increase from 2014 in seized fentanyl forensic exhibits tested by labs, totaling 13,000. These fentanyl products were either stolen from healthcare facilities and pharmacies or crudely manufactured in labs and smuggled into the United States through Mexico. Adding another element to the complications of abuse, substantial amounts of the illegally obtained fentanyl are often added to heroin and other drugs to increase potency, leading to disastrous effects. Due to the high potency of the drug, it often takes multiple doses of naloxone to negate the effect of the opioid during an overdose (Esposito).

A more recent report published in a September 2017 issue of *The New York Times* demonstrates that the opioid epidemic has only grown worse, especially regarding fentanyl and its analogues. In 2016, about 64,000 people in the United States died from drug overdoses, 22% higher than the 52,404 from 2015. Of those 64,000 overdoses, just under 50,000 were the result of opioid overdoses. What is especially startling from this report is the prevalence of fentanyl overdoses, reaching a record high at 20,100 deaths. Three years prior in 2013, fentanyl was the cause of only 3,000 overdose deaths. This drastic increase of about 17,000 cases has far reaching implications as local and state municipalities have experienced a strain on their resources. This epidemic has caused an increase in healthcare and police expenditures, specifically relating to the purchasing, distribution, and use of naloxone. Additionally, resources have been directed into the foster care system as the number

of children orphaned and neglected continues to rise. This trend challenges the notion of the opioid epidemic as a problem in rural, white America where Appalachia and New England have been hit particularly hard. This epidemic is spreading rapidly and while we do not know what the numbers from 2017 hold in store, it is likely to only grow worse (Katz).

### **CASE STUDY**

Opioid addiction is a problem that affects individuals from all walks of life as evidenced by the cases of American musicians Tom Petty and Prince. The struggle of addiction transcends society's notion of the typical drug user as more and more people struggle with opioids. Both Petty and Prince fell victim to overdoses at the hands of fentanyl, fentanyl analogues, and other opioids. Initially, there was an air of mystery surrounding the death of Prince. Just weeks before his death, after postponing a concert in Atlanta, Prince was flying home when his plane was diverted and made an emergency landing in Moline, Illinois. Reports alleged Prince had become seriously ill from a case of the flu and needed treatment. However, this report was inaccurate as it was later revealed he had lost consciousness during the flight, and upon landing, was revived with naloxone by emergency services. Several weeks later, Prince was found unresponsive in his home where he was then declared dead. A toxicology screening revealed the cause of death to be an accidental overdose from self-administered Fentanyl (Eligon and Kovaleski).

This came as a shock to many family, friends, and fans. According to Rolling Stone magazine, those closest to him were under the impression that his health was not a serious concern (Grow, Prince's Cause of Death: Opioid Overdose). However, decades of touring and performing took its toll on Prince's physical condition. After a surgery in the mid-2000's, Prince still struggled with debilitating hip pain (Eligon and Kovaleski). To cope with this pain and continue performing, Prince began a regimen of self-administered Fentanyl. At the time of his death, Prince was planning to enroll in a treatment program for his opioid addiction (Eligon and Kovaleski). This comes decades after he struggled with cocaine and Percocet abuse (Grow, Prince's Cause of Death: Opioid Overdose).

Upon further investigation, authorities found controlled substances in Prince's Chanhassen, Minnesota home. What raises a red flag here is not the possession of the controlled substances, rather the containers in which

those substances were found. Instead of typical prescription pill bottles, the controlled substances were found in other places such as vitamin bottles (Flanagan and Tsioulcas). This begs the question of "Why?". It is entirely plausible that the controlled substances were placed in these bottles by Prince to hide what medication he was taking, even if it was legally prescribed. It is also possible that these drugs were placed in vitamin bottles because Prince obtained them illicitly. Prince's personal physician had seen him the day before his death and had been prescribing him medication, although an official affidavit used to obtain a search warrant made no mention of specific drugs (Eligon and Kovaleski). No legal action was taken against Prince's physician, so it is likely that he was not directly responsible for the musician's death.

