2016

Analysis of increased public access to naloxone as a method to control the recent fentanyl epidemic

BOSTON UNIVERSITY

SCHOOL OF MEDICINE

Thesis

ANALYSIS OF INCREASED PUBLIC ACCESS TO NALOXONE AS A METHOD TO CONTROL THE RECENT FENTANYL EPIDEMIC

by

ERIC PELLEGRINI

B.S., University of California Los Angeles, 2014

Submitted in partial fulfillment of the

requirements for the degree of

Master of Science

2016

Approved by

First Reader

Gwynneth D. Offner, Ph.D.
Associate Professor of Medicine

Second Reader

Karen Symes, Ph.D.
Associate Professor of Biochemistry

ACKNOWLEDGMENTS

I would like to thank everyone involved with this project from Boston University for their generous support and advice throughout this endeavor. Also, I sincerely appreciate my girlfriend Krista for her relentless encouragement and assistance in helping me accomplish my academic goals.

ANALYSIS OF INCREASED PUBLIC ACCESS TO NALOXONE AS A METHOD TO CONTROL THE RECENT FENTANYL EPIDEMIC

ERIC PELLEGRINI

ABSTRACT

The opioid fentanyl is becoming an increasingly popular drug of abuse across the United States. With a potency up to 100 times greater than the common opioid morphine, fentanyl use can easily lead to overdoses. This is especially true as fentanyl is increasingly found mixed into other illicit drugs without users' knowledge. However, there exists an antidote for opioid overdoses called naloxone. Naloxone is a pure antagonist at μ-opioid receptors in the brain and produces little known side-effects. Recently, the FDA has approved naloxone delivery devices designed for individuals without medical training, making naloxone layperson friendly. Under today's policy, naloxone is a prescription medication. This means physicians must write a prescription for take-home naloxone or issue a standing order allowing other healthcare professionals to distribute naloxone. However, there are little federal laws governing naloxone as most of the statutes discussing naloxone access and administration are determined by individual states. For example, only some states allow physicians to prescribe naloxone to non-patients. Additionally, many states have differing laws regarding criminal liabilities for physicians who prescribe the drug and for laypersons who administer the drug. In the U.S. there exists a dilemma with naloxone, as topics ranging from public policy to

insurance coverage are controversial. With increasing information on fentanyl and naloxone being published, the U.S. is currently looking into the idea of making naloxone more accessible as a way to reduce overdose deaths.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

CDC ..... Center for Disease Control and Prevention

DEA……... Drug Enforcement Administration

EC……... Effective Concentration

ED……... Emergency Department

EMT……... Emergency Medical Technician

EMS……... Emergency Medical Services

GABA…….. Gamma-Aminobutyric Acid

GCS…… Glasgow Coma Scale

IC……... Inhibitory Concentration

IDU……... Intravenous Drug User

IM……... Intramuscular

IN……... Intranasal

IV……... Intravenous

MOR ..... Mu Opioid Receptor

QALY……... Quality-Adjusted Life-Year

SAMHSA…… U.S. Substance Abuse and Mental Health Services Administration

SC……... Subcutaneous

$t_{1/2}$…….. Half-Life

V_d……. Volume of Distribution

VTA……... Ventral Tegmental Area

INTRODUCTION

Opioids

The opioid epidemic in the United States is a well-known public health issue. Opioids have long been used for their medicinal value and are still regularly prescribed to help treat chronic pain. However, doctors face a major dilemma. Physicians want to improve their patient's quality of life, but opioid treatment may lead to dependency or addiction [1]. The increased misuse of opioids correlates with the increased amount and availability of prescription opioids. Since 2000, the use of prescription opioids to treat moderate to severe pain has risen by over 250% [2]. For some, prescription opioids are the beginning, as drug abuse and misuse can lead to individuals seeking more potent analgesics. A study by the National Survey on Drug Use and Health found that individuals who reported prior use of nonmedical prescription pain relievers were 19 times more likely to switch to heroin [3].

The leading issue with the opioid crisis is the rate at which individuals are dying from overdoses. Between the years 2000-2014, there was over a 200% increase in deaths from opioids (**Figure 1**) [4]. More recently, the rate of opioid related deaths increased from 7.9 per 100,000 persons in 2013 to 9.0 per 100,000 persons in 2014 [4]. Within this one-year period, there was an 80% increase in age-adjusted rate of death from synthetic opioids (such as fentanyl), whereas heroin and prescription opioid pain reliever related overdoses increased by 26% and 9% respectively [4]. While classic opioids like heroin still remain a significant problem in the United States, a recent influx of synthetic opioids proves to be a new obstacle. Information from the DEA indicates that there has been a

steady increase in the number of fentanyl drug seizures around the country between 2012-2014 (618 in 2012; 945 in 2013; 4,585 in 2014) [5]. With fentanyl being significantly more potent than both intravenous morphine and heroin, there is an increased risk for overdose and respiratory depression [6]. This rise in availability of illicit fentanyl presents a growing concern in many communities, such as Massachusetts, where 13.7% of the total fentanyl drug seizures in the U.S. occurred in 2014 [5].

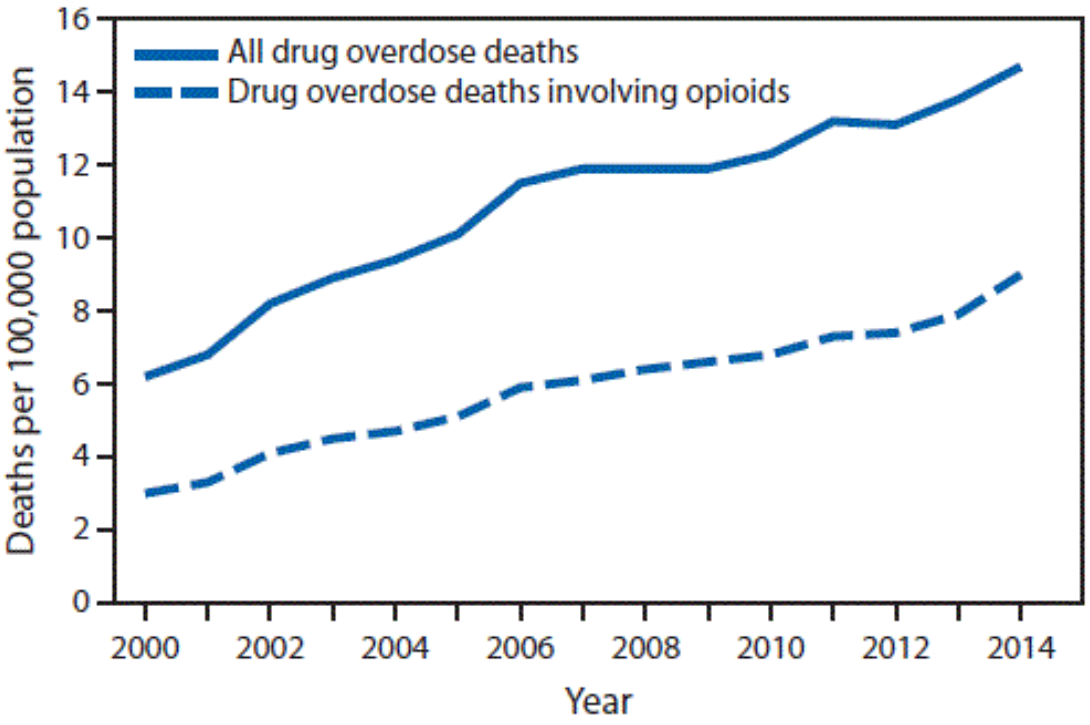

Figure 1. **Opioid Drug Deaths**. Between the years 2000-2014, drug overdose deaths related to opioids more than doubled. Opioids in this graph are categorized as morphine, oxycodone, hydrocodone, heroin, methadone, fentanyl, and tramadol[4].

Fentanyl

Fentanyl was first discovered in the 1960s by Dr. Paul Janssen as an opioid analgesic and was quickly introduced into the medical field for anesthesia purposes [7]. Today, fentanyl is used regularly both inside and outside the hospital for medical purposes in the forms of IV medications, transdermal patches, and buccal tablets. Specifically, transdermal fentanyl has proven to be both an effective and safe treatment option to relieve postoperative pain [8]. Other implications for transdermal patches include use in palliative care and in cancer patients suffering from chronic pain [9]. In regards to buccal or transmucosal fentanyl tablets, recent studies have indicated their effectiveness in the management of breakthrough pain [10]. Breakthrough pain is described as a transitory increase in pain in an individual who manages chronic pain with opioid drugs [11]. In these cases, fentanyl is used sparingly to treat the increased pain that is normally controlled with the patients' usual opioid prescriptions.

The issue with fentanyl stems from its narcotic use outside of medical purposes. While some individuals seek this drug out on the streets, many others use fentanyl unknowingly. In a study looking at recent drug use, it was found that 29% of individuals who used drugs within the past three days tested positive for fentanyl, while 73% of those who tested positive did not report ever taking fentanyl [12]. This indicates that fentanyl is showing up in other drugs, such as cocaine and heroin, without the users knowing what they are taking. The issue is that this can lead to overdoses because drug users may think they are injecting their normal dosage, but if the drug is laced with fentanyl, the "normal dose" can become lethal.

Naloxone

Naloxone is the common antidotal therapy for opioid overdoses. The drug functions as a neutral antagonist at the μ-opioid receptor in the brain, competing with the opioid for the ability to bind the receptor [13]. There are several ways in which naloxone can be administered, including intravenous (IV), subcutaneous (SC), intramuscular (IM), and intranasal (IN) routes. While IV and IM delivery are still routinely used in the medical field, the emergence of IN systems has proven to be a safe and effective means of administering naloxone without the need for needles [14,15]. The advent of IN delivery has led to the expanded distribution of naloxone to first responders, such as EMTs, firefighters, and police officers, in several states [16]. As the opioid epidemic continues to grow, there has been an increased push for more public access to the antidote naloxone due to its remarkable effectiveness in reversing overdoses. Specifically, some communities have already begun to increase this access to naloxone through distribution programs to drug abusers, prescriptions to at risk patients, and bill proposals to change naloxone to an over the counter medication [17].

Specific Aims

The Specific Aims for this work are to:

1. Examine the illegal use of the opioid fentanyl and the reasons for its recent prevalence. Additionally, a pharmacological review of fentanyl will be conducted in order to highlight the dangers of fentanyl abuse.

2. Investigate the drug naloxone, including the pharmacology and route of administration, in order to evaluate the drug's effectiveness in reversing fentanyl overdoses.
3. Analyze increased public access to naloxone as a means of reducing fentanyl related overdose deaths, including extended access to opioid users, friends of users, families of users, first responders, and laypersons.

FENTANYL

Fentanyl Use

Fentanyl is a potent opioid used for anesthetic purposes and in the treatment of both acute and chronic pain. Depending on the study, fentanyl has been shown to have a potency that is between 75-100 times that of the prominent opioid morphine[18]. Potency is a quantitative term that reflects a drug's half maximum effective concentration (EC_{50}). The EC_{50} is the concentration of a drug that produces fifty percent of its maximal effect. Thus, with fentanyl, one only needs approximately a hundredth of the concentration of morphine to produce the half maximal effect.

Today, fentanyl abuse is found in many forms, and the drug itself can be procured as non-pharmaceutical fentanyl produced illegally or pharmaceutical fentanyl that is diverted from a medical setting. While non-pharmaceutical fentanyl is found in powder or pill form, diverted pharmaceutical fentanyl can be in the form of transdermal patches, buccal tablets, or lozenges[19]. Specifically, some individuals will wear transdermal fentanyl patches despite not having a prescription for the medication or others will wear more than one patch at a time to increase the dosage[20]. Drug abusers have also developed methods for extracting fentanyl out of the transdermal patch to be used intravenously. For example, a documented account of a fentanyl abuser depicts a method by which a transdermal patch was placed in a vinegar solution and microwaved to produce a liquid form suitable for injection[21]. Another method describes boiling several used transdermal patches in 20ml of water to make a fentanyl solution[22].

The problem with these methods of abuse is that the risk of overdose is extremely high. Extracting fentanyl from a patch is unpredictable with several variables. Most importantly, it is impossible to predict the potency of the solution, as the concentration is unknown. For fentanyl this could prove fatal. Additionally, transdermal fentanyl patches come in several different doses from 12μg/h to 100μg/h[23]. Even the smallest transdermal device dose contains 10-20 times the concentration of drug than a therapeutic IV dose of fentanyl (1.25mg vs 50-100μg)[24]. Therefore, the combination of extracting an unknown quantity from a potentially unknown initial concentration makes this form of intravenous fentanyl use especially dangerous.

In the medical field, it is established that the physicians most likely to abuse opioids are surgeons and anesthesiologists[25]. There have been several documented cases of physicians diverting pharmaceutical fentanyl for use outside the hospital[26]. Diversion in this case refers specifically to the use of pharmaceutical drugs for recreational purposes. One theory suggests that those physicians who work in the operating room, such as surgeons and anesthesiologists, may unknowingly become sensitized to aerosolized opioids when intravenous anesthetic fentanyl or propanol is given to the patient[25]. This study detected aerosolized fentanyl or propanol in operating rooms when intravenous doses of the respective drug was used; the operating room should have no detected opioids of any concentration in the air[25]. While more testing is being conducted on the subject in order to make a definitive statement, the possibility that operating room exposure to fentanyl can increase the risk of opioid addiction proposes a unique issue worth addressing.

Overall, fentanyl causes several costs to society. Specifically, poor health, crime, social irresponsibility, personal neglect, decreased job performance, and economic loss can severely impact communities[27]. In addition to these indirect consequences, fentanyl use can also lead to addiction and further drug seeking behavior.

Pharmacokinetics

Depending on the route of administration, fentanyl shows different absorption kinetics. For intravenous injection, the drug becomes completely bioavailable as the drug is delivered directly into the blood system. However, the transdermal delivery device has much slower absorption due to the surface layers of dead, keratinized cells. As the drug is slowly released from the reservoir or matrix designed system, it rapidly diffuses into the epidermal layer of the skin[24]. The delivery of fentanyl from the epidermis to the dermal layer of skin is the rate limiting step, and a depot of drug develops in the epidermal layer leading to the slow, continuous delivery of fentanyl characteristic of the transdermal patch[24]. Lastly, both intravenous and transdermal administrations avoid first-pass metabolism by hepatic enzymes. This allows for the maximal amount of fentanyl to be absorbed as none of it is initially degraded or metabolized to an inactive substance.

