Disparity in Naloxone Availability and the Impact of Sociodemographic Determinants

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Abstract

Opioid overdose is the most common cause of unintentional death in the United States. Three main classes of opioids contributing to the crisis are: synthetic opioids, prescription opioids and heroin. Naloxone is an opioid receptor antagonist used to overturn an overdose. Naloxone access laws are highly inconsistent across different states. Many major barriers to naloxone access are impacted by sociodemographic determinants. Rural populations and counties with higher income levels are more likely to have naloxone access. There are conflicting findings regarding the existence of racial disparity in naloxone access. A harm reduction approach to the opioid crisis should take into account each of these determinants separately in evaluating ways to improve national naloxone access without disparities.

Introduction

In the early 2000's, opioid misuse in America began steadily rising below the radar. In 1999, the number of people who reported using OxyContin, a commonly prescribed opioid, was 400,000.¹ By 2002, that number had risen to 1.9 million, and by 2003, 2.8 million.¹ By the 2010's, there were well over 10 million Americans misusing opioids¹. Due to their dangerous and addictive nature, opioid misuse often leads to overdose and can be fatal. In 2018, 128 people died each day of opioid overdose in America.²

The opioid crisis took off rapidly and involves three primary classes of opioids, entirely disparate from one another, making it harder to stop or even slow. The primary classes of opioids are prescription drugs, synthetic opioid compounds that are imported, manufactured and sold illegally, and heroin, a morphine derivative. There are two main strategies which have been used to combat the opioid crisis. One strategy, the top-down approach, is to limit the supply of opioids and mitigate unnecessary prescribing practices. Minimizing the overall amount of opioids circulating in the country is undoubtedly a necessary step. However, it is difficult to truly limit the distribution of the drug when it comes from so many different places. Some people get prescriptions for opioids at their local pharmacies, others order them from China on the dark web and others buy locally produced drugs on the street.³ For this reason, a harm reduction strategy, while emphasized less in the U.S., is just as necessary. A harm reduction strategy takes a bottom-up approach by attempting to mitigate the negative effects of overdose events. While America in particular has failed to legalize many harm reduction practices that have been hugely successful in other countries, one harm reduction practice which America has embraced is the use of naloxone.⁴ Naloxone, or Narcan, as a popular commercial product is named, is a medication used to reverse the effect of opioids. It is nearly 100% successful in overturning opioid overdose events.⁵ While the value of this medication is widely recognized in the U.S., its availability is less widespread. Regulations require prescriptions to obtain naloxone in some states and in other areas, despite lax regulations, pharmacies either don't carry it or carry a limited supply of it. In order to successfully and efficiently improve harm reduction practices in the U.S., discrepancies in naloxone availability must be understood and addressed. Importantly, some of the clearest predictors of naloxone availability for a given population are sociodemographic determinants.

In many ways, the United States' current opioid crisis is rooted in history. The way the crisis has unfolded over the course of the past two decades must be understood within the greater context of opioid use in this country. Only with such a historical background can the pressing issues of the present be addressed properly. While archaeological records indicate that naturally occurring opiates have been used since the Neolithic Era⁶, the first modern opiate extract used medicinally was morphine isolated from opium in the early 19th century by German Scientist Friedrich Serturner.⁷ With the invention of the hypodermic needle several decades later, humans finally found a way to safely administer an opiate extract intravenously. Widespread opioid use in the U.S. dates back to the civil war, when injured soldiers were given morphine to help deal with pain. The Union army alone supposedly distributed almost 10 million opioid pills to its soldiers.⁸ In the aftermath of the Civil War, many soldiers returned home already addicted to opioids and demand skyrocketed. By 1895, an estimated 1 in 200 Americans were addicted to opioids.⁸