Musician Tom Petty's death bears some parallels to that of Prince. At the height of what Petty considered one of his most important tours, he was found unresponsive in his home in California. Petty was later pronounced dead at the UCLA Medical Center from cardiac arrest. Despite struggling with emphysema, knee pain, and a fractured hip, Petty continued to tour as to not disappoint his fans. A toxicology screening later revealed he had fentanyl (opioid), oxycodone (opioid), temazepam (benzodiazepine), alprazolam (benzodiazepine), citalopram (anti-depressant), Acetyl fentanyl (illicit opioid), and Despropionyl fentanyl (illicit opioid) in his system. While he was prescribed most of these medications, questions were raised about Acetyl fentanyl and Despropionyl fentanyl, which are illicit fentanyl analogues that are not prescribed in the United States. Moreover, Petty was taking four forms of opioids with two forms of benzodiazepines and an anti-depressant, creating a deadly cocktail of drugs – a practice highly discouraged according to the CDC's 2016 Opioid Prescription Guidelines (The Centers for Disease Control and Prevention). However, it is currently unclear as to how Petty came into possession of these illicit drugs (Coscarelli).

Petty's death comes just months after another musician, rapper Lil Peep died of an overdose from alprazolam (Xanax) laced with fentanyl. A toxicology report revealed the rapper had several other drugs including cocaine and other opioids in his system (Grow, Lil Peep Cause of Death Revealed). The deaths of Prince, Tom Petty, and Lil Peep highlight the potency fentanyl and the danger associated with its use, especially when mixed with other drugs opioids and other depressants. Moreover, these deaths bring the opioid epidemic into the limelight, as it just does

not affect what is thought to be the typical drug addict. Prince and Petty were household names and Lil Peep was a rising star in his genre. This epidemic transcends social, economic, and regional boundaries as people from all walks of life have fallen victim.

### **MEDICAL ISSUES**

#### **CLASSIFICATION AND MECHANISM OF ACTION**

Opioid analgesics refer to an extensive class of medications widely used today for the management of severe acute pain and for the treatment of chronic cancer pain. They are derived from the opium poppy plant identified in 3400 BC and initially named the Hul Gil, the “joy plant” (Rosenblum). Opioids are involved in the pain pathway, which are communication signals between the site of injury, spinal cord and brain through ascending and descending pathways to guide individuals to interpret pain and meaning, as well as initiate appropriate responses (e.g. moving a finger out of harm’s way). Along these pathways, receptors for endogenous opioids such as endorphins responsible for modulations of pain, reinforcement and reward mechanisms, mood and stress are widespread and located in both the central and peripheral nervous system (Rosenblum). Opioid analgesic medications mimic endogenous opioids to act as agonists and bind to receptors including the mu, kappa and delta opioid peptide receptors. However, the activation of the mu-opioid receptor mainly produces the analgesic and reinforcing effects (Rosenblum). The physiologic response of the extensive binding between the opioid analgesic agent and receptor can inhibit or mitigate pain through the ascending and descending pain pathways, respectively. However, individuals respond to pain differently despite pharmacological similarities in receptor binding due to multiple psychological factors including past experiences, emotional state, genetics and variations of reinforcement and reward mechanisms (Pergolizzi).

Opioid analgesics vary in potency, available formulations (e.g. lozenge, injection), onset of action, metabolism, and degree of lipophilicity and duration of action. Opioids can be classified in three categories: naturally occurring opiates, semi-synthetic opiates and synthetic opioids. Naturally occurring opioids include morphine and codeine, while semi-synthetic opioids refer to medications synthesized from the naturally occurring opiates such as oxycodone (Table 1). Fentanyl is a synthetic pure mu opioid available as an injection, transdermal and transmucosal formulation. It is currently indicated for severe

acute pain, and surgical anesthesia, as well as for chronic cancer pain for individuals tolerant to opioids. Due to its high lipid solubility and low molecular weight, fentanyl is rapidly diffused across the blood brain barrier compared to morphine, resulting in a rapid onset of action once the drug is absorbed from the administration site. Fentanyl is a highly potent opioid, as it is approximately 75 to 100 times more potent compared to morphine on a mg-to-mg basis. The pharmacological properties of fentanyl including the high degree of potency and lipophilic properties have added to the complexity of abuse particularly with “fentanyl laced heroin,” in which illegally obtained fentanyl is mixed with heroin to amplify the potency.