Fentanyl acts as a potent opioid in part due to its lipophilic nature and low molecular weight. These properties allow fentanyl to readily cross the blood-brain barrier and thus issue its analgesic effects. The blood-brain barrier consists of a series of tight junctions between vascular endothelial cells that permits the access of water, gases, and lipid-soluble molecules, such as fentanyl, into the brain[28]. Another interesting feature of fentanyl is its large volume of distribution within the body[28]. The volume of distribution

refers to the volume of the body into which the drug appears to have distributed and is defined as the dose administered divided by the concentration in the plasma (V_d = Dose/C_p). Therefore, since fentanyl has a large volume of distribution, for a given dose there will be small concentration of fentanyl in plasma. This can be explained as fentanyl exhibits a two-compartment model of distribution[28]. As soon as fentanyl enters the blood, it starts to distribute into other tissues and extravascular spaces. Thus, fentanyl will persist within the body for a longer period of time than a water soluble drug because fentanyl must redistribute back into the vascular compartment before it can be eliminated. This poses as a significant problem when fentanyl is abused and overdoses occur.

Fentanyl undergoes metabolism by the cytochrome P450 3A4 isoenzyme[23]. P450 enzymes have the highest activity in the liver and function by catalyzing the addition of molecular oxygen to the drug. For fentanyl, this oxidative reaction produces norfentanyl and other inactive metabolites that can be excreted[23]. Furthermore, the importance of the CP450 3A4 isoezyme is shown through the addition of a CYP450 3A4 inhibitor. This results in a rapid rise in blood fentanyl concentration as fentanyl is not metabolized[29]. While over 75% of fentanyl is eliminated in the urine as metabolized product, a small fraction is excreted in the urine unchanged (roughly 10%) and the rest is passed in the feces[28]. In regards to half-life ($t_{1/2}$), there exists a noticeable difference between fentanyl delivered intravenously and the transdermal application. The half-life of a drug is the time in which it takes for the blood concentration to decrease by half. Specifically, the $t_{1/2\ I.V.}$ = 7 hours while the $t_{1/2\ transdermal}$ = 20-27 hours[23]. Due to the collection of fentanyl within the epidermal layer of the skin, there remains a constant influx of drug into the

blood for some time even after the transdermal patch has been pulled off. Therefore, the half-life of transdermal delivery is measured to be longer.

Pharmacodynamics

Like other opioids, fentanyl has a similar mechanism of action in which the drug binds to μ-opioid receptors to exert its effect. These receptors are concentrated primarily in brain regions that regulate pain perception, induce emotional responses to pain, and stimulate neural reward regions[30]. μ-opioid receptors are also located in other brain regions, such as the brainstem, which are responsible for the respiratory depression associated with fentanyl overdose[30]. The μ-opioid receptor is classified as a class A, rhodopsin-like G protein-coupled receptor (GPCR) that binds to several endogenous ligands, including enkephalins and beta-endorphins[31]. GPCRs are seven-transmembrane spanning proteins that produce signal transduction via a second messenger system. Specifically, the μ-receptor is part of the G-inhibitory family and has been shown to inhibit the release of substance P, a neuropeptide associated with pain[32].

Fentanyl is clinically used for its analgesic properties. As alluded to above, opioids have a specific mechanism of action within the pain pathway. Pain, simply put, is transmitted to the brain from the periphery by a series of neurons. Primary ascending pain fibers enter the dorsal horn of the spinal cord and synapse with nociceptor interneurons[33]. These interneurons then proceed to communicate in the dorsal horn with cells that give rise to the ascending spinothalamic tracts that enters the brain[33]. When μ-opioid receptors located at the presynaptic ends of the nociceptor interneurons bind an opioid, the cell becomes hyperpolarized and substance P release is inhibited[33]. It is believed that the

hyperpolarization event inhibits the opening of voltage-gated calcium channels that induce the release of substance P[32].

The clinical efficacy of fentanyl shows a direct concentration-effect relationship between the plasma concentration of fentanyl, analgesia, and respiratory depression[34]. A study on healthy volunteers and postoperative patients concluded that a plasma concentration between 0.6 – 2ng/ml provided adequate analgesia without resulting in respiratory depression[34]. This range between 0.6 and 2ng/ml can be referred to as the therapeutic window, which references the range of doses that are efficacious without producing adverse effects. However, according to this study many factors can influence this therapeutic window including age of the individual, interaction with other drugs, and pharmacokinetic or pharmacodynamic differences[34]. Another study concluded that the average IC_{50} for steady state infusion of fentanyl was 1.4ng/ml[35]. The IC_{50}, or inhibitory concentration, in this situation refers to the plasma concentration of fentanyl at which the pain level of an individual is reduced by 50%. This dose of 1.4ng/ml fits well within the therapeutic window.

Fentanyl is a selective depressant of the central nervous system and can cause various side effects. While analgesia is the goal, the decrease in sensation to pain can be accompanied with drowsiness, mood alteration, and the feeling of mental cloudiness. Other side effects include nausea, vomiting, miosis, constipation, and respiratory depression[27]. The most drastic of these side effects is respiratory depression. In humans, apnea was noted to occur after delivery of 2.9ng/ml of fentanyl intravenously[36]. A study in rats illustrated that respiratory depression resulted in a reduced tidal volume, reduced

partial pressure of O_2, increased partial pressure of CO_2, and a decrease in blood pH[37]. These effects are what ultimately lead to death in fentanyl overdose victims.

Tolerance

Tolerance is the need for increased amounts of a substance in order to achieve the desired effect. In other words, it can be defined as a diminished effect with the continued use of the same amount of a substance. For fentanyl and other opioids, tolerance develops to analgesia, sedation, euphoria, and respiratory depression. Frequency plays an important role because the rate at which tolerance develops depends on the degree of intermittency of drug delivery and is most significant when administration occurs on a daily basis[27]. Opioids can produce a degree of tolerance that is exceptionally large, with some habitual users needing up to 500 times the therapeutic dose to feel the desired effects[27].

The mechanism by which tolerance to opioids develops is believed to be a pharmacologic phenomenon with events leading to the internalization and direct desensitization of μ-opioid receptors. This explanation makes sense because less active receptors on the cell surface means less opioid can bind and the desired effect is unable to be achieved. However, this does not necessarily explain the complex issue of tolerance entirely. For example, β-arrestin2 knockout mice do not become tolerant to the antinociceptive effects of continuous morphine infusion, yet tolerance develops for other specific opioids such as fentanyl[38]. β-arrestin is a protein part of a regulatory system that limits the function of GPCRs. These proteins work by binding to the GPCR and target the

internalization of the GPCR through endocytosis. Thus, internalization by the β-arrestin system fails to explain the concept of tolerance on its own.

Additionally, it was shown in mice that the extrinsic efficacy of an opioid is inversely related to its tolerance after continuous infusion, but not during intermittent administration[39]. In this study, morphine, which is a less efficacious drug, produced more tolerance than fentanyl during continuous infusion for seven days. However, intermittent administration of efficaciously equivalent doses of morphine and fentanyl produced the same degree of tolerance[39]. This shows that both efficacy and frequency play a role in determining fentanyl's relative tolerance.

Dependence vs Addiction

The concept of drug dependence can manifest itself in the form of physical and psychological dependence. Physical dependence results from the chronic use of a drug that has produced tolerance and negative physical symptoms of withdrawal upon discontinuation of use. On the other hand, psychological dependence refers to the intense craving an individual has for a drug. While the intensity of dependence parallels the increase in dosage, an individual can start to become dependent on opioids even with small doses that reside within the therapeutic window[27]. In a study on mice that determined the relative physical dependence induced by various opioids, fentanyl proved to produce the strongest physical dependence.

Withdrawal is the feeling of physiological and or psychological symptoms that occurs following abstinence from a drug that has been used repeatedly. For opioids, the severity of abstinence syndrome correlates directly with the degree to which an individual

is dependent upon the narcotic[27]. During the period of withdrawal, changes occur in most major organs and body systems. The signs and symptoms of opioid withdrawal include: anxiety, restlessness, irritability, lacrimation, generalized body aches, insomnia, perspiration, dilated pupils, hot flashes, nausea, vomiting, diarrhea, fever, increased heart rate, hypertension, malaise, muscle cramps, and dysphoria[27]. Although the symptoms for physiological withdrawal disappear within approximately a week, the psychological withdrawal may persist for a longer period of time and is important to address in the treatment process to avoid relapse[27].

Addiction is inherently different from dependence. While almost all opioid addicts are dependent upon the drug, not all individuals who are dependent on opioids are addicted to the drug. For example, some individuals who use fentanyl patches to treat chronic pain associated with cancer will experience withdrawal symptoms if they stop using the medication, but they are not addicted to fentanyl. Addiction is a complex process that is modulated by genetic, developmental, and environmental factors[40]. The concept of addiction is defined as a behavioral pattern characterized by an overwhelming involvement with using a drug and securing its supply. Individuals who are considered addicts regularly understand what they are doing is wrong and frequently realize the adverse consequences associated with the use of opioids. Despite this comprehension, addicted individuals are unable to quit or have a significant tendency to relapse after quitting.

Opioids have a significant tendency to be abused because the drug provides a relief from worry, tension, and fatigue, while also producing an altered sensation that is

interpreted as euphoric. The euphoria and pleasurable feelings are directly linked to the reward pathway within the mesolimbic dopamine system. Fentanyl works within the mesolimbic dopamine system by binding to its μ-opioid receptor on GABA interneurons in the ventral tegmental area (VTA) of the brain. GABA interneurons produce an inhibitory signal that acts on the VTA. When opioids bind to their receptors on the GABA interneuron, a negative signal is produced that inhibits the GABA interneuron. This is called disinhibition. Therefore, fentanyl binding inhibits an inhibitory process, which ultimately activates VTA neurons. The now more active VTA neurons increase their firing rate and proceed to release more dopamine into the nucleus accumbens (see **Figure 2**). Ultimately, the feelings of desire and pleasure are promoted as more dopamine enters the nucleus accumbens, which is a collection of neurons in the forebrain.

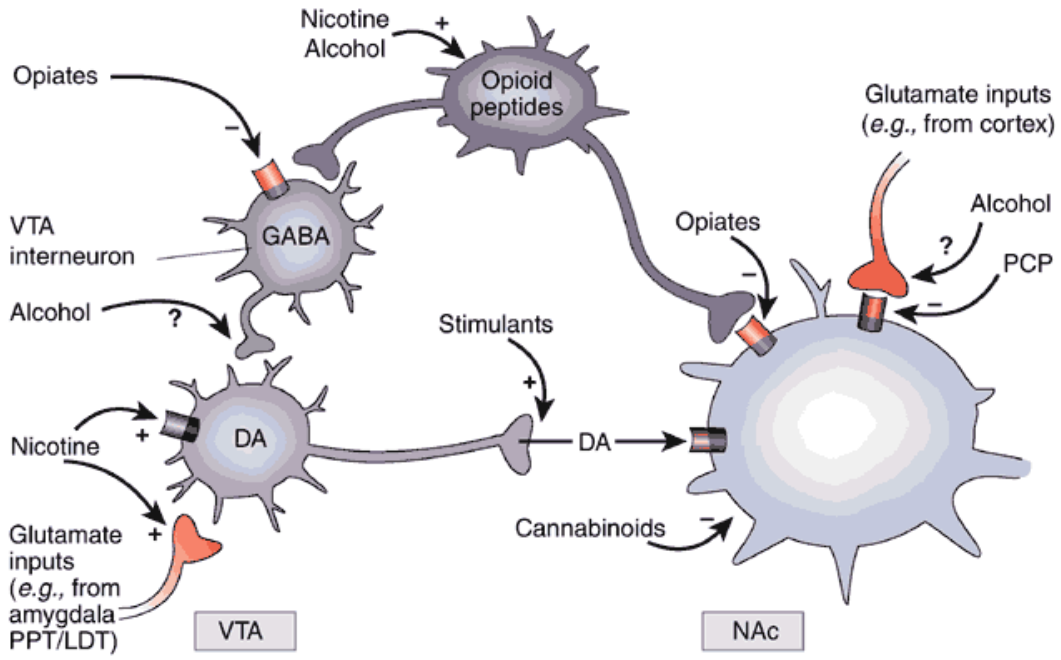

Figure 2. **Simplified Schematic of Drug Action on Mesolimbic Dopamine System**. Opioids act directly on GABAergic interneurons resulting in disinhibition of VTA dopamine neurons. The result is more dopamine reaching the nucleus accumbens. DA = dopamine; Nac = nucleus accumbens; VTA = ventral tegmental area[41].

One popular hypothesis on addiction supports the idea that over time an individual goes from positive drug reinforcement to negative drug reinforcement. Specifically, positive reinforcement describes the gain in pleasure associated with drug use while negative reinforcement reflects the relief of stress and negative affect. The switch from positive to negative reinforcement occurs because of allostasis, or the process of maintaining apparent reward stability through changes in the reward system pathway[42]. This means that as a user continues to abuse a drug, his or her mood fails to return within the normal homeostatic range. Instead, a new homeostatic set point is established that is below the original level and remains chronically deviated. Now instead

of taking the drug for a euphoric effect or "high", an abuser takes the drug to reach the original or "normal" state. Supporting evidence for this idea of allostatic dysregulation showed that in a cohort of chronic pain patients, those that misused opioids exhibited significantly attenuated natural reward processing relative to the patients who used opioids as prescribed[43].

Recent Fentanyl Prevalence

The recent increase in fentanyl prevalence, especially in the Northeast, is a complex phenomenon with no exact explanation. As discussed previously, between 2012 and 2014, there has been an approximate 740% increase in fentanyl drug seizures in the United States[5]. According to the DEA, the majority of cases related to fentanyl morbidity and mortality are related to non-pharmaceutical fentanyl, as opposed to diverted pharmaceutical fentanyl[4]. Non-pharmaceutical fentanyl is sold in the drug market by itself or frequently combined with other drugs, such as heroin. It has been shown that most of the areas affected by fentanyl overdoses are in the eastern United States, an area dominated by white powder heroin[19]. White powder heroin, which comes from South America, is significantly different and more popular compared to black tar heroin that comes from Mexico[19]. The DEA has discovered that fentanyl is found to be most commonly mixed into white powder heroin or sold disguised as this product because fentanyl has become cheaper to manufacture than heroin[19]. Thus, due to the greater use of heroin in the Northeast and given the type of heroin used in the Northeast, there exists a correlation to the increased amount of fentanyl overdoses in this region.