Subsequent legal action over the course of the next 30 years successfully limited opioid use, finally culminating in the Anti-Heroin Act of 1924, which expressly banned the use, import, possession or synthesis of opioids.⁹ For the next 40 years or so, opioid use was cer-

tainly existent, but was much less common.¹⁰ However, after the Vietnam war, many U.S soldiers returned home addicted to opioids, which were much more easily accessible in Vietnam.⁸ Around the same time, new medicinal opiates such as Vicodin and Percocet were first introduced to the market. The amalgamation of these factors contributed to a steady but slow rise in opioid use throughout the duration of the 70's running all the way through the 90's. Then, the seeds for the country's second opioid crisis were planted when OxyContin, an oxycodone drug which would later become one of the country's deadliest drugs, hit the market in 1996.¹¹ Over the course of the next 15 years, the rates of recreational opioid use and overdose deaths increased at unprecedented rates. Between 1999 and 2010, the rate of prescription opioid overdose deaths increased by an average of 13.4% annually. ¹² ¹³ ¹⁴ The family of oxycodone drugs proved to be highly effective as a measure of treatment, but for several years, its degree of addictiveness and the dangers it presents went largely undetected on a national level. More recently, much of this damage has been attributed primarily to the campaigns of the company that produces OxyContin, Purdue Pharma¹⁵. While prescription opioids other than OxyContin existed before it and continue to exist today, doctors were historically more hesitant to prescribe opioids due to the potential dangers involved.¹⁶ Purduecommissioned focus groups found that doctors' biggest fear in prescribing the drug was, unsurprisingly, its abuse potential.¹⁶ However, paralleling OxyContin's entrance to the market, Purdue led several campaigns targeted at destigmatizing the prescribing of opioids. They held medical conferences for doctors where they presented research which served to downplay the dangers of such drugs and encourage physicians to broaden the list of instances in which they would prescribe them.¹⁶ These campaigns were largely successful and led to the widespread overprescribing of opioids across the country.¹⁷ In 2012, there were over 81 opioid prescriptions written for every 100 Americans.¹⁸ In different terms, in 2010 there were enough opioid prescriptions written that the entire American population could have been provided with a 5 mg dose of hydrocodone (another opioid) every four hours for an entire month.¹⁹ With the help of more recent policy making targeting overprescribing practices, the national rate has since decreased to 51.4 prescriptions per 100 people.¹⁸ However, the rate remains shockingly high in many regions, such as Martinsville City, VA, which had a rate of 293.5 prescriptions

per 100 people in 2018.²¹²² Around 2010, state governments began implementing prescription monitoring programs and overprescription has steadily decreased since²³ (Table 1).

Table 1. Total number and rate of opioid prescriptions dispensed per 100,000 people,United States, 2006–201818

| Year | Total Number of Prescriptions | Prescribing Rate Per 100 Persons |
|------|----------------------------------|-------------------------------------|
| 2006 | 215,917,663 | 72.4 |
| 2007 | 228,543,773 | 75.9 |
| 2008 | 237,860,213 | 78.2 |
| 2009 | 243,738,090 | 79.5 |
| 2010 | 251,088,904 | 81.2 |
| 2011 | 252,167,963 | 80.9 |
| 2012 | 255,207,954 | 81.3 |
| 2013 | 247,090,443 | 78.1 |
| 2014 | 240,993,021 | 75.6 |
| 2015 | 226,819,924 | 70.6 |
| 2016 | 214,881,622 | 66.5 |
| 2017 | 191,909,384 | 59.0 |
| 2018 | 168,158,611 | 51.4 |

Note: Peak prescribing practices were in 2012. Prescribing of opioids has fallen significantly since.

However, despite the lower number of prescriptions being given, overdose deaths continued to increase through 2017 (Figure 2). This was due to an unprecedented stage in the current opioid epidemic which involves synthetic opioids. Fentanyl, a synthetic opioid, for example, is 50 times more potent than heroin and 100 times more potent than morphine.⁴² While fewer prescriptions were being given for opioids each year, illegal sales and production of fentanyl-based drugs increased exponentially beginning in 2013 (Figure 3)²⁶.

Figure 2. Number of Reported Law Enforcement Encounters Testing Positive for Fentanyl in the US: 2015 – 2015²⁷



Note: y-axis is number of reported law enforcement encounters which resumed in testing positive for fentanyl. Exponential growth is seen in years 2013 and 2014.