#### **SIDE EFFECTS**

Opioid analgesics share common adverse effects based on the type of receptor binding and their pharmacological mechanism. The severity of side effects vary based on individualized tolerance, administered dose, frequency of administration and/or duration of therapy. Common adverse effects include nausea, vomiting, drowsiness, pruritus, urinary retention and respiratory depression, which can occur with prescribed dosing regimens. On the other hand, some opioid analgesics have specific side effects which are not observed with the rest of the drug class, such as tramadol and its increased risk for serotonin syndrome when combined with serotonergic agents. It is important to note adverse effects such as respiratory depression can be intensified due to synergistic effects with concomitant use of other medications such as benzodiazepines and antidepressants (Jones). An opioid overdose can occur particularly during drug initiation or dose escalation, in which the mu-opioid receptors are oversaturated and the individual experiences a greater degree of adverse effects such as respiratory depression and sedation. Severe respiratory distress and excessive sedation can be reversed with an opioid receptor antagonist, such as naloxone which inactivates and reverses the effects of the mu-opioids upon receptor binding. Adverse reactions such as opioid-induced constipation persist despite varying doses and duration of opioids, and remains the most commonly reported side effect of opioid use (Manchikanti). The potential adverse effects of opioids and clinical response are influenced by psychological contributions, which lead to an intricate combination of pain management and abuse.

#### **ADDICTION TOLERANCE AND WITHDRAWAL**

Opioid usage in clinical practice is often limited by

acquired tolerance, physical dependence and/or addiction, which can collectively play a significant role in the frontal cortex and circuits of reward, motivation and memory. Tolerance is a predictable drug effect and a consequence of repeated or prolonged drug administration leading to a diminished pharmacological response (e.g. pain relief) over time. Acquired tolerance requires an increasing amount of drug in order to achieve the same effect. The development of opioid tolerance is mediated by a large complexity of neurotransmitters including serotonin, dopamine and N-methyl-D-aspartate (NMDA) which causes variation amongst individuals based on hereditary predisposition, duration of opioid use and dosing regimen (Dumas). Tolerance varies from physical dependence, which is a state of adaption represented by a characteristic set of withdrawal signs and symptoms produced by abrupt cessation, rapid dose reduction and/or administration of the drug antagonist. Similar to tolerance, physical dependence is a predictable drug effect due to the chronic use of many classes of medications including those not commonly associated with addictive properties (e.g. beta blockers, antidepressants). Signs and symptoms of opioid withdrawal include sweating, yawning, muscle aches, tachycardia, diarrhea and hot and cold flashes. Unlike tolerance and physical dependence, addiction is a chronic, neurobiological disease with environmental, genetic and psychosocial factors. The brain reward structures are essential in the manifestations of altered impulse control, dysfunctional pursuit of reward and altered judgement (ASAM 2011). Addiction is characterized by the American Society of Addiction Medicine as the inability to consistently abstain, impairment in behavioral control (i.e. “hunger” for drugs or rewarding experiences), cravings, diminished recognition of significant problems and a dysfunctional emotional response. Behaviors associated with physical dependence and addiction is not clearly distinguished and can easily be misdiagnosed. Individuals exhibiting behaviors characterized by addiction may be reflective of a different process such as a psychiatric disorder, a cognitive disorder or pseudo-addiction, resembling problematic behaviors out of desperation due to unrelieved pain (Rosenblum). Similar to any chronic disease state, addiction is a chronic disease characterized by cycles of relapse and remission.

### **LEGAL ISSUES**

The opioid epidemic is not solely a medical problem. There are legal issues that arise when dealing with both drug addicts and those who facilitate opioids (drug dealers, physicians, pharmacies, pharmaceutical

companies). These pertinent issues raise questions such as: Should addicts who are arrested for illegal possession be jailed or offered rehabilitative treatment? Should the use of prescription opioids be legally restricted to cases where all other pain management options have failed? Should individual physicians and pharmaceutical companies be held responsible for creating and fostering this epidemic? Who will lead the legal battle against those deemed responsible for the epidemic? What can be done, in a legal context, to ameliorate this problem? While these questions, at first glance, may seem to be ethical in nature, they have very tangible, practical, and substantial legal ramifications that should be pursued.