From an economics standpoint, however, there appears to be a valid theory for the increase in non-pharmaceutical fentanyl overdoses in the Northeast. While looking at opioid drug markets, there is a connection between decreasing heroin purity and the increase in non-pharmaceutical fentanyl overdoses[44]. Due to an elastic market where opioid abusers can seek other competitive drugs, such as prescription opioids, declining heroin purity would result in loss of heroin consumers. Therefore, the evidence supports the concept that fentanyl overdoses are related to drug suppliers' efforts to increase the potency of impure heroin by mixing in fentanyl in an attempt to keep consumers as prescription opioids become increasingly available[44]. While this theory is shown to prove true in several drug markets, it is not universal as some Northeastern heroin markets did not see a rise in fentanyl mixed into the heroin supply[44].

Conclusion

As discussed, fentanyl is becoming an increasingly prevalent drug with the potential for severe consequences. With opioid users inevitably becoming tolerant to their drug of choice, the search is ever present for a cheaper, more potent fix. Fentanyl fits this profile. The drug's ability to produce a greater analgesic effect and subsequent euphoria, with a smaller dosage, makes fentanyl an enticing opioid, albeit dangerous, since fentanyl is known to show up in other drugs without the user knowing. This further adds to the danger of the highly potent opioid because overdoses can occur easily due to the narrow therapeutic window of fentanyl.

NALOXONE

Naloxone Use

Naloxone is the primary treatment for a suspected opioid overdose. This drug functions as a competitive antagonist at the μ-opioid receptor[45]. Specifically, this means that naloxone will compete with the other opioids, such as fentanyl, in order to be bound to the receptor (see **Figure 3**). Since naloxone is a "neutral" or "pure" antagonist, the action of binding to the μ-opioid receptor does not elicit a response in itself[46]. However, a much discussed topic is the degree to which naloxone binding to μ-opioid receptors and displacing the opioid drug results in acute withdrawal syndrome. This topic will be addressed more in detail while exploring the pharmacology of naloxone and its various routes of administration to determine if this drug is an effective treatment for fentanyl overdoses.

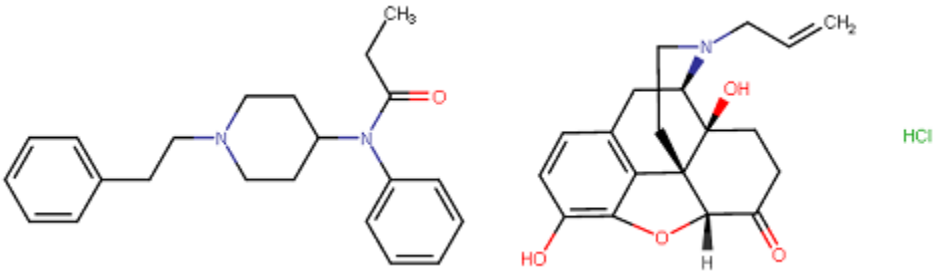

Figure 3. Fentanyl vs Naloxone. Naloxone (right) acts as a neutral antagonist at the μ-opioid receptor. This prevents fentanyl (left) from binding and evoking a response[47,48].

Pharmacokinetics

Naloxone is limited to IV, IM, SC, and IN routes of administration. Oral forms of the drug do not provide the necessary efficacy because of rapid first-pass liver metabolism[49]. A study examining rat liver slices confirmed that extensive naloxone metabolism occurs before entry into the blood stream[49]. With first-pass metabolism, it is not naloxone that enters the plasma, but rather the metabolite naloxone-3-glucoronide, which is significantly less effective and results in the lower potency for oral doses[50]. Intravenous administration continues to be the standard for ensuring maximum absorption and bioavailability of naloxone; however, other options continue to be explored.

The volume of distribution for naloxone is large due to its lipophilic nature. It was found that in rats, the maximum amount of naloxone in the calculated plasma volume was 1.04% of the administered intravenous dose[49]. This experiment illustrates that most of the drug has distributed throughout the body, as opposed to staying within the hydrophilic plasma compartment. The characteristic large and rapid volume of distribution helps naloxone be an effective antidote because the drug can readily cross the blood-brain barrier. Further supportive evidence for naloxone's distributive properties comes from a study that quantified brain to serum drug ratios. Naloxone was proven to achieve a markedly higher brain to serum ratio (0.25%) than the opioid morphine (0.02%). This 10-fold difference in distribution indicates that naloxone more readily disperses into lipophilic areas of the body, such as the brain, where it can compete with opioids for the μ-opioid receptor[51].

Irrespective of the route of administration, naloxone has been found to be rapidly cleared from the body[50]. Naloxone is metabolized in the liver primarily by cytochrome P450 enzyme conjugation with glucuronic acid[52]. Interestingly, depending on the given study and route of administration, the half-life ($t_{1/2}$) for naloxone differs greatly even when looking at a similar 0.4mg dosage. For example, the $t_{1/2\ I.V.}$ values range from 0.55 hours to 1.68 hours, with the drug label indicating a mean value of 1.06 hours[52,53,54]. The drug label for intramuscular naloxone cited the $t_{1/2\ I.M.}$ to be 1.28 (+/- 0.48) hours[52], whereas the $t_{1/2\ I.N}$ was shown to be 2.08 hours[55]. These grossly varying results can stem from several variables. These tests were each performed by different scientists on a unique cohort of subjects. Additionally, the subjects themselves could vary in body size, body composition, and ability to metabolize the drug naloxone, leading to a range of results.

Pharmacodynamics

Clinically, naloxone is used to produce reversal of the miosis, analgesia, and respiratory depression that results from opioid overdose[56]. Moreover, naloxone can be used to antagonize opioid-induced seizures[45]. While this drug has the ability to bind other opioid receptors, including kappa and sigma, naloxone has the most selectivity for the μ-opioid receptor[57].

The effective dose of naloxone depends on the amount of the opioid taken, the time in which the opioid was taken, the weight of the patient, and the relative affinity of naloxone for the μ-opioid receptor compared to the opioid[58]. Due to this complexity, debate stems over what standardized dose of naloxone should be initially administered.

The concept is to try to find a minimum dose that will reliably work without causing any adverse effects associated with acute withdrawal. A study that looked at recent medical sources for naloxone dosages discovered that out of 22 sources, 12 recommend an initial dose of 0.04mg to 0.05mg while the others endorse an initial dose of 0.4 to 0.5mg[59]. Recently, a case study proposed that low dose naloxone at 0.04mg is sufficient to reverse opioid overdose in some individuals and that small dose titrations every 3 min, for those individuals who need additional naloxone, is the safest method to avoid acute withdrawal[59]. Out of the small cohort of patients who received this dosage treatment, 40% required a single dose (0.04mg), 40% required two doses (0.08mg), and the last 20% required three doses (1.2mg)[60]. This experiment showed that every patient significantly increased his or her respiratory rate and oxygen saturation levels with a dose significantly smaller than the 0.4mg that has frequently been used as the standard.

In contrast to this smaller dose, bystanders, first responders, and some physicians utilize naloxone dosages of 0.4mg (IM & IV) and 4mg (IN)[52,55]. While the debate continues over the dosage to use in the hospital setting, there could be several reasons for keeping the higher dosages in the prehospital setting. For example, the individuals issuing the drug are less trained than physicians, and thus it may be more prudent to issue the higher dosage that has the greater percentage of working without the need for additional administrations. Additionally, in the case of a bystander issuing naloxone, there might only be one dose of naloxone available. This follows the same argument that a sufficiently strong dosage should be administered in the hopes that the naloxone provided works in the patient. Lastly, and most importantly, reducing the respiratory depression is

more crucial than avoiding withdrawal syndrome. Therefore, the higher 0.4 mg dose, while potentially providing more discomfort, gives the patient the best chance of survival compared to the 0.04mg dose.

Regardless of the dose of naloxone, it is agreed upon that if the initial response does not occur within 2-3 minutes, another dose of equal amount should be administered[52,54,55,60]. With naloxone being a neutral antagonist, there is no risk for a naloxone overdose. Also, with naloxone's rapid absorption and extensive distribution, the effects of the drug, if there are any, should occur within the short time frame of a few minutes. Thus, additional naloxone should be administered at a time interval of 2-3 minutes until the respiratory depression is reversed.

Naloxone's effectiveness as the emergency antidote for opioid overdoses is highly conserved. In a study on morphine, naloxone was able to create a parallel shift of the dose-response curve to the right[56]. This action indicates that more morphine is needed to achieve the same desired effect, or rather that naloxone competes with the opioid for the μ-opioid receptors. However, the extent to which naloxone binding to the μ-opioid receptor is needed to cause a reversal of an overdose is still unknown. It was shown that the dose needed to occupy 50% of available μ-opioid receptors in the brain of a non-opioid dependent human was 13μg/kg, or 0.91mg in a 70kg man[61]. The data from this study fits within the recommended naloxone dose of 0.4-2mg/70kg in some literature[45]. Therefore, from clinical practice and research, it can be inferred that in order to block an opioid overdose in an opioid naïve individual, naloxone needs to occupy approximately

50% of the available opioid receptors[61]. While this information may prove useful, it is important to consider that this only applies to non-dependent individuals.

Side Effects and Toxicity

Although naloxone shows no agonistic properties, and thus does not illicit a response from the μ-opioid receptors, there are several potential side effects to consider after delivering a dose of naloxone. First, in opioid-dependent individuals, naloxone binding to the μ-opioid receptors can potentially activate signs of acute withdrawal. The most common symptoms of opioid withdrawal syndrome induced by naloxone includes: anxiety, nausea, vomiting, diarrhea, abdominal cramps, tachycardia, aggressiveness, piloerection, yawning, and rhinorrhea[45,52,62]. While most agree that a withdrawal response can be activated in opioid-dependent individuals with naloxone, as proven by increased neural activity in functional MRIs[63], the debate revolves around the medical significance and extent to which naloxone is responsible for clinically observed side effects. In one study that examined 1,192 patients treated with naloxone in the prehospital setting, an adverse event occurred 45% of the time; however, in only 3 cases were individuals hospitalized because of the adverse event[62]. This is interesting as it illustrates the mostly benign nature of naloxone side effects. Even though seizures were reported in some patients following naloxone administration, it was concluded that the seizures more likely occurred because of hypoxia following respiratory depression as opposed to the naloxone itself[62].

Nevertheless, other cases present arguments that naloxone may contribute to more substantive side effects, including pulmonary edema and death. In respect to pulmonary

edema, there is controversy as to whether naloxone is the leading cause or whether opioid overdoses themselves are the underlying factor. Several specific examples of individuals being diagnosed with acute pulmonary edema following naloxone administration have been documented[64,65]. These reports call for naloxone to be used discriminately and for health care professionals to be aware of potential compounding variables, like expansion of intravascular blood volume, before administering naloxone[65]. However, others claim that pulmonary edema following naloxone administration is coincidental or related to the opioids themselves. For example, one case reports that pulmonary edema was diagnosed following naloxone, but that the cause was an upper airway obstruction that occurred simultaneously to drug delivery, ultimately leading to the negative pressure pulmonary edema[66]. Additionally, a study on heroin overdoses concluded that non-cardiogenic pulmonary edema found in overdose patients is attributed to the use of opioids themselves[67]. Regardless if naloxone directly causes pulmonary edema, which remains to be determined, this side effect is something to be considered and providers should be prepared for this during opioid overdose treatment.

It is known that ventricular fibrillation has been reported in patients following naloxone administration if they have prior cardiac history, such as hypertension or pulmonary edema[68]. Nonetheless, there are two cases of healthy women, without prior cardiac history, dying of unexplained cardiac arrest following the administration of 0.4mg dosages of naloxone. These deaths are speculated to be linked to an increase in blood catecholamine levels precipitated by the naloxone[68]. However, these are only a few

reports that do not contain an exact detailed explanation for the physiological or pharmacological events that occurred following naloxone administration.

Special Considerations

In regards to the pharmacodynamics of naloxone, there are a few special considerations that need to be acknowledged. First, the effective duration of naloxone may be shorter than the duration of action of most opioids[52,55]. If the opioid outlasts naloxone, some patients can potentially slip back into an opioid overdose and subsequent respiratory depression. The reason for naloxone's short duration of action is complex. It is speculated that naloxone's large volume of distribution and its high metabolic clearance rate are the principal reasons for the short duration of action relative to opioids[50].

To put this into numerical perspective, the brain levels of the prominent opioid morphine stay constant for at least an hour, whereas the concentration of naloxone declines by roughly 50% in the same time period[51]. However, this is not to say that opioid toxicity recurrence happens every time. In a study examining opioid toxicity recurrence in emergency departments, only 31% of naloxone responders required another dose of naloxone[69]. Therefore, approximately 1 in 3 patients who initially respond to a bolus of naloxone will require another dose. The study also found that recurrence of toxicity occurred more commonly with long-acting opioids and was irrespective of the route of opioid exposure[69]. One way to prevent this recurrence from happening is to administer an IV infusion of naloxone. A study examining naloxone in order to develop an infusion dosing nomogram discovered that a dose of naloxone equal to 2/3 the amount initially

given to reverse the opioid intoxication, delivered over each subsequent hour, will maintain plasma naloxone levels equal to or greater than levels that would have existed 30 minutes following the initial bolus dose[70]. This continuous infusion is believed to maintain naloxone levels at an adequate level that will help treat patients without them becoming intoxicated again.

Lastly, pediatrics patients are a special population that merits mention. If a child accidentally ingests opioids, it is usually at a higher dose than adults per kilogram of body weight simply due to the size of the child[58]. From this information, it can be deduced that children may require larger doses of naloxone to reverse the effects of the overdose.

Routes of Administration

There are various methods by which one can deliver naloxone to a patient. The most commonly used are intravenous, intramuscular, subcutaneous, and intranasal routes of administration. In this section, the common dosages for each route will be discussed, as well as the benefits and potential problems that present with the different methods.