There are two approaches that can be taken in trying to address the opioid crisis. A top-down approach involves cutting down the supply of non-medical opioids at their roots and preventing overprescription of medicinal opioids. This is accomplished by means of government crackdowns on illegal drug production and distribution, policy-making which directly targets the overprescription of opioids while incriminating the doctors responsible for overprescribing and finally, large lawsuits against pharmaceutical companies that distribute an excess of opioid-based drugs unlawfully. A bottom-up approach, centered around harm reduction, involves treating overdose events to prevent death, as opposed to limiting the overall circulating supply of opioids. It has become clear that the opioid epidemic cannot be

fought from a top-down perspective alone. Decreasing the number of prescriptions was a crucial step in lowering the number of overdoses, and it is essential that this trend continues. However, as fentanyl use increased alongside a decrease in prescriptions, the number of total opioid-related overdose deaths increased (Figure 3). This was largely because people who could not get prescription opioids turned to the more potent, illegal synthetic opioids. Evidently, it is not enough to lower the number of prescriptions, as necessary as it is. Rather, the necessary course of action which the CDC has been advocating is to combine bottom-up and top-down approaches. The most dominant bottom-up strategy involves increasing the availability of naloxone, which has been tremendously successful in lowering opioid overdose deaths.²⁸ Summed up well in an AJPH article,

"Addressing our opioid overdose crisis requires more than supply side [top-down] interventions. A multifaceted supply and demand–based response is required.²⁰ In addition to important national policies to combat the opioid and larger drug crisis, emphasis should be placed on developing locally and regionally tailored interventions. Ultimately, interventions are unlikely to be effective if they do not consider the diverse social and economic profiles of places and if they do not address structural upstream contributors to the opioid crisis".²⁹

Naloxone is nearly foolproof in its capacity to overturn an overdose. By increasing its availability, overdose death rates can be lowered.³⁰ However, there have been a number of hurdles which have been faced in increasing naloxone's availability. It used to be a prescription-only drug, which already made it difficult to acquire for people who don't have access to doctors, people who can't afford doctors, or people who were too embarrassed to ask for a naloxone prescription. However, a more complex challenge in increasing the availability of the drug is that naloxone is not uniformly accessible across the country. Firstly, different policies in different states result in widely varying processes in getting a naloxone kit. For example, in some areas it's as simple as walking into a local pharmacy and buying a kit, whereas in other states, regulations mandate that a person must first see a doctor, obtain a prescription for naloxone and then have that prescription filled at a pharmacy. Additionally,

even within the borders of one state with uniform policies surrounding the distribution of naloxone, there are large discrepancies in the availability of naloxone between different counties and towns within the state. Disparities like such have been shown to correlate close-ly with sociodemographic factors. Poorer areas are less likely to have pharmacy shelves stocked with naloxone kits than wealthier areas are.^{31 32 33 34 35 36}



Figure 3. Overdose Death Rates Involving Opioids, by Type, United States, 1999-2018³⁷

Understanding the root of these disparities is a complex issue because it requires a prior understanding of how socioeconomic determinants impact the opioid crisis overall, as well as the differences between the two types of naloxone and different modes of opioid use which do not necessitate naloxone intervention uniformly. Additionally, it is difficult to compare data even from neighboring states without taking into account potential legal discordance surrounding naloxone. Finally, it is also important to discuss naloxone distribution outside of the pharmacy in places like safe-injection sites, or through naloxone distribution programs which have taken place across the country and have made a significant impact as well.

Note: Overdose deaths per 100,000 people for: synthetic opioids, heroin, common prescription opioids and total. The largest uptick in the total death rate coincides with the spread of synthetic opioids

Demographics of the Crisis

Various demographic groups have been hit harder at different stages of the ongoing opioid crisis. However, the way certain demographic groups have experienced prescription opioid overdose events does not necessarily parallel the way they have experienced heroin overdose events. Various classes of opioids such as prescription, synthetic and heroin impact demographic groups in different ways. Furthermore, overdose events within a given demographic group are typically dissimilar in separate regions of the country. Additionally, leaving demographic groups aside, it is still difficult to ascertain any regional trends in opioid overdose when considering the variety of substances contributing to the crisis. Even within one county, there could be a variety of different types of opioids circulating. From a top-down perspective, the source of each type of opioid must be identified and addressed individually. For example, if there is one doctor who is overprescribing opioid drugs in a particular county, penalizing him won't do anything to change the levels of illegally imported synthetic opioids, such as fentanyl, in the county. This highlights the importance of harm reduction and naloxone, which unchangingly work against all opioid classes.