Financial and efficacy concerns are often raised when discussing the issue of incarceration compared to treatment. A report from the Justice Policy Institute provides four findings in favor of treatment and rehabilitation. The first of these findings states that treatment is less expensive than imprisonment. A 24-month alternative treatment program in New York was found to cost half of what a 25-month prison sentence costs. The program reduced drug use and recidivism as well as increased job prospects for participants who completed the program. Similar programs in Maryland cost only 20% of what incarceration would cost. The report’s second finding asserted that treatment was more cost-effective than imprisonment. Cost-benefit analyses show that treatment more effectively lowers the social cost of drug use than imprisonment does. The third finding shows that treatment reduces recidivism. Findings show that drug use after treatment was substantially lower than use before the programs, unlike incarceration. The final finding highlights successful models that already exist around the country, specifically in Maryland. Programs like “Break the Cycle,” “Correctional Options Program,” and drug courts have been shown to lower the rate of abuse and recidivism among participants through treatment and education (McVay, Schiraldi and Ziedenberg).

More recently in 2018, New York City launched two new courts aimed at misdemeanor drug offenders, who were opioid users. Similar to the “Correctional Options Program,” these courts allow offenders to seek voluntary treatment over imprisonment. After treatment is completed, these courts will facilitate job training, housing opportunities, and other services, allowing former offenders to get back on their feet. Individuals who complete this program will have their cases dismissed and sealed (The

Associated Press).

An additional issue surrounding the opioid epidemic falls directly on the shoulders of physicians – informed consent. According to the Pennsylvania Healthcare Services Malpractice Act of 1996, informed consent is defined as:

Consent of a patient to the performance of healthcare services by a physician... that... has informed the patient of the nature of the proposed procedure and treatment and of the risks and alternatives to treatment or diagnosis that a reasonable patient would consider material to the decision whether or not to undergo treatment or diagnosis.

Misuse or abuse of these drugs often stems from a lack of adequate education on the proper use, potential side effects, and inherent risks associated with this class of drugs. It is the physicians' responsibility to educate their patients on the use of and risks associated with these drugs, and, if possible, seek alternative treatments. If physicians fail to do so, they are not receiving informed consent from their patients and ought to be held liable for subsequent abuse and misuse. Moreover, pharmaceutical companies have a duty to educate physicians on the use of these drugs in the same way.

Unfortunately, physicians are not always properly educated on the use of opioid analgesics. Author Mike Mariani's article "How the American Opiate Epidemic Was Started by One Pharmaceutical Company" asserts that Purdue Pharma's OxyContin was approved for wide use by the Food and Drug Administration (FDA). In a ten year period, through aggressive marketing campaigns directed toward physicians who prescribe the most pain medication, OxyContin cornered nearly 30% of the pain management market (Mariandi). With the public's greater understanding of the long-term risks, critics claim that to be approved for such wide use, Purdue Pharma must have misled both the FDA and physicians, minimizing the risks associated with opioids. While this may seem like conjecture, federal reports from the United States General Accounting Office in 2003 accuse Purdue Pharma of making unsubstantiated claims about OxyContin and its risks, producing promotional videos that minimize the risks associated with OxyContin use, and selectively targeting physicians that were not adequately trained in pain management (Office). Many of these physicians claim they were deliberately misled by the pharmaceutical company.

Complicating matters further is the pharmaceutical industry's lobbying power in Congress. In April of 2016,

Congress passed a more "industry friendly law," crippling the Drug Enforcement Agency's (DEA) ability to enforce laws and regulations against pharmaceutical companies and the companies responsible for drug distribution. Under this new law, the DEA has lost the ability to freeze suspicious shipments of opioids to suspected pill mills. In the long run, this would allow for corrupt physicians and pharmacies to continue selling opioids illicitly, flooding the streets with hundreds of millions of controlled pain pills while pocketing billions of dollars in profits. Pennsylvania Representative Tom Marino (Rep.) was this new law's greatest advocate, working tirelessly to get it passed. Senator Orrin Hatch of Utah (Rep.) finalized the law with the DEA before it passed in the Senate (Higham and Bernstein).