IV administration of naloxone can be delivered in one of two ways: as a single, immediate dose or as an infusion. For the single dose, a 0.4mg bolus of naloxone is delivered per milliliter of solution[54]. This type of administration has the greatest bioavailability and the fastest onset of action[52]. On the other hand, the IV infusion method is used to deliver a given dose over an extended period of time. Naloxone can be added to 0.9% sodium chloride (saline) or 5% dextrose, with a typical dose being 2mg in

500ml solution[54]. The extended release of naloxone from IV infusion is beneficial in preventing opioid intoxication from recurring.

While IV administration may be the preferred route and recommended in severe emergencies, there are some drawbacks for this method, such as establishing access to the vein[54]. Not only does this take time, but it also may be difficult to obtain during opioid overdoses due to collapsed veins or phlebitis if the patient frequently injects drugs. Lastly, using a needle provides a risk to the medical provider because there is the potential for accidental needle-stick injuries. In the United States, injection drug use is the primary risk factor for infection with the Hepatitis C virus and a leading cause for HIV transmission[71,72]. Using needles to administer naloxone places the provider at risk for blood borne viruses, and it can be concluded that IV administration is not the safest route for providing the antidote.

The next routes of administration to consider are IM and SC. These are grouped together because they share similar properties in regards to dosage and injection site. For instance, the 0.4mg dose can be delivered by a standard needle or by a prefilled autoinjector that recently became FDA approved in 2014 (see **Figure 4**)[52]. Additionally, the typical injection site is in the lateral thigh. In this injection region, the drug may be absorbed either intramuscularly or subcutaneously depending on how deep the needle is inserted into the patient.

Figure 4. IM/SC Naloxone Autoinjector. A depiction of EVZIO's naloxone autoinjector illustrating the design and safety features of the device. The autoinjector comes equipped with a speaker that verbally instructs an individual through the naloxone administration process[52].

The advent of the autoinjector is unique for naloxone and proves beneficial for several reasons. First, the autoinjector is easy to use with automated instructions and no need for prior medical training. This allows both medical professionals and laypersons (family, friends, bystanders) to use the device. Moreover, the autoinjector proves to be safer as the needle is initially hidden and retracts back within a case after the device has been used. With the transfer of blood-borne viruses being a major concern, the autoinjector's ability to retract the needle and lock it into place helps eliminate some of the danger. Furthermore, since the needle is hidden the entire time, laypersons who have adverse reactions to the sight of needles will be more willing to help an individual during an overdose. Lastly, both IM and SC routes of administration avoid the first-pass metabolism effect.

However, there are potential problems with the use of the autoinjector and IM/SC routes of administration. Specifically, the absorption is slower than IV. While one may

save time with how quickly they can administer the dose IM or SC, the pharmacokinetics are indeed slower than IV. Also, if the naloxone is delivered via the autoinjector, then only one dose may be available if additional autoinjectors are not present. This could prove problematic if the patient does not respond to the initial 0.4mg dose and further medical help is not nearby.

Intranasal naloxone is becoming increasingly popular as a needle-free way of administering the opioid antagonist (see **Figure 5**). In November of 2015, IN naloxone became FDA approved for the first time, but prior to this, off-label IN delivery of naloxone via atomizers frequently occurred[55]. There are recent papers and studies evaluating the effectiveness of IN administration of naloxone compared to IV and IM routes[73,74,75,76]. The common conclusion amongst all these studies is that the IN route is an efficacious and safe method to administer the drug. IN naloxone has been shown to increase GCS scores and increase respiratory rate among opioid overdose patients[74]. GCS refers to the Glasgow Coma Score, which is a neurological exam that provides insight into an individual's state of consciousness. Additionally, a few studies discovered that among opioid overdose patients, the IN route of delivery of naloxone is as clinically effective as IV naloxone at reversing the depressive respiratory effects[74,75]. In particular, one study looked at the effectiveness of IN delivery in the prehospital setting[76]. For suspected opioid overdoses in this study, paramedics would administer IN naloxone prior to establishing IV access, after which they would deliver another dose parenterally. The results indicated that 83% of patients awoke from their opioid induced state before IV

naloxone could be administered[76]. All of these clinically relevant examples illustrate the effectiveness of IN delivery of naloxone in emergency situations.

Figure 5. Naloxone Nasal Spray. The picture depicts the IN naloxone delivery device by NARCAN. Each device contains one dose that is sprayed into the nostril of an individual who is experiencing an opioid overdose[77].

The popular brand name naloxone, NARCAN, contains a dose of 4mg per 0.1ml spray, and the package insert recommends to deliver one spray in each nostril[55]. This increased dose accounts for the poorer bioavailability of the spray naloxone compared to the injectable version. The specific benefits of the IN route of administration include its safety, ease of use, and rapid administration. With no needles involved, the risk of obtaining a needlestick injury and potentially HIV or HCV is substantially reduced. Furthermore, the easy to use nasal spray makes the drug available to be used by non-medical professionals, such as bystanders and police officers. This rapid administration

device could also make the IN route superior in times of emergency until IV access is gained. Lastly, the IN route provides additional benefit due to its non-invasive nature, avoidance of first-pass metabolism, and administration into the nostril where there is a large surface area for absorption[78]. However, there are potential risks involved. The most significant downside to IN delivery is that the patient must have adequate blood flow through the nose[76]. If there is a problem with this perfusion, the drug will not necessarily work.

A less prominent method for using naloxone, but one that should be considered, is administration via a nebulizer. There have been documented accounts of physicians in the emergency department (ED) using a nebulizer to deliver naloxone over an extended period of time when intravenous access could not be gained for an infusion. One case describes the effectiveness of mixing 2mg of naloxone with 3ml of saline in reversing methadone intoxication[79]. Within 5 minutes of administration, the patient's oxygen saturation improved from 61% to 100%[79], indicating the successful delivery of the naloxone. Similarly, one study was conducted in an ED where suspected opioid intoxicated patients, with a respiratory rate greater than 6 breaths per minute, received 2mg of naloxone mixed with 3ml of saline via a nebulizer[80]. The study found that nebulized naloxone decreased the need for supplemental oxygen while also improving the patients level of consciousness[80].

Although this method proved effective in the aforementioned cases, there are many cautions and unanswered questions in regards to nebulized naloxone. First, the patient must still have some form of respiratory drive in order to receive the drug into the

airways where it will be absorbed[79]. Secondly, this route of administration is not well studied or documented.

Overall, the route of administration is not as important as ensuring adequate naloxone is delivered to the patient in a timely manner. Each method discussed has its own benefits and may be utilized effectively in specific situations. With the efficacy proven for IM, SC, and IN methods, and with the advent of newer delivery devices, such as EVZIO's autoinjector, the ability to utilize the medication is no longer limited to trained personnel. Rather, the tools are now in place for the discussion to shift to who should be allowed access to the medication and how to implement this decision nationwide.

Efficacy of Naloxone on Fentanyl Overdose

In the previous sections, the pharmacology of naloxone and its role in the treatment of opioid overdoses has been discussed. While the clinical efficacy of naloxone has been demonstrated in general for the opioid class, the following will describe the therapeutic benefits of naloxone in regards to fentanyl overdoses.

There are several case studies illustrating naloxone's effectiveness in reversing fentanyl overdoses. First, in a study regarding fentanyl based anesthesia, it was found that 10μg/kg (0.7mg/70kg) and 15μg/kg (1.05mg/70kg) of naloxone was needed to restore spontaneous respiration and minute volume in individuals experiencing respiratory depression after having been given 0.1mg and 0.2mg of fentanyl respectively[81]. This report shows that naloxone is an effective antidote and that an increasing dose-response relationship exists. This means that more naloxone is needed to reverse a fentanyl

overdose as the fentanyl dosage increases. Another example of naloxone effectively restoring respiration comes from a case report of an individual who overdosed on heroin that was unknowingly cut with fentanyl. In this situation, the patient was in respiratory arrest and received a total of three doses of naloxone, with one intranasal dose given on scene by his wife, one by paramedics in route to the ER, and a third by physicians in the ER[82]. This case report illustrates several interesting factors. Specifically, naloxone was able to reverse the overdose, showing naloxone's effectiveness on reversing fentanyl overdoses. However, the case also showed that multiple doses of naloxone may be needed to overturn a fentanyl overdose, reflecting the lethality of fentanyl. It is important to note that fentanyl's half-life ranges from 7-27 hours depending on the route of administration, as described before[23]. Moreover, the dose of fentanyl will play a contributing factor. Larger doses of fentanyl are expected to induce lasting effects because the plasma level of fentanyl will remain above the threshold level for respiratory depression during the distribution phase[83]. With naloxone's half-life lasting only 0.55 to 2.08 hours, the need for additional medical follow up after the first dose of naloxone appears warranted[52,53,54,55]. This is due to the fact that recurrent respiratory depression can also result from mobilization of fentanyl from tissue stores, which is the rate limiting step for fentanyl elimination[83]. While these examples only represent a small sample size, naloxone is shown to have the potential of reversing fentanyl overdoses.

By looking at binding kinetic data, it is possible to analyze how fentanyl and naloxone work at the μ-opioid receptor to gather additional insight into naloxone's effectiveness as the antidote. k_{on} and k_{off}, which represent association and dissociation

rate constants, are important defining characteristics of these drugs. For instance, fentanyl has a $k_{on} > 100\mu mol^{-1}min^{-1}$ and a $k_{off} > 100min^{-1}$ [84]. This information is significant because the greater the rate constant, the quicker the molecule can bind or dissociate from the receptor. Since fentanyl has both a k_{on} and k_{off} greater than $100\mu mol^{-1}min^{-1}$ and $100min^{-1}$ respectively, it will bind to and dissociate from the μ-opioid receptor almost instantaneously. On the other hand, naloxone has a $k_{on} = 47 +/- 21\mu mol^{-1}min^{-1}$ and a $k_{off} = 0.85 +/- 0.33min^{-1}$ (see **Table 1**)[85]. With both of these numbers being significantly smaller than fentanyl's rate constants, the data indicates that naloxone's binding characteristics are much different. The numbers show that while naloxone may take longer to bind to the μ-opioid receptor, it will stay bound for longer than fentanyl. This helps reverse the fentanyl overdose as fentanyl is unable to bind the occupied receptors. Additionally, naloxone shows greater affinity for the μ-opioid receptor compared to fentanyl[85]. This was determined based off of the K_i values ($K_i = k_{off}/k_{on}$), with the smaller K_i reflecting a greater affinity for the μ-opioid receptor. These values were discovered for both fentanyl and naloxone based off of their ability to displace bound [^{3}H]Alvimopan and [^{3}H]Diprenorphrine from the μ-opioid receptor (see **Table 1**)[85]. The results indicate that less naloxone was needed to displace the bound μ-opioid receptors regardless of the molecule initially bound, thus reflecting naloxone's lower K_i value and higher affinity for the receptor than fentanyl. This information is also evidence of naloxone's effectiveness as an antidote for fentanyl overdoses because once naloxone is bound, fentanyl is less likely to displace it due to binding affinities.

Table 1. Binding Kinetics at the μ-Opioid Receptor.

	k_{on} ($\mu mol^{-1}min^{-1}$)	k_{off} (min^{-1})	K_i (nM) [^{3}H]Alvimopan	K_i (nM) [^{3}H]Diprenorphrine
Naloxone	47	0.85	5.4 (3.5-8.3)	3.3 (2.7-4.1)
Fentanyl	>100	>100	34 (20-57)	14 (6.6-30)
Morphine	45.3	7.25	28 (16-50)	20 (13-31)

When referring to binding kinetics, it follows that an opioid with lower values of k_{on} and k_{off} is more difficult to displace from the μ-opioid receptor with naloxone[53]. This means an opioid that binds for a longer period of time will be more difficult to reverse and may require prolonged delivery of naloxone via an intravenous infusion[53]. To relate this concept to our current topic, a comparison will be made between fentanyl and the prominent opioid morphine in order to illustrate the potential therapeutic benefits of naloxone on fentanyl. First, morphine has both a smaller k_{on} and k_{off} value than fentanyl (see **Table 1**). These values indicate that morphine takes longer to both associate and dissociate from the μ-opioid receptor than does fentanyl. However, fentanyl has a greater ED_{50} and a quicker time to peak effect than morphine, which shows fentanyl's greater potency[86]. Fentanyl, which was shown to reach its peak effect in 5 minutes compared to morphine in 15 minutes, is more lipophilic than morphine and is therefore capable of penetrating fatty areas more rapidly, such as the blood-brain barrier[86]. In short, morphine, with its extended duration of action at the μ-opioid receptor, will be more difficult to reverse with naloxone compared to fentanyl, as long as naloxone is given promptly following the overdose.

Although only a few studies detailing naloxone effectiveness in overturning fentanyl overdoses exist in the literature, there are numerous reports of naloxone's benefits on morphine overdoses. For example, there are cases of naloxone reversing oral morphine overdoses, intrathecal morphine overdose, and even accidental morphine overdoses in newborns[87,88,89]. Since morphine is kinetically more difficult to displace then fentanyl, these morphine overdoses illustrate that naloxone has the potential to reverse fentanyl overdoses. While additional factors, such as time of naloxone administration and fentanyl's greater ED_{50}, will play a significant role in reversing a fentanyl overdose, this comparison to morphine allows one to conclude that naloxone can theoretically be used as a successful antidote for fentanyl.

To conclude, naloxone has been shown clinically and pharmacologically to work on reversing the effects of a fentanyl overdose. While a single dose of naloxone may or may not be adequate, as described in the previous clinical examples, naloxone proves to be the most effective emergency treatment option currently. Furthermore, the kinetics work in naloxone's favor. When receptor kinetics are fast for the opioid agonist, such as with fentanyl, it is proven that higher doses of the antagonist naloxone will result in a faster reversal[53]. Therefore, with the overall documented safety of naloxone as a μ-opioid receptor antagonist and with the demonstrated clinical benefits of providing multiple doses of naloxone in combating fentanyl overdoses, naloxone can ultimately be effective both inside and outside the hospital even if multiple doses need to be given to a patient.

Although IV fentanyl is not considered a long acting opioid, the transdermal patch can produce these effects. Thus, an initial dose of naloxone may provide the necessary

initial relief from respiratory depression, but IV infusion may be required for long term reversal. Moreover, there may be unforeseen complications if a patient swallows a long-acting transdermal fentanyl patch or if an individual abuses multiple patches because a significant reservoir of the drug can build up subcutaneously. With naloxone's half-life being shorter than fentanyl's, an intravenous infusion of naloxone may be the only method to reverse these special situations.

PUBLIC ACCESS TO NALOXONE

Overview

In the previous sections, the details and dangers of abusing the recently popular opioid fentanyl were established. The antidote naloxone was also shown to be a safe drug that was easy to administer, with scientific evidence and documented accounts illustrating its effectiveness on reversing fentanyl overdoses. The topic now transitions to public access to the antidote as a means of combating the fentanyl epidemic. Currently, there is no uniform structure amongst individual states' naloxone access laws[90]. As of February 2016, 42 of 51 jurisdictions in the United States (all 50 states plus the District of Columbia) do have laws that address access to naloxone for people at risk of opioid overdose[91].

The main issue from a public health perspective lies in making naloxone readily available to the individuals who need it. There exist several pertinent variables that divide individuals' opinions on the topic. For example, expanding access to naloxone requires clear rules governing the prescribing and dispensing of the medication. Additional consideration is also needed to devise a plan with the purpose of addressing the counseling of patients, their contacts, and their families regarding recognition of overdoses, administration of naloxone, provision of rescue breathing, and calling of 911 for emergency support[92]. The interesting factor underlying this subject is that the patients who require naloxone administration must rely on others, a so-called "Good Samaritan", to administer the drug because individuals who are overdosing on opioids are rendered

incapacitated. This raises legal issues, since the drug prescribed to a particular person will ultimately be administered by a 3rd party or delivered to someone who was not prescribed the drug. In certain jurisdictions, this action raises red flags as it would be considered practicing medicine without a license[91]. Therefore, there are several legal barriers that must be examined, including prescriber ability to write an unusual prescription for naloxone, prescriber immunity from legal action, and Good Samaritan immunity from legal action[92].

Also, in some jurisdictions basic EMT services do not stock naloxone and/or are not permitted to administer any medication by injection. On top of this, emergency response times can vary greatly depending on where one lives. Rural locations, which are the sectors most stricken by fentanyl, are thought to be hindered the greatest. However, this also hinges on the fact that an ambulance is actually called. It is known that some 3rd parties fail to call for help due to fear of being arrested by police authorities who would additionally respond to the scene of an overdose[92]. Lastly, expanding access to naloxone may help to decrease healthcare cost because overdose patients who are revived with naloxone in the prehospital setting could require less additional procedures, such as intubation, in the emergency department[93]. With the recent development and FDA approval of newer naloxone delivery systems[52,55], the stage appears as receptive as ever for a push to expand the public's access to naloxone.

Current Naloxone Access

Many of the laws governing the availability of naloxone are reflected in its status as a prescription medication. Physicians, prehospital first responders, and laypersons are

important groups factored into the naloxone discussion and each have a defined role within the current system. The following section will investigate the regulations and consequences surrounding the aforementioned players, while also analyzing the distribution and coverage of naloxone.

Physicians are ultimately the most powerful individuals under today's laws regarding naloxone access. Since naloxone is a prescription medication, a physician must physically write a prescription for take-home naloxone or issue a standing order allowing others to distribute the drug. In regards to the physical prescriptions, these can either be written to a patient or a 3rd party, such as friends or family. According to the U.S. Substance Abuse and Mental Health Services Administration (SAMHSA), physicians should consider prescribing naloxone to several groups of at risk patients, such as individuals discharged from the ED for opioid overdose or past opioid abusers who are recently released from prison[94]. With respect to 3rd parties, it is interesting to note that as of February 2016, only 39 of 51 jurisdictions authorize physicians to write naloxone prescriptions to non-patients[91]. While legally some physicians may be unable to write these prescriptions, other are self-limited by their willingness. In a study examining physicians' knowledge and enthusiasm for prescription naloxone, it was found in almost 600 physicians that only 23% had heard of prescribing naloxone to intravenous drug users (IDUs) and 54% indicated they would never consider prescribing naloxone to an IDU patient[95]. Despite the small sample size, it is obvious that some physicians have negative attitudes towards IDUs that can hinder these individuals' access to naloxone. Another factor influencing physicians' willingness to prescribe naloxone is the potential

liability that may come with these prescriptions. This fear has legal basis as only 30 jurisdictions currently provide criminal immunity for physicians who prescribe, dispense, or distribute naloxone to laypersons[91]. Even though naloxone-related legal action may reflect other risky aspects inherent to the usual practice of medicine, some articles that target physicians and prescribers preach conservative values and apprehension on the topic of naloxone. Specifically, one article states that despite the evidence demonstrating the safety and effectiveness of prescription naloxone to laypersons, physicians should try to mitigate risk because more comprehensive naloxone access laws are still needed before physicians are void of legal action[90].

When discussing the topic of prehospital first responders, unique groups, such as paramedics, emergency medical technicians (EMTs), and police officers, will be considered. In terms of medical training and experience, it follows that paramedics have the most, whereas police officers possess the least. It is established that within all U.S. jurisdictions, paramedics are able to deliver naloxone[96]. The problem with EMS structure, however, lies with the basic EMT level where only select jurisdictions permit EMT delivery of naloxone. While more jurisdictions are looking to modify their existing laws allowing for greater access, there still exists other hurdles to clear, as states vary in EMS naloxone dosages and routes of administration[96]. These discrepancies are potential road blocks for sweeping reform, but the FDA approval of IN naloxone could help alleviate these stresses.

Although police officers are not medically trained, they are in a unique position to provide assistance in times of fentanyl overdoses. Police officers will be dispatched to

reports of drug overdoses and may be the first to arrive on scene, making their access to the antidote imperative. In 2014, more than 220 U.S. law enforcement agencies permitted their officers to carry naloxone, and the number of agencies has most likely substantially grown since[97]. For police officers to be able to administer naloxone, current regulations require they do so under standing protocol from a physician[97].

For layperson distribution of naloxone to be a possibility, 3rd parties must have legal protections to be able to obtain the drug and further administer the medication to someone else. Presently, there are only 30 jurisdictions that make laypersons immune from criminal liability when administering naloxone to someone who is thought to be overdosing[91]. This can cause problems as laypersons may be reluctant to act in an emergency situation due to the potential repercussions. Along this same line is the idea of laypersons being labeled as Good Samaritans when actively responding to overdose victims. The first Good Samaritan laws with regards to overdoses were passed in 1997 with the idea of incentivizing laypersons to seek help when they witness an overdose. This was in response to individuals who would flee the scene or try to solely provide medical treatment out of fear of being arrested by police for laws they may be breaking themselves. Today, 36 jurisdictions have laws that address Good Samaritan overdose prevention[98]. However, only 13 jurisdictions provide individuals with complete protection from arrest, charge, and prosecution from controlled substance possession laws. Other jurisdictions that have immunity laws may only protect against drug charges and subsequent prosecution, but the statutes do not guarantee that a person will not be arrested. In some jurisdictions that do not provide full immunity, there exist laws that

protect people from prosecution for possession of drug paraphernalia (24 jurisdictions) or that will consider the actions of the Good Samaritan as a mitigating factor during sentencing (18 jurisdiction)[98]. A mitigating factor for these individuals includes any evidence or information presented to the court regarding the defendant that might result in reduced charges or a lesser sentence; thus, this potentially incentivizes laypersons to call for help even if they themselves were breaking the law with a controlled substance. Overall, these criminal laws pre-date the growing overdose epidemic and reform may be needed to welcome the help of bystanders in the public health fight against fentanyl deaths.

As alluded to before, naloxone can be distributed to laypersons from a pharmacy through a direct prescription from a physician or under the pharmacist's discretion if acting under a standing order from a physician. There are currently 33 jurisdictions that authorize prescriptions of naloxone by standing order for individuals at risk of opioid overdose[91]. A standing order refers to a specific physician's order that can be carried out by other healthcare workers, such as a pharmacist or trained employee of a harm reduction program, when predetermined conditions outlined in the protocol are met[91]. In a small study researching pharmacy practices across the U.S., it was discovered that 83% of the pharmacies require a physician's prescription prior to dispensing naloxone while only 17% are able to exercise pharmacist prescriptive authority and actively seek out at risk patients to discuss take-home naloxone under standing protocol[99].The majority of pharmacies in this study illustrate the more traditional model of dispensing naloxone pursuant to a prescription, whereas the 17% depict a public health model in which

naloxone distribution is proactively sought out by pharmacists[99]. Another method of distribution follows more of this public health model as naloxone distribution programs try to target at risk patients outside the pharmacy setting[100,101,102]. Some of these programs date back to 2003 where they target their population through public health measures, such as needle exchange services. While these successfully exemplify the use of standing order from a physician, there were only approximately 200 of these programs distributing naloxone across the U.S. as of 2014[102]. Additional reports about these services also suggest that they struggle to obtain and distribute naloxone for periods of time due to the cost of naloxone relative to the available funding[103].

Traditionally, since naloxone was previously only an FDA approved injectable drug, the medication was not covered under most outpatient prescription plans, including state Medicaid programs[99]. Now with the approval of naloxone via both autoinjection and nasal spray, insurance has responded accordingly by increasing coverage. However, depending on an individual's carrier, coverage for naloxone can vary significantly. For example, an insurance company may cover emergency naloxone delivered in a medical setting, but may not reimburse for take-home naloxone prescriptions. This is not trivial as the price of naloxone can be expensive, especially if part of the targeted audience includes poorer, opioid abusers. EVZIO's suggested price for their autoinjector product ranges from $450-600[104]. Comparing this to the generic IV injectable form that retails for as low as $7 per dose in the US, trying to pay for naloxone out of pocket is not feasible. While insurance would bear most of this cost, it requires that the insurance actually reimburses for a naloxone prescription[104].

Discussion

Proposed Plan

There are several complex components and key variables that need to be considered when facing the possibility of expanding naloxone access to the public. It will take more than addressing one law or rewriting a given statute to resolve a public health crisis of this magnitude. With this in mind, federal agencies are most adept to implement an initiative through their ability to increase nationwide awareness, fund the operation, and coordinate naloxone access[105].

The proposed changes will be discussed in a top down fashion beginning with physicians. Assuming naloxone is to remain a prescription drug, both laws and educational sessions must be developed to incentivize providers to support this movement. First, there should be unequivocal protection provided to physicians from criminal liability when they provide naloxone to patients or 3rd parties. Additionally, physicians should be able to prescribe naloxone to anyone, as long as there is valid reasoning, and should not be limited in their ability to write standing orders for naloxone distribution by other health care workers. These changes not only provide needed protection to physicians, but also offer them the platform to initiate change themselves without fear of repercussions. For example, it allows physicians to proactively target at risk patients for fentanyl overdose, such as individuals using long-acting transdermal fentanyl patches. This initiative would encourage providers to potentially co-prescribe naloxone with fentanyl patches and thus propose the idea of take-home naloxone in a less

confrontational manner[99]. Lastly, a development to provide continuing education to physicians on the subject of naloxone can help increase awareness of the importance surrounding prescription naloxone and influence personal bias against opioid addicts. It is known that many physicians possess negative attitudes towards intravenous drug users and fear professional disapproval for treating these individuals[95]. Therefore, helping to target this problem at its source will positively influence physicians to bolster the public health effort to cut down on fentanyl related overdose deaths. Overall, it is pertinent that physicians feel protected and are comfortable prescribing naloxone as their participation is crucial to driving this project.

In regards to first responders, it was already stated that every paramedic is able to legally deliver naloxone while only certain jurisdictions permit basic EMTs to provide the antidote[96]. With the FDA approval of IN naloxone, every first responding agency should carry naloxone and should be allowed to deliver the medication. A study concluded that the average EMT arrival time to their patient was 5.9 minutes, while paramedic arrival was more prolonged at 11.6 minutes. If EMTs on scene had to request paramedic support, however, arrival time proved to be even longer at 16.1 minutes[96]. Since EMTs arrive significantly earlier to their patient than paramedics, it would make sense that they should be allowed to deliver naloxone. This is further supported by the fact that earlier naloxone delivery will also significantly increase a patients chance of survival during a fentanyl overdose. Moreover, basic EMTs outnumber paramedics approximately 3 to 1[97]. Being able to equip more individuals, especially medically trained personnel, with naloxone is the ultimate goal. Thus, EMTs must be afforded the power to

carry and deliver IN or SC autoinjection naloxone while covered under similar protections awarded to paramedics.

Another group of first responders that should be extended full protection from criminal liability in regards to delivering naloxone is law enforcement officers. Police officers are approximately 10 times more numerous than EMTs nationwide, and as referenced earlier, they regularly are the first to respond on scene of an overdose[97]. With naloxone administration carrying similar or lower risks than the routine activities that officers commonly engage in, federal agencies should put laws in place to actively encourage every officer to carry and deliver naloxone to suspected overdose victims[97]. Using the same time argument as before, police officers also may be able to deliver the medication the quickest out of all first responders and therefore could save potential lives from fentanyl overdoses. In short, there needs to be an implemented statute explicitly permitting law enforcement officers to administer naloxone in the event of an overdose emergency. This in turn will stimulate more participation from police officers and will incite law enforcement agencies to be more proactive in establishing naloxone training programs for their officers[97].

Both the autoinjector and intranasal spray are naloxone administration devices designed to be used by non-clinicians. The safety and performance of layperson use of the autoinjector was evaluated in a study where random subjects were compared to nurses. It was concluded that SC administration via an autoinjection by laypersons was similar in performance and safety to SC administration via a syringe by nurses, and even proved to better in terms of pain and patient preference[106]. Since laypersons are more

than capable of delivering naloxone with currently FDA approved devices, Good Samaritan laws should be expanded so that all laypersons are immune from criminal liability when administering naloxone. Furthermore, it has been demonstrated in multiple studies that take-home naloxone kits for laypersons are greatly beneficial[102,107,108]. There exists a strong correlation between take-home naloxone programs and overdose survival, as a study indicated with a 96% success rate on over 2,300 naloxone administrations across 21 different states[108]. A compiled data set from surveyed organizations in the U.S. between 1996 and 2014 depicted successful overdose reversals in at least 26,000 cases[107]. This report states that over 150,000 naloxone kits were provided during this time frame and the number of successful overdose reversals is likely grossly underreported. These studies indicate the effectiveness of wider distribution of naloxone to laypersons. With laws granting greater accessibility and protection for 3rd parties, the amount of naloxone kits distributed nationwide will greatly increase along with successful overdose reversals. Wider access and distribution to community members, who have already proven to be proficient at delivering naloxone, will ensure individuals affected by the fentanyl epidemic are provided the greatest chance at survival in the event of an emergency overdose.