What is most concerning about the passing of this law is the ease with which it was done. Political action committees acting on behalf of the pharmaceutical industry contributed upwards of \$1.5 million to 23 of the law's most staunch supporters. Rep. Marino received \$100,000 and Hatch, \$177,000. Between 2014 and 2016, the pharmaceutical lobby spent over \$102 million buying influence in Congress on various bills and legislation. The DEA allegedly had its hands tied and was unable to stop the passing of the new law. A spokesman for Hatch said after a change in the leadership at the DEA, the agency did not oppose the bill. This convenient change in leadership should cause concern for all Americans. Even more troublesome is Marino's statement that in the past the DEA has been too aggressive when enforcing laws and regulations against drug distribution companies – this being said while our nation faces the worst drug epidemic in its history (Higham and Bernstein).

However, big pharmaceutical companies and corrupt politicians are not the only ones to blame. The physicians who accept promotional materials and "gifts," prescribe new drugs without adequate research, or fail to comply with federal and state laws and regulations are equally as culpable (Drug Marketing: OxyContin Ads Called Misleading). These questionable business practices raise serious concerns, because false advertising is not only illegal, but also unethical. Furthermore, if doctors cannot be trusted to do research into drugs, be unbiased when prescribing medication, or comply with laws and regulations, can those same doctors be trusted to act in the best interest of their patients? Physicians who overlook background checks in Prescription Drug Monitoring Programs (PDMP), ignore telltale signs of abuse and addiction, or sell prescriptions for

money or favors not only put their patients at risk, but also endanger the whole community by facilitating the acquisition of prescription opioids that may be abused or even sold.

To help combat situations like this, many states have Prescription Drug Monitoring Programs (PDMP). These state-run, online databases are designed to monitor the distribution of controlled substances, as well as allow pharmacies and physicians to access a patient's history regarding controlled substances. The ethical issue here is to what extent is this information known and how often is it used. A physician failing to comply with these resources is subject to criminal or civil fines (Health). With the accessibility to these databases, there is no excuse for physicians to neglect checking a patient's history with controlled substances.

Therefore, in a legal context, we as a society must decide who is truly responsible for the epidemic. Is it the user? Is it the prescriber? Is it the companies who distribute the drugs to pharmacies? Or is it the companies who manufacture and market the drugs? Once this has been clarified, we then must decide the appropriate levels of punishment and restitution. Is the prescriber that grants access to the drugs without thorough education or comprehensive background checks to be held liable for someone's addiction? Should pharmaceutical companies even be allowed to incentivize physicians to use and distribute their products without rigorous third-party testing and research? Finally, how can one prove informed consent when it comes to addiction? Once these questions are answered, the necessary legislation will more readily define these issues and appropriate punishment will be levied for a breach of ethical practice.

### **ETHICAL ANALYSIS**

Opioid addictions increase daily and health care professionals must face this sweeping epidemic immediately and realistically. It has become clear opioid abusers are seeking numerous alternatives to address withdrawal symptoms and find alternatives with euphoric properties. Fentanyl has both medical and illicit uses. In the past few years it has become a viable alternative to heroin as an illicit drug on the streets. Listed as a Schedule II drug, fentanyl is used to treat patients in severe pain or with a high tolerance to opioids. However, due to over-prescribing by physicians and aggressive marketing by the pharmaceutical industry, fentanyl has become not only a medical issue but also an