Intravenous drug users themselves represent a special group of individuals that need consideration for additional safeguards. Specifically, like 13 current jurisdictions, all individuals should be protected from arrest, charge, and protection from controlled substance possession laws; this is assuming the individual is not a known drug dealer and the amount found is minor. This law is imperative because 3rd parties need to be

emboldened to stay with overdose patients and call for additional emergency assistance. Therefore, it is obligatory to try to reduce fear of potential arrest and subsequent consequences in bystanders responding to fentanyl overdoses. Drug users are also critically important individuals to target with naloxone access because of their likelihood to witness or experience an overdose themselves. While this appears to be common sense, numerical data showcases the essential nature of this proposed initiative. Depending on the study, it is reported that opioid abusers are roughly 50% likely to personally experience at least one overdose in their lifetime and 76-79% likely to witness at least one overdose[102,109]. This places opioid users in an advantageous position to provide naloxone to another individual. Furthermore, drug users' receptiveness to drug education and naloxone training is well documented[100,109,110]. Brief educational sessions have proven effective in increasing the use of naloxone during overdose[100,110]. Reports also indicate that individuals who attended these training initiatives had previously acquired drug knowledge and proceeded to share the newly learned knowledge with family and peers[109,110]. Simply put, opioid users may be the most important individuals to carry naloxone and should be incentivized, via more liberal Good Samaritan laws, to deliver the antidote and to remain with overdose victims until further help arrives. The ability of federal agencies to actively engage this target group will prove vital in reducing fentanyl overdose deaths.

If the proposed naloxone access changes are made, there will be increased opportunities for expanded distribution to make naloxone readily accessible to the laypersons who need it most. Pharmacists are in a unique position to contribute. If

physicians are protected and incentivized to issue more standing orders, pharmacists would be able to target additional populations that may be missed. An example of this may be individuals with prescribed transdermal fentanyl patches who may not be in contact with existing providers of take-home naloxone. Also, pharmacists would be able to distribute naloxone to individuals who are fentanyl abusers who may be avoiding distribution services due to concerns of anonymity[111]. Increased standing orders will further allow other specialized services to provide naloxone education, training, and distribution to laypersons. Specifically, programs such as needle exchanges, substance abuse treatment facilities, veterans administration health care systems, primary care clinics, emergency departments, HIV clinics, and jails have heightened access to target populations who could greatly benefit from naloxone distribution. There needs to be added support and funding to these services, which are known to struggle with financial and reimbursement issues, in order to influence growth and ensure certain populations can obtain the necessary safety training and education to accompany their take-home naloxone. One entity that expanded reform should prioritize is emergency departments. Results from a study on opioid overdoses discovered that there is a direct association between frequent ED visits for overdoses and greater risk for subsequent hospitalizations and near fatal events[93]. This demonstrates the need for increased availability of take-home naloxone for at risk individuals upon exit from the ED. A hospital based study took this approach and adopted policy to provide overdose education and naloxone to all patients deemed high-risk prior to discharge from the ED through the use of both inpatient and outpatient pharmacies. Upon follow up communication with this targeted

group, it was revealed that over one-third of these individuals witnessed an overdose and delivered naloxone successfully to the victim[112]. It is for these aforementioned reasons that federal support in growing preexisting and in developing new naloxone distribution programs is paramount in spreading the antidote to additional at risk sectors plagued by fentanyl overdoses.

Under naloxone's current status as a prescription drug, federal agencies are needed to make naloxone more affordable. One area to address is state run Medicaid insurance programs. To advance fentanyl overdose prevention, all state insurance programs should cover naloxone allowing all individuals the capability of procuring naloxone if prescribed. Also, there needs to be encouraged development of generic versions of IN naloxone. Federal funding is a required factor to this plan because the naloxone market is not widely considered to be a valuable investment by pharmaceutical companies[105]. Therefore, additional help and resources must be given to these companies to develop an affordable generic alternative to the easily-administrable, branded products.

An alternative approach to bypass insurance and availability issues would be to switch naloxone to over-the-counter status. In order to switch a drug's status to over-the-counter in the U.S., a manufacturing company typically requests the change and must provide the necessary studies and endure the administrative processes[95]. However, drug companies may not choose this route for monetary reasons because they believe product sales would not generate the same profit that prescription medications covered by health insurance would confer[104]. Despite this, autoinjector and nasal spray naloxone devices are well positioned for the switch to over-the-counter market as they have already been tested

to be used by laypersons without medical supervision[104]. If pharmaceutical companies are not incentivized to make the switch by the public health community, then the FDA may need to exercise its legal authority to pursue reclassification of naloxone to over-the-counter status in the interest of the public[95]. The advent of an affordable, easy to use naloxone product with over-the-counter status would undoubtedly facilitate greater public access and further advance prevention of fentanyl overdoses.

Although there are several factors to pursue when discussing the plan of increasing public access to naloxone, it is fair to state that a liberal initiative where the priority is to reach the most individuals is warranted to combat the growth of fentanyl. Laws encouraging the prescription of naloxone and granting bystanders more protective Good Samaritan rights have few negative effects, can be implanted at little or no cost, and have the potential to save both lives and resources[113]. These proposed statutes should be implemented immediately while a plan to switch naloxone to over-the-counter status is further developed. If and when naloxone is to move to over-the-counter status, many of the legal barriers that currently exist will be eliminated and this action may prove to be the easiest overall solution to reducing fentanyl overdose deaths.

Concerns

While many positives have been explained regarding the public expansion of naloxone, there are several concerns about implementation and feasibility that must be discussed. First, there is the idea that labeling a population as "at risk" patients, in order to supply naloxone to, may create personal and public stigma[111]. This notion is valid and the proposed plan described before has measures to diminish this fear. Primarily, the

proposed plan will approach the fentanyl overdose death problem as a public health measure with heavy community involvement. With this in mind, the increased distribution of naloxone will also be accompanied by increased educational services targeting everyone from physicians to drug users themselves. Physicians will be trained to co-prescribe naloxone with fentanyl patches as a preventive measure, while community pharmacists can approach targeted groups from a non-confrontational manner. Although certain at risk groups will be identified, such as overdose patients upon exit from the ED, the expansion of naloxone access and protection laws reach other groups as well. This plan additionally pushes for greater first responder involvement and tries to encourage laypersons to actively participate with more liberal Good Samaritan laws.

Another concern involves the perception that greater naloxone access will act as a safety net, increasing substance abuse or inappropriate self-medication practices by pain patients[111]. Currently, there is no evidence to support this speculation and the fentanyl epidemic continues to grow rapidly under the current naloxone policy, which insists changes need to be made. Expanding public access through distribution studies has only produced positive results and wider scale implementation should be tested. Although, there is a realistic concern that laypersons delivering or receiving the antidote may think naloxone is the remedy and may avoid seeking further medical follow up. Since there is a likely chance that a single dose of naloxone will deliver initial positive results, all individuals involved in the overdose may believe the patient has completely overcome the problem, not realizing the possibility of intoxication and respiratory depression

recurring. To avoid this potentially fatal misjudgment, the devised plan has educational sessions integrated into naloxone distribution to instruct laypersons on this danger and to call for additional emergency assistance. Also, with more laws protecting laypersons from criminal liability and potential drug related crimes, these individuals are incentivized to follow the teaching provided with the naloxone kits.

In terms of the drug market, there is growing apprehension with the current state of naloxone. With the development of the newer delivery systems and patent protections, the concern is that the price of naloxone will increase as market exclusivity will prevent new drug entry[104]. This is where the FDA and other federal agencies become critically important. The proposed plan hinges on the fact that these agencies must financially support the development of affordable generics for laypersons or initiate the switch of naloxone to over-the-counter status. In order for the proposed solution to the fentanyl problem to come to fruition, federal agencies need to play an integral role in developing change.

An additional question to address is whether the proposed changes are economically feasible or even worthwhile. Policymakers generally assess this by measuring quality-adjusted life-years (QALYs), with an incremental cost of less than $50,000 per QALY gained considered to be cost-effective. In a study evaluating the cost-effectiveness of naloxone, the results indicated that expansive naloxone distribution would be expected to reduce mortality and be cost-effective even under conservative assumptions[114]. If cost-effectiveness is measured in relation to reducing healthcare spending, public access to naloxone may also prove beneficial in this manner. Another

study on 19,831 unique overdose patients reported that 58% of ED visits led to hospitalization and 10% led to more fatal events, which all contributed to high healthcare spending[93]. Public distribution of naloxone may help reduce this spending by limiting the severity of hospitalizations since patients brought to the ED following naloxone administration may require fewer additional procedures. A study showed that the majority of patients with opioid overdoses, who still had pulses and blood pressures by the time paramedics arrived, were easily resuscitated with naloxone in the prehospital setting. Out of 443 patients treated with naloxone and transported to the hospital, only 12 (2.7%) were admitted to inpatient care[115]. By reducing in-hospital spending and demonstrating a cost much less than the standard threshold per increase in QALY, naloxone will prove cost-effective. However, unless federal agencies help implement change for more affordable generic versions, naloxone will likely prove too costly for resource-constrained community or governmental distribution programs[104].

Gaps do exist within this current study that merit comment. First, many of the mentioned studies and referenced laws were conducted or written when only IM/SC and IV naloxone routes of administration were FDA approved. This is significant for a couple of reasons. One, this gives exciting indications regarding future implementation of public access to autoinjector and nasal spray naloxone. If so many overdose reversals and successful outcomes came from laypersons using needle injections, only additional positive results will follow with more user friendly devices. The other significant reason is that approval of IN delivery may be the piece that was critically needed to persuade public policy makers to move forward with more liberal access laws due to the increased

safety measures. However, a potential drawback with the referenced studies is the built in bias as many results relied exclusively on self-reported outcomes from the laypersons who issued naloxone to overdose victims[108]. This could result in skewed data in either direction, meaning successful results could be over or under reported. Importantly, though, is the general consensus that layperson use of naloxone is effective to some degree and saves more lives than the alternative of no naloxone access. With this in mind, public health agencies need to conduct more advanced studies during the proposed increase in naloxone access and distribution to conclude more accurately on naloxone's effectiveness. Also, with FDA approval of IN devices being so recent, additional studies should concurrently evaluate the differences in performance between nasal spray and autoinjection devices.

Conclusion

In general, the public is becoming increasingly aware of the fentanyl epidemic, as evidenced by recent celebrity deaths, but the public has yet to be instructed on a response. The suggested plan in this paper incorporates the encompassing aspects of several smaller-scaled opioid overdose and naloxone distribution programs tested in the United States[101,116]. The core element is an integrated approach where all members of the community are recruited and incentivized to help reduce overdose deaths. These programs clearly illustrate that effective public health interventions through increased naloxone access successfully lower opioid overdose mortality rates. Up until this point, the country has made some initial steps, such as the FDA approving a Risk Evaluation and Mitigation Strategy for extended release opioids[117], to try and reduce the opioid

overdose epidemic; however, it is clearly not enough as fentanyl death rates continue to grow at an alarming rate.

Realistically, a comprehensive plan where the prevention of fentanyl overdoses is approached from every angle, especially at the drug source, will take multiple years to develop and enact. With fentanyl abuse increasing, it is more evident than ever that a public health minded solution is needed now in the meantime to save lives. Increasing naloxone access to all individuals through increased protections placed on providers, first responders, and Good Samaritans alike is an easy to implement and cost-effective strategy that will make a significant impact immediately. The successful reduction in fentanyl overdose deaths will depend on community participation, and it is pertinent that the country acts now. It is for these reasons that the U.S. community demands reform to promote greater public access to naloxone with increased distribution.

REFERENCES

1. Manchikanti L, Kaye AM, Kaye AD. Current State of Opioid Therapy and Abuse. *Current Pain Headache Reports*. 2016;20(5):34. doi:10.1007/s11916-016-0564-x.

2. Nations U. *Report of the International Narcotics Control Board for 2008*. United Nations Publications; 2009.

3. CBHSQ Data Review: Associations of Nonmedical Pain Reliever Use and Initiation of Heroin Use in the United States. http://archive.samhsa.gov/data/2k13/DataReview/DR006/nonmedical-pain-reliever-use-2013.htm#endnote2. Accessed April 10, 2016.

4. Increases in Drug and Opioid Overdose Deaths — United States, 2000–2014. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6450a3.htm. Accessed April 10, 2016.

5. HAN Archive - 00384|Health Alert Network (HAN). http://emergency.cdc.gov/han/han00384.asp#_edn1. Accessed April 10, 2016.

6. Saunders DL, Messina J, Darwish M, Xie F, Leary KJ, Cantilena LR. Assessment of the Relative Potency of Fentanyl Buccal Tablet to Intravenous Morphine in Healthy Volunteers Using a Thermally Induced Hyperalgesia Pain Model. *Journal of Clinical Pharmacology*. 2012;52(6):870-879. doi:10.1177/0091270011407496.

7. Stanley TH. Fentanyl. *Journal of Pain and Symptom Management*. 2005;29(5, Supplement):67-71. doi:10.1016/j.jpainsymman.2005.01.009.

8. Arshad Z. Comparison between Transdermal Buprenorphine and Transdermal Fentanyl for Postoperative Pain Relief after Major Abdominal Surgeries. *Journal of Clinical Diagnosis and Research*. 2015. doi:10.7860/JCDR/2015/16327.6917.

9. Takakuwa O, Oguri T, Maeno K, et al. Long-term use of a once-a-day fentanyl citrate transdermal patch in lung cancer patients. *Oncology Letters*. March 2015. doi:10.3892/ol.2015.3022.

10. Prommer E, Ficek B. Fentanyl transmucosal tablets: current status in the management of cancer-related breakthrough pain. *Patient Preference and Adherence Journal*. 2012;6:465-475. doi:10.2147/PPA.S20655.