ethical issue. Ethically, physicians are to always act in the best interest of their patients. Patients with severe pain whether it is acute or chronic, have the right to have their pain assessed and managed by their physician. Opioids may achieve this goal, but may not be in the best interest of the patient. Studies have shown that in cases of noncancer pain, or pain that is not due to a terminal condition, other methods of treatment such as NSAIDs and acetaminophen are just as effective. (Teater) *Physicians can find themselves in a situation where an opioid may treat the person's pain but at the same time may not be in the patients' best interest because there is suspicion of drug abuse or misuse. In addition, physicians face the challenge of patient satisfaction scores on how they manage a patient's pain. This creates a very dangerous incentive for physicians to prescribe powerful and potentially addictive painkillers. Ethically, the physician has the responsibility to treat the patient, but must take special care when considering the course of treatment lest he or she be prosecuted civilly or criminally for negligence. The ethical nature of the use and misuse of fentanyl will be evaluated by using basic ethical principles of respect for persons, beneficence, nonmaleficence and justice.*

Respect for persons incorporates two ethical convictions: first, individuals should be treated as autonomous agents; and second, persons with diminished autonomy are entitled to protection. The principle of respect for persons divides two separate moral requirements: requirement to acknowledge autonomy and requirement to protect those with diminished autonomy. (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research) The patient-physician relationship is a covenant based on mutual respect and trust. A fiduciary relationship based on honesty. Ethicist Edmund Pellegrino argues the patient-physician relationship is composed of three elements: the patient who is ill and seeking assistance with a need, the physician who will take responsibility for assisting with the needs, and the act of medicine. (Pellegrino) In this relationship the patient is vulnerable needing assistance of the physician to help make correct medical decisions. "The decision-making process initiates the relationship between the two and will result in a chosen form of treatment." (Pellegrino) Physicians must be sensitive to the patient's vulnerability and respect patient autonomy unless it violates the conscience of the physician. The next phase is medical intervention. The physician employs his or her skills to help restore the patient to health or alleviate as much pain and suffering as possible. The patient and physician are in a



relationship that hopefully results in a particular medical treatment. Ethicists Pellegrino and Thomasma argue among obligations that arise from the patient-physician relationship is technical competence: the act of the medical professional is inauthentic and a lie unless it fulfills the expectation of technical competence. (Pellegrino and Thomasma) This means that patients can expect their physicians to offer the same standard of diagnostic and therapeutic services to all patients. The final phase of the relationship is outcome. The effect of the caring activity is assessed according to the physical well-being of the patient. Reciprocity of the relationship completes the patient-physician relationship and upholds respect and dignity of the patient. Physicians must not only be aware of the use and misuse of fentanyl, but they have the medical and ethical responsibility to treat the patient holistically. If NSAIDs and non-opioid therapies are as effective to treat chronic and acute pain and if it will decrease the possibility of addiction, then physicians have the medical and ethical responsibility to prescribe those therapies, even if it is over the objection of the patient. Professionally and as a matter of conscience, physicians have the medical and ethical responsibility to act in the best interest of the patient. If there is any suggestion of possible abuse or misuse of opioids, physicians have the responsibility to protect their patients to the best of their ability. Opioid abusers lack autonomy because the addiction is an impediment to his/her reason. These individuals are not thinking clearly, are abusing their bodies, and their addiction has the potential to lead to serious injury and even death. Failure to care for the patient holistically clearly violates the ethical principle of respect for persons. One way to protect patients and society as a whole is the use of Prescription Drug Monitoring Programs (PDMP) that many states have implemented. These state-run, online databases are designed to monitor the distribution of controlled substances, as well as allow pharmacies and physicians to access a patient's history regarding controlled substances. The ethical issue here is to what extent is this information known and how often is it used. A physician failing to comply with these resources is subject to criminal or civil fines. (Pennsylvania Department of Health) With the accessibility of these databases, there is no excuse for physicians to neglect checking a patient's history with controlled substances. If physicians are committed to treating every person with dignity and respect, then the barriers to addiction and treatment must be lifted to ensure this commitment, and emphasis must be placed on patient dignity and respect. Recognizing the impact of fentanyl abuse and advocating for

new regulations will help to achieve this goal.