11. Portenoy RK, Hagen NA. Breakthrough pain: definition, prevalence and characteristics. *Pain*. 1990;41(3):273-281.

12. Amlani A, McKee G, Khamis N, Raghukumar G, Tsang E, Buxton JA. Why the FUSS (Fentanyl Urine Screen Study)? A cross-sectional survey to characterize an emerging threat to people who use drugs in British Columbia, Canada. *Harm Reduction Journal*. 2015;12(1). doi:10.1186/s12954-015-0088-4.

13. Wang D, Raehal KM, Bilsky EJ, Sadée W. Inverse agonists and neutral antagonists at μopioid receptor (MOR): possible role of basal receptor signaling in narcotic dependence. *Journal of Neurochemistry*. 2001;77(6):1590-1600. doi:10.1046/j.1471-4159.2001.00362.x.

14. Merlin MA, Saybolt M, Kapitanyan R, et al. Intranasal naloxone delivery is an alternative to intravenous naloxone for opioid overdoses. *American Journal of Emergency Medicine*. 2010;28(3):296-303. doi:10.1016/j.ajem.2008.12.009.

15. Kerr D, Kelly A-M, Dietze P, Jolley D, Barger B. Randomized controlled trial comparing the effectiveness and safety of intranasal and intramuscular naloxone for the treatment of suspected heroin overdose. *Addiction*. 2009;104(12):2067-2074. doi:10.1111/j.1360-0443.2009.02724.x.

16. Davis CS, Ruiz S, Glynn P, Picariello G, Walley AY. Expanded Access to Naloxone Among Firefighters, Police Officers, and Emergency Medical Technicians in Massachusetts. *American Journal of Public Health*. 2014;104(8):e7-e9. doi:10.2105/AJPH.2014.302062.

17. Kim D, Irwin KS, Khoshnood K. Expanded Access to Naloxone: Options for Critical Response to the Epidemic of Opioid Overdose Mortality. *American Journal of Public Health*. 2009;99(3):402-407. doi:10.2105/AJPH.2008.136937.

18. Peng PWH, Sandler AN. A Review of the Use of Fentanyl Analgesia in the Management of Acute Pain in Adults. *Journal of the American Society of Anesthesiologists*. 1999;90(2):576-599.

19. hq052215_National_Heroin_Threat_Assessment_Summary.pdf. http://www.dea.gov/divisions/hq/2015/hq052215_National_Heroin_Threat_Assessment_Summary.pdf. Accessed May 25, 2016.

20. Moon JM, Chun BJ. Fentanyl Intoxication Caused by Abuse of Transdermal Fentanyl. *Journal of Emergency Medicine*. 2011;40(1):37-40. doi:10.1016/j.jemermed.2007.10.075.

21. Firestone M, Goldman B, Fischer B. Fentanyl use among street drug users in Toronto, Canada: Behavioural dynamics and public health implications. *International Journal of Drug Policy*. 2009;20(1):90-92. doi:10.1016/j.drugpo.2008.02.016.

22. Schauer CKMW, Shand JAD, Reynolds TM. The Fentanyl Patch Boil-Up – A Novel Method of Opioid Abuse. *Basic and Clinical Pharmacology and Toxicology*. 2015;117(5):358-359. doi:10.1111/bcpt.12412.

23. Full Prescribing Information for DURAGESIC® (fentanyl transdermal system) - DURAGESIC_PI.pdf. https://www.janssenmd.com/pdf/duragesic/DURAGESIC_PI.pdf. Accessed May 16, 2016.

24. Transdermal fentanyl: Pharmacology and toxicology - 13181_2009_Article_BF03178274.pdf. http://www-ncbi-nlm-nih-gov.ezproxy.bu.edu/pmc/articles/PMC3550407/pdf/13181_2009_Article_BF03178274.pdf. Accessed May 12, 2016.

25. McAuliffe PF, Gold MS, Bajpai L, et al. Second-hand exposure to aerosolized intravenous anesthetics propofol and fentanyl may cause sensitization and subsequent opiate addiction among anesthesiologists and surgeons. *Medical Hypotheses*. 2006;66(5):874-882. doi:10.1016/j.mehy.2005.10.030.

26. Clark JR. Mother's Little Helper: The Problem of Narcotic Diversion. *Air Medical Journal*. 2011;30(6):294-296. doi:10.1016/j.amj.2011.08.006.

27. Walsh, C. T. , Schwartz-Bloom, R. D. *Levine's Pharmacology: Drug Actions and Reactions*. Seventh Edition. Taylor & Francis; 2005.

28. Foster D, Upton R, Christrup L, Popper L. Pharmacokinetics and Pharmacodynamics of Intranasal Versus Intravenous Fentanyl in Patients with Pain after Oral Surgery. *Annals of Pharmacotherapy*. 2008;42(10):1380-1387. doi:10.1345/aph.1L168.

29. Research C for DE and. Postmarket Drug Safety Information for Patients and Providers - Information for Healthcare Professionals: Fentanyl Transdermal System (marketed as Duragesic and generics) (07/15/05). http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm125844.htm. Accessed May 16, 2016.

30. H Akil, S J Watson, E Young, M E Lewis, H Khachaturian, Walker and JM. Endogenous Opioids: Biology and Function. *Annual Review of Neuroscience*. 1984;7(1):223-255. doi:10.1146/annurev.ne.07.030184.001255.

31. Fredriksson R, Lagerström MC, Lundin L-G, Schiöth HB. The G-protein-coupled receptors in the human genome form five main families. Phylogenetic analysis, paralogon groups, and fingerprints. *Molecular Pharmacology*. 2003;63(6):1256-1272. doi:10.1124/mol.63.6.1256.

32. Mudge AW, Leeman SE, Fischbach GD. Enkephalin inhibits release of substance P from sensory neurons in culture and decreases action potential duration. *Proceeding of the National Academy of Science of the United States of America*. 1979;76(1):526.

33. Pain Modulation and Mechanisms (Section 2, Chapter 8) Neuroscience Online: An Electronic Textbook for the Neurosciences | Department of Neurobiology and Anatomy - The University of Texas Medical School at Houston. http://neuroscience.uth.tmc.edu/s2/chapter08.html. Accessed May 20, 2016.

34. Nimmo WS, Todd JG. Fentanyl by Constant Rate I.v. Infusion for Postoperative Analgesia. *British Journal of Anaesthesia*. 1985;57(3):250-254. doi:10.1093/bja/57.3.250.

35. Hill HF, Chapman CR, Saeger LS, et al. Steady-state infusions of opioids in human. II. Concentration-effect relationships and therapeutic margins. *Pain*. 1990;43(1):69-79.

36. Dahan A, Yassen A, Bijl H, et al. Comparison of the respiratory effects of intravenous buprenorphine and fentanyl in humans and rats. *British Journal of Anaesthesia*. 2005;94(6):825-834. doi:10.1093/bja/aei145.

37. Chevillard L, Mégarbane B, Risède P, Baud FJ. Characteristics and comparative severity of respiratory response to toxic doses of fentanyl, methadone, morphine, and buprenorphine in rats. *Toxicology Letters*. 2009;191(2–3):327-340. doi:10.1016/j.toxlet.2009.09.017.

38. Raehal KM, Bohn LM. The role of beta-arrestin2 in the severity of antinociceptive tolerance and physical dependence induced by different opioid pain therapeutics. *Neuropharmacology*. 2011;60(1):58-65. doi:10.1016/j.neuropharm.2010.08.003.

39. Duttaroy A, Yoburn BC. The Effect of Intrinsic Efficacy on Opioid Tolerance. *Journal of the American Society of Anesthesiologists*. 1995;82(5):1226-1236.

40. Kulhara P, Gupta S. Cellular and molecular mechanisms of drug dependence: An overview and update. *Indian Journal of Psychiatry*. 2007;49(2):85. doi:10.4103/0019-5545.33253.

41. Nestler EJ. Is there a common molecular pathway for addiction? *Nature Neuroscience*. 2005;8(11):1445-1449. doi:10.1038/nn1578.

42. Koob GF, Le Moal M. Drug Addiction, Dysregulation of Reward, and Allostasis. *Neuropsychopharmacology*. 2001;24(2):97-129. doi:10.1016/S0893-133X(00)00195-0.

43. Garland EL, Froeliger B, Howard MO. Allostatic dysregulation of natural reward processing in prescription opioid misuse: Autonomic and attentional evidence. *Biological Psychology*. 2015;105:124-129. doi:10.1016/j.biopsycho.2015.01.005.

44. Hempstead K, Yildirim EO. Supply-Side Response to Declining Heroin Purity: Fentanyl Overdose Episode in New Jersey. *Health Economics*. 2014;23(6):688-705. doi:10.1002/hec.2937.

45. AccessMedicine | Content. http://accessmedicine.mhmedical.com.ezproxy.bu.edu/content.aspx?bookid=348&sectionid=40381661. Accessed June 4, 2016.

46. Osterlitz HW, Watt AJ. Kinetic parameters of narcotic agonists and antagonists, with particular reference to N-allylnoroxymorphone (naloxone). *British Journal of Pharmacology and Chemotherapy*. 1968;33(2):266.

47. FentanylAndAnalogues. http://livertox.nih.gov/FentanylAndAnalogues.htm. Accessed June 28, 2016.

48. Naloxone. http://livertox.nih.gov/Naloxone.htm. Accessed June 28, 2016.

49. Weinstein SH, Pfeffer M, Schor JM, Franklin L, Mintz M, Tutko ER. Absorption and Distribution of Naloxone in Rats after Oral and Intravenous Administration. *Journal of Pharmacological Sciences*. 1973;62(9):1416-1419. doi:10.1002/jps.2600620903.

50. Fishman J, Roffwarg H, Hellman L. Disposition of Naloxone-7,8-3h in Normal and Narcotic-Dependent Men. *Journal of Pharmacology and Experimental Therapeutics*. 1973;187(3):575-580.

51. Berkowitz BA, Ngai SH, Hempstead J, Spector S. Disposition of naloxone: use of a new radioimmunoassay. *Journal of Pharmacology and Experimental Therapeutics*. 1975;195(3):499-504.

52. 205787Orig1s000lbl.pdf. http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205787Orig1s000lbl.pdf. Accessed June 4, 2016.

53. Olofsen E, van Dorp E, Teppema L, et al. Naloxone Reversal of Morphine- and Morphine-6-Glucuronide-induced Respiratory Depression in Healthy Volunteers: A Mechanism-based Pharmacokinetic–Pharmacodynamic Modeling Study. *Anesthesiology*. 2010;112(6):1417-1427. doi:10.1097/ALN.0b013e3181d5e29d.

54. Aminosyn¨ II in Dextrose Injection - EN-1367_tcm81-5515.pdf. https://www.hospira.com/en/images/EN-1367_tcm81-5515.pdf. Accessed June 6, 2016.

55. NARCAN (naloxone hydrochloride) nasal spray - 208411lbl.pdf. http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/208411lbl.pdf. Accessed June 4, 2016.

56. Evans JM, Hogg MIJ, Lunn JN, Rosen M. Degree and Duration of Reversal by Naloxone of Effects of Morphine in Conscious Subjects. *British Medical Journal*. 1974;2(5919):589.

57. Clarke SFJ. Naloxone in opioid poisoning: walking the tightrope. *Emergency Medicine Journal*. 2005;22(9):612-616. doi:10.1136/emj.2003.009613.

58. Boyer EW. Management of Opioid Analgesic Overdose. *New England Journal of Medicine*. 2012;367(2):146-155. doi:10.1056/NEJMra1202561.

59. Slide 1 - QR_Abstract_QR31.pdf. http://www.acmt.net/_Library/2014_ASM_Posters/QR_Abstract_QR31.pdf. Accessed June 8, 2016.

60. Kim HK, Nelson LS. Reversal of Opioid-Induced Ventilatory Depression Using Low-Dose Naloxone (0.04 mg): a Case Series. *Journal of Medical Toxicology*. 2016;12(1):107-110. doi:10.1007/s13181-015-0499-3.

61. Melichar JK, Nutt DJ, Malizia AL. Naloxone displacement at opioid receptor sites measured in vivo in the human brain. *European Journal of Pharmacology*. 2003;459(2–3):217-219. doi:10.1016/S0014-2999(02)02872-8.

62. Buajordet I, Naess A-C, Jacobsen D, Brørs O. Adverse events after naloxone treatment of episodes of suspected acute opioid overdose. *European Journal of Emergency Medicine*. 2004;11(1):19-23.

63. Chu LF, Lin JC, Clemenson A, et al. Acute opioid withdrawal is associated with increased neural activity in reward-processing centers in healthy men: A functional magnetic resonance imaging study. *Drug and Alcohol Dependence*. 2015;153:314-322. doi:10.1016/j.drugalcdep.2015.04.019.

64. Schwartz JA, Koenigsberg MD. Naloxone-induced pulmonary edema. *Annals of Emergency Medicine*. 1987;16(11):1294-1296. doi:10.1016/S0196-0644(87)80244-5.

65. Nath S, Tripathi M, Pandey C, Rao B. Naloxone-induced pulmonary edema: A potential cause of postoperative morbidity in laparoscopic donor nephrectomy. *Indian Journal of Medical Sciences*. 2009;63(2):72.

66. Horng H-C, Ho M-T, Huang C-H, Yeh C-C, Cherng C-H. Negative Pressure Pulmonary Edema Following Naloxone Administration in a Patient With Fentanyl-induced Respiratory Depression. *Acta Anaesthesiologica Taiwan*. 2010;48(3):155-157. doi:10.1016/S1875-4597(10)60050-1.

67. Mell HK, Sztajnkrycer MD. Clinical Images in Medical Toxicology: Heroin Overdose with Non-Cardiogenic Pulmonary Edema. *Clinical Toxicology*. 2006;44(4):399-399. doi:10.1080/15563650600671803.

68. Andree RA. Sudden Death following Naloxone Administration. *Anesthesia and Analgesia*. 1980;59(10):782-784.

69. Watson WA, Steele MT, Muelleman RL, Rush MD. Opioid toxicity recurrence after an initial response to naloxone. *Journal of Clinical Toxicology*. 1998;36(1-2):11-17.

70. Goldfrank L, Weisman RS, Errick JK, Lo MW. A dosing nomogram for continuous infusion intravenous naloxone. *Annals of Emergency Medicine*. 1986;15(5):566-570.

71. Hepatitis C Virus Infection Among Adolescents and Young Adults --- Massachusetts, 2002--2009. http://www.cdc.gov.ezproxy.bu.edu/mmwr/preview/mmwrhtml/mm6017a2.htm. Accessed June 8, 2016.

72. Substance Use | HIV Risk and Prevention | HIV/AIDS | CDC. http://www.cdc.gov/hiv/risk/substanceuese.html. Accessed June 8, 2016.

73. Kerr D, Kelly A-M, Dietze P, Jolley D, Barger B. Randomized controlled trial comparing the effectiveness and safety of intranasal and intramuscular naloxone for the treatment of suspected heroin overdose. *Addiction*. 2009;104(12):2067-2074. doi:10.1111/j.1360-0443.2009.02724.x.

74. Merlin MA, Saybolt M, Kapitanyan R, et al. Intranasal naloxone delivery is an alternative to intravenous naloxone for opioid overdoses. *American Journal of Emergency Medicine*. 2010;28(3):296-303. doi:10.1016/j.ajem.2008.12.009.

75. Sabzghabaee AM, Eizadi-Mood N, Yaraghi A, Zandifar S. Naloxone therapy in opioid overdose patients: intranasal or intravenous? A randomized clinical trial. *Archives of Medical Science*. 2014;2:309-314. doi:10.5114/aoms.2014.42584.

76. Barton ED, Colwell CB, Wolfe T, et al. Efficacy of intranasal naloxone as a needleless alternative for treatment of opioid overdose in the prehospital setting. *Journal of Emergency Medicine*. 2005;29(3):265-271. doi:10.1016/j.jemermed.2005.03.007.

77. Naloxone. http://bha.dhmh.maryland.gov/NALOXONE/Pages/Naloxone.aspx. Accessed June 28, 2016.

78. Costantino HR, Illum L, Brandt G, Johnson PH, Quay SC. Intranasal delivery: Physicochemical and therapeutic aspects. *International Journal of Pharmaceutics*. 2007;337(1–2):1-24. doi:10.1016/j.ijpharm.2007.03.025.

79. Mycyk MB, Szyszko AL, Aks SE. Nebulized Naloxone gently and effectively reverses methadone intoxication. *Journal of Emergency Medicine*. 2003;24(2):185-187. doi:10.1016/S0736-4679(02)00723-0.

80. Baumann BM, Patterson RA, Parone DA, et al. Use and efficacy of nebulized naloxone in patients with suspected opioid intoxication. *American Journal of Emergency Medicine*. 2013;31(3):585-588. doi:10.1016/j.ajem.2012.10.004.

81. Tigerstedt I. Antagonism of Fentanyl with Naloxone during N2O+O2+ Halothane Anaesthesia. *Acta Anaesthesiologica Scandinavica*. 1977;21(6):470-480. doi:10.1111/j.1399-6576.1977.tb01248.x.

82. Fareed A, Buchanan-Cummings AM, Crampton K, Grant A, Drexler K. Reversal of overdose on fentanyl being illicitly sold as heroin with naloxone nasal spray: A case report. *American Journal on Addictions*. 2015;24(5):388-390. doi:10.1111/ajad.12230.

83. McClain DA, Hug CC. Intravenous fentanyl kinetics. *Clinical Pharmacology and Therapeutics*. 1980;28(1):106-114. doi:10.1038/clpt.1980.138.

84. Yassen A, Olofsen E, Romberg R, et al. Mechanism-based PK/PD Modeling of the Respiratory Depressant Effect of Buprenorphine and Fentanyl in Healthy Volunteers. *Clinical Pharmacology and Therapeutics*. 2007;81(1):50-58. doi:10.1038/sj.clpt.6100025.

85. Cassel JA, Daubert JD, DeHaven RN. [3H]Alvimopan binding to the μ opioid receptor: Comparative binding kinetics of opioid antagonists. *European Journal of Pharmacology*. 2005;520(1–3):29-36. doi:10.1016/j.ejphar.2005.08.008.

86. Kissin I, Kerr CR, Smith LR. Assessment of anaesthetic action of morphine and fentanyl in rats. *Canadian Journal of Anesthesia*. 1983;30(6):623-628.

87. Upadhyay S, Jain R, Chauhan H, Gupta D, Mishra S, Bhatnagar S. Oral Morphine Overdose in a Cancer Patient Antagonized by Prolonged Naloxone Infusion. *American Journal of Hospice and Palliative Medicine*. 2008;25(5):401-405. doi:10.1177/1049909108319260.

88. M K. Successful treatment of intrathecal morphine overdose. *Neurology India*. 2003;51(3):410.

89. Niemarkt H, Halbertsma F, Andriessen P, Bambang Oetomo S. Amplitude-integrated electroencephalographic changes in a newborn induced by overdose of morphine and corrected with naloxone. *Acta Pædiatrica*. 2008;97(1):132-134. doi:10.1111/j.1651-2227.2007.00583.x.

90. Brodrick JE, Brodrick CK, Adinoff B. Legal regimes surrounding naloxone access: considerations for prescribers. *American Journal of Drug and Alcohol Abuse*. 2016;42(2):117-128. doi:10.3109/00952990.2015.1109648.

91. PHLR - Naloxone Overdose Prevention Laws - LawAtlas - Policy Surveillance Portal. http://lawatlas.org/query?dataset=laws-regulating-administration-of-naloxone. Accessed June 19, 2016.

92. Wermeling DP. Review of naloxone safety for opioid overdose: practical considerations for new technology and expanded public access. *Therapeutic Advances in Drug Safety*. 2015;6(1):20-31. doi:10.1177/2042098614564776.

93. Hasegawa K, Brown DFM, Tsugawa Y, Camargo CA Jr. Epidemiology of emergency department visits for opioid overdose: a population-based study. *Mayo Clinic Proceedings*. 2014;89(4):462+.

94. SAMHSA Opioid Overdose Toolkit - SMA16-4742.pdf. http://store.samhsa.gov/shin/content//SMA16-4742/SMA16-4742.pdf. Accessed June 22, 2016.

95. Beletsky L, Ruthazer R, Macalino GE, Rich JD, Tan L, Burris S. Physicians' Knowledge of and Willingness to Prescribe Naloxone to Reverse Accidental Opiate Overdose: Challenges and Opportunities. *Journal of Urban Health*. 2007;84(1):126-136. doi:10.1007/s11524-006-9120-z.

96. Davis CS, Southwell JK, Niehaus VR, Walley AY, Dailey MW. Emergency Medical Services Naloxone Access: A National Systematic Legal Review. *Academic Emergency Medicine*. 2014;21(10):1173-1177. doi:10.1111/acem.12485.

97. Davis CS, Carr D, Southwell JK, Beletsky L. Engaging Law Enforcement in Overdose Reversal Initiatives: Authorization and Liability for Naloxone Administration. *American Journal of Public Health*. 2015;105(8):1530-1537. doi:10.2105/AJPH.2015.302638.

98. PHLR - Good Samaritan Overdose Prevention Laws - LawAtlas - Policy Surveillance Portal. http://www.lawatlas.org/query?dataset=good-samaritan-overdose-laws. Accessed June 19, 2016.

99. Bailey AM, Wermeling DP. Naloxone for Opioid Overdose Prevention: Pharmacists' Role in Community-Based Practice Settings. *Annals of Pharmacotherapy*. 2014;48(5):601-606. doi:10.1177/1060028014523730.

100. Behar E, Santos G-M, Wheeler E, Rowe C, Coffin PO. Brief overdose education is sufficient for naloxone distribution to opioid users. *Drug and Alcohol Dependence*. 2015;148:209-212. doi:10.1016/j.drugalcdep.2014.12.009.

101. Walley AY, Xuan Z, Hackman HH, et al. Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis. *British Medical Journal*. 2013;346:f174.

102. Clark AK, Wilder CM, Winstanley EL. A systematic review of community opioid overdose prevention and naloxone distribution programs. *Journal of Addiction Medicine*. 2014;8(3):153-163. doi:10.1097/ADM.0000000000000034.

103. Community-Based Opioid Overdose Prevention Programs Providing Naloxone — United States, 2010. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6106a1.htm. Accessed June 4, 2016.

104. Beletsky L. The Benefits and Potential Drawbacks in the Approval of EVZIO for Lay Reversal of Opioid Overdose. *American Journal of Preventive Medicine*. 2015;48(3):357-359. doi:10.1016/j.amepre.2014.09.011.

105. Beletsky L, Rich JD, Walley AY. Prevention of Fatal Opioid Overdose. *Journal of American Medical Association*. 2012;308(18):1863. doi:10.1001/jama.2012.14205.

106. Berteau C, Schwarzenbach F, Donazzolo Y, et al. Evaluation of performance, safety, subject acceptance, and compliance of a disposable autoinjector for subcutaneous injections in healthy volunteers. *Journal of Patient Preference and Adherence*. 2010;4:379.

107. Opioid Overdose Prevention Programs Providing Naloxone to Laypersons — United States, 2014. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6423a2.htm. Accessed June 27, 2016.

108. McDonald R, Strang J. Are take-home naloxone programmes effective? Systematic review utilizing application of the Bradford Hill criteria. *Addiction*. 2016;111(7):1177-1187. doi:10.1111/add.13326.

109. Strang J, Manning V, Mayet S, et al. Overdose training and take-home naloxone for opiate users: prospective cohort study of impact on knowledge and attitudes and subsequent management of overdoses. *Addiction*. 2008;103(10):1648-1657. doi:10.1111/j.1360-0443.2008.02314.x.

110. Tobin KE, Sherman SG, Beilenson P, Welsh C, Latkin CA. Evaluation of the Staying Alive programme: Training injection drug users to properly administer naloxone and save lives. *International Journal of Drug Policy*. 2009;20(2):131-136. doi:10.1016/j.drugpo.2008.03.002.

111. Nielsen S, Van Hout MC. What is known about community pharmacy supply of naloxone? A scoping review. *International Journal of Drug Policy*. 2016;32:24-33. doi:10.1016/j.drugpo.2016.02.006.

112. Dwyer K, Walley A, Langlois B, et al. Opioid Education and Nasal Naloxone Rescue Kits in the Emergency Department. *Western Journal of Emergency Medicine*. 2015;16(3):381-384. doi:10.5811/westjem.2015.2.24909.

113. Davis C, Webb D, Burris S. Changing Law from Barrier to Facilitator of Opioid Overdose Prevention. *Journal of Law, Medicine, and Ethics*. 2013;41:33-36. doi:10.1111/jlme.12035.

114. Coffin PO, Sullivan SD. Cost-Effectiveness of Distributing Naloxone to Heroin Users for Lay Overdose Reversal. *Annals of Internal Medicine*. 2013;158(1):1-9. doi:10.7326/0003-4819-158-1-201301010-00003.

115. Sporer KA, Firestone J, Isaacs SM. Out-of-hospital treatment of opioid overdoses in an urban setting. *Academic Emergency Medicine*. 1996;3(7):660-667.

116. Albert S, Brason FW, Sanford CK, Dasgupta N, Graham J, Lovette B. Project Lazarus: community-based overdose prevention in rural North Carolina. *Pain Medicine*. 2011;12 Suppl 2:S77-85. doi:10.1111/j.1526-4637.2011.01128.x.

117. Research C for DE and. Information by Drug Class - Questions and Answers: FDA approves a Risk Evaluation and Mitigation Strategy (REMS) for Extended-Release and Long-Acting (ER/LA) Opioid Analgesics. http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm309742.htm#Q9. Accessed June 18, 2016.

VITA

ERIC PELLLEGRINI

Email: ericpell@bu.edu
Birth Year: 1992

Education

Boston University, Boston, MA
M.S., Medical Sciences, Candidate July 2016

University of California Los Angeles, Los Angeles, CA
B.S., Integrative Biology and Physiology, August 2014

Employment

03/13-05/15: **EMT and Field Training Officer (FTO)**

UCLA EMS, Los Angeles, CA

I worked as an EMT and FTO for a 911-emergency response ambulance service. The service responds to more than 1,500 medical aid calls per year that occur on the UCLA campus and the surrounding West Los Angeles community. As an FTO, I was responsible for teaching new EMTs on shift and running simulation sessions multiple times a week.

05/10-09/10: **Lead Lifeguard**

Camelot Golfland, Anaheim, CA

Camelot is a family fun center that has four waterslides. As a lead lifeguard, I was the supervisor on each shift I worked. Additionally, I would conduct practice simulations with the other lifeguards and evaluate them on their rescuing and medical techniques. If there were any medical emergencies during the shift, I would oversee proper treatment and documentation of the events.

Research

09/13-04/15: **Pediatric Drug Administration**

UCLA Center for Prehospital Care, Los Angeles, CA

Through the UCLA Center for Prehospital Care with the David Geffen School of Medicine, I participated in a research project studying pediatric drug administration by paramedics. Paramedics volunteered to complete a written and practical exam that evaluated their competency in basic med math, drug knowledge, and drug administration.

01/14-03/14: **Drosophila Neural Circuits**

The Frye Lab, Los Angeles, CA

In Dr. Frye's lab, I focused on helping with the identification of neural circuits responsible for the sensory-motor regulation of complex behaviors in flies. My role was to manually remove the intact brains out of these flies and fix them in preparation for visualization and photography.

Volunteer Work

03/14: **MEDLIFE**

MEDLIFE, Lima, Peru

With MEDLIFE, I traveled to Lima, Peru to participate in a weeklong volunteering trip where we set up mobile clinics and aided in a developmental project by building staircases. In the mobile clinics, local Peruvian nurses, dentists, gynecologists, and doctors assessed and treated patients while we helped take vitals, package medication, and teach kids about proper dental hygiene. We set up over twenty mobile clinics and built five staircases for these individuals in Lima.

09/11-04/12: **Patient Escort**

UCLA Ronald Reagan Medical Center, Los Angeles, CA

As a patient escort, I would respond to rooms throughout the hospital to assist in patient transportation. This included wheelchairing discharged patients from their rooms to their cars or to their families who were picking them up, as well as moving patients to different floors of the hospital for tests and scans.

Other Experiences

09/10-05/14: **UCLA Club Soccer; Captain, President, Safety Officer**

UCLA Club Sports, Los Angeles, CA

UCLA Men's Club Soccer is a student-run collegiate club sport. We practiced and played year round, participating in leagues and tournaments in the fall, winter, and spring quarters. I played on the club soccer team for four years, while being team captain for the latter three years. I additionally held positions as President (3^{rd} year) and Safety Officer (4^{th} year) for the team.