Beneficence involves the obligation to prevent and remove harms and to promote the good of the person by minimizing possible harms and maximizing possible benefits. Beneficence includes nonmaleficence, which prohibits the infliction of harm, injury, or death upon others. In medical ethics this principle has been closely associated with the maxim *Primum non nocere*: Above all do no harm. A number of initiatives can be instituted by physicians, state and federal regulatory departments to help maximize benefits and minimize harms. First, physicians need to become better educated on the types of pain medications available, their uses and misuses and all viable alternatives. Second, physicians must become better educated about the use of Palliative Care. "Palliative care is care given to improve the quality of life of patients who have a serious or life-threatening disease, such as cancer. The goal of palliative care is to prevent or treat, as early as possible, the symptoms and side effects of the disease and its treatment, in addition to the related psychological, social, and spiritual problems. The goal is not to cure. Palliative care is also called comfort care supportive care and symptom management." (National Cancer Center) Palliative care professionals can assist physicians by giving viable alternatives to opioids for pain and symptom management. Third, states can impose regulations on the prescribing of opioids. For example, Governor Charlie Baker of Massachusetts signed a law in 2016 that forbid physicians from writing opioid prescriptions for more than a seven-day supply. (Editorial) In 2016, the Governor of Vermont signed a law that the severity and duration of pain would be used to determine the specific limit for a prescription of opioids. "For example, for a minor procedure producing moderate pain, a provider would be limited to prescribing nine to twelve opioid painkiller pills, depending on the medication. The limit would be higher for more complicated procedures, and there would be exceptions for the treatment of severe pain." (Bromwich) Fourth, the Centers for Disease Control and Prevention "Guideline for Prescribing Opioids for Chronic Pain" issued in 2016 should be adopted by all 50 states. These standards are well-reasoned and could make a great difference in curbing the alarming increase in prescription drug deaths. These 12 recommendations can be summarized as follows:

1. Opioids are not first-line therapy. Nonpharmacologic therapy and nonopioid therapy are preferred for chronic pain.
2. Establish goals for pain and function.
3. Discuss risks and benefits.

4. Use immediate-release opioids when starting.
5. Use the lowest effective dose.
6. Prescribe short durations for acute pain.
7. Evaluate benefits and harms frequently.
8. Use strategies to mitigate risk.
9. Review Prescription Drug Monitoring Program Data.
10. Use urine drug testing.
11. Avoid concurrent opioid and benzodiazepine prescribing.
12. Offer treatment for opioid use disorder. (Dowell, Haegerich and Chou)

Fifth, any misuse or abuse of fentanyl by health care professionals must be immediately reported to the proper state, national and medical authorities. This may mean reporting fellow physicians who might be abusing the prescribing of fentanyl. This is the only way to protect patients and society as a whole. Abuse of fentanyl requires yearly review for new legislation and regulations. This will promote the good of the person, minimizing potential harms and maximizing potential benefits. There is no doubt that there will be push-back from the pharmaceutical industry and some medical professions, however, profit can never stand in the way of patient safety. These actions would satisfy the tests of both beneficence and nonmaleficence.

Finally, the principle of justice recognizes each person should be treated fairly, equitably, and given his or her due. Justice pertains to distributive justice, which concerns fair and equitable allocation of resources, benefits and burdens, according to a just standard. Inequality concerning access to medical care is a well-documented fact. To allow individuals addicted to opioids, to have easy access to a drug like fentanyl when there are effective viable alternatives like NSAIDs and other non-opioid therapies is an egregious violation of the principle of justice. Justice dictates people should be treated in a similar manner if at all possible. If there are pain medications that are good for patients like fentanyl, but these medications are being abused and there are viable and effective alternatives, then failure to protect vulnerable patients violates the basic tenet of justice, that is, to treat all people fairly and equitably. Regulations can be instituted like giving a limited amount of fentanyl to patients, using alternatives like NSAIDs and non-opioid therapies, and implementing and using Prescription Drug Monitoring Programs so that those addicted to opioids or those who potentially could be become addicted would not have easy access to this drug. The Centers for Disease Control and Prevention has issued “Guidelines for Prescribing Opioids for Chronic Pain.” Among the 12 recommendations in the Guidelines, there are three principles that will serve as the foundation for improving

patient care and safety:

1. Nonopioid therapy is preferred for chronic pain outside of acute cancer, palliative, and end-of-life care.
2. When opioids are used, the lowest possible effective dosage should be prescribed to reduce risks of opioid use disorder and overdose.
3. Clinicians should always exercise caution when prescribing opioids and monitor all patients closely. (Dowell, Haegerich and Chou)

If federal regulations potentially minimize the number of patients overdosing on fentanyl, not only would medical resources be saved but many lives as well. This meets the condition of justice but more specifically, the conditions of distributive justice in regards to fair and equitable allocation of medical resources. People have the right to have access to medications that are beneficial to them. However, if a medication can be abused and limitations can be placed that protects all individuals, then ethically these limitations must be established. Implementing the CDC “Guideline on Prescribing Opioids for Chronic Pain” can save medical resources and save lives. Failure to regularly assess the need for implementation of these regulations is ethically irresponsible and morally objectionable.

## **CONCLUSION**

Since the mid 1990’s, the rate at which opioids like fentanyl and OxyContin have been prescribed has increased dramatically. Due to this spike in opioid use, rates of abuse, misuse, and addiction have increased so precipitously that opioid abuse is now an epidemic. The cases of Tom Petty and Prince highlight the growing popularity and danger of fentanyl among abusers as well as seemingly ordinary people. As such, medical, legal and ethical issues arise. Medical issues include whether opioids are being properly prescribed to manage severe pain, or over-prescribed for more moderate, chronic pain. Additional medical issues include the long-term health consequences of abuse such as dependency, infection, and death. Legal issues arise when considering incarceration or treatment for drug addicts, as well as lobbying and deliberate false advertising on the part of pharmaceutical companies. Ethical issues arise for physicians and healthcare professionals when considering whether they (the physicians) are acting in the best interest of their patients, and complying with rules and regulations for the prescription of opioids. Moreover, physicians ought to understand the fiduciary nature between patient and

healthcare provider. As such, the ethical principles of respect for persons, beneficence, nonmaleficence, and justice must be upheld.

Unfortunately, the opioid epidemic will only get worse before it gets better. However, the common adage, "it's always darkest before dawn" becomes explicitly applicable in this situation. To address this epidemic, the healthcare profession, lawmakers, and the American people must work together and act quickly. Moving forward, there are several options that can be explored and initiated to help remedy this epidemic. In 2003, the city of Vancouver, Canada founded Insite, a safe injection site in which drug users have access to clean needles, and can use drugs in a safe environment under the supervision of medical professionals. Insite was found to reduce overdose related deaths, reduce rates of HIV and Hepatitis-C, provide an avenue for addicts to begin treatment, discourage open drug use, and is likely cost-effective in the long run (Vancouver). This program has seen such significant success, that Philadelphia, one of the United States' hardest hit cities, is now considering the option of safe injection sites. With the endorsement of Philadelphia's Mayor and District Attorney, this is a step in the right direction (Gordon).

In addition to safe injection sites, alternative treatments to opioids ought to be more thoroughly explored. NSAIDs and other non-opioid therapies, which have proven to be as effective, if not more so than opioids, are a viable alternative to opioid therapy. Additionally, studies have shown that medical marijuana is safer and more effective in treating both chronic and neuropathic pain. Currently, 29 states and the District of Columbia allow for the legal use of medical marijuana. The effectiveness of this drug is backed by numerous thorough and comprehensive studies (Hill). However, medical marijuana is not without risks. There is a need for additional research as current findings are limited by short duration, variability in dosing, and unknown long-term neurocognitive effects. Greater consideration ought to be given to expanding medical marijuana legislation to other states, and moving marijuana from a Schedule I drug to a Schedule II drug immediately to promote research and offer additional avenues of treatment. While these options are controversial, they are backed with substantial evidence and should at least be under consideration in combatting the opioid epidemic. There is no single, easy solution as drug use, addiction, and distribution of illicit substances are multifaceted problems. Rather than waiting for the epidemic to resolve itself, when it realistically will only grow worse,

the medical community, legislators, and the American people must bring this issue to the forefront of discussion and act as quickly as possible, because human lives hang in the balance.

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***Fentanyl: Heroin Yielding to a Deadlier Street Cousin***

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