Figures 4 shows a map of the United States divided into ten different regions, as split up by the U.S. Census. Figures 5-6 show overdose-related hospitalizations by racial group within each of nine of the ten regions for the years 2012-2014. Only the pacific region including Hawaii and Alaska is excluded from the data set in Figures 5-6. Figure 5 shows that whites are more adversely affected by prescription opioids, a phenomenon which is exacerbated in the East South Central region, including Kentucky Tennessee, Alabama and Missouri (Figure 4). However, in some regions, such as Mid Atlantic (NY, NJ, PA) or East North Central (WI, MI, IL, IN, OH) (Figure 4), the prescription opioid-related hospitalization rates per 100,000 people are pretty similar between whites, blacks and hispanics (Figure 5). This shows that understanding the opioid crisis and its roots cannot be done without taking into account each of the distinct sociodemographic or geographic determinants separately. Further, Figure 6 shows that for heroin deaths, the picture is even more complex and it is difficult to even identify an overall trend, as hospitalization rates vary tremendously from one

region to the next, even within one demographic group. For these reasons, in order to make any broad conclusions about the opioid crisis in the U.S, factors such as geographic location, race, gender, socioeconomic status and class of opioid each must be considered independently of one another. The fact that there exist different classes of opioids is a particularly challenging factor to take into account because there have been numerous waves in the current opioid crisis, with each spike featuring a rise in use of different types of opioids in different regions and different causes for each. Therefore, in order to properly understand the disparity in naloxone availability across demographic groups, several important demographic trends relating to the crisis must first be identified.





Note: Nine different geographic regions in the United States, as named and divided for the purpose of the U.S. Census

Figure 5. Prescription Opioid-Related Hospitalizations Across Black, White and Hispanic Racial Groups for U.S. Census Regions 2012-2014³⁸



Note: All regions referred to are outlined clearly in Figure 4. The pacific region defined in Figure 4 is excluded from this data set. Prescription opioid-related hospitalizations is abbreviated POD

Figure 6. Heroin Opioid-Related Hospitalizations Across Black, White and Hispanic Racial Groups for U.S. Census Regions 2012-2014³⁸



Note: All regions referred to are outlined clearly in Figure 4. The pacific region defined in Figure 4 is excluded from this data set. Heroin opioid-related hospitalizations is abbreviated HOD

Figure 7. Geographic Distribution of Opioid Mortality Classes by County 2002-2016³⁸



Note: This map differentiates between three major classes of opioids: heroin, synthetic and Rx, and adds in four additional categorizations: emerging heroin, syndemic, low overdose and unclassified. Unclassified categorizations stem from insufficient data. Syndemic refers to a more complicated mix of multiple classes.

Despite the difficulty involved in analyzing the trends in opioid related hospitalizations on a broader regional scale, when looking at the map of opioid class trends on a county level (Figure 7), several patterns emerge. Firstly, high prescription opioid overdose class is more commonly found in the central and western regions of the country (Figure 7). Secondly, the north east has a complex slew of just about every type of opioid issue there is. Finally, the larger pockets of areas affected by high numbers of prescription opioid overdoses are in regions which don't seem to be otherwise struggling with the remaining opioid classes. This is likely due to the fact that prescription opioids are the most difficult to keep a steady supply of, because they necessitate going through a doctor³⁹. Therefore, in areas where the other opioid classes are more prevalent, there is no need for a user to go through the hassle of relying on prescription opioids, whereas users in areas with a limited supply of street drugs, or nonprescription opioids, are more likely to turn to their doctors to get the drug because there is no other option. In some instances, decreased availability, or potency of one class of opioids turns dependent users towards other classes of opioids, such as in 2010, when the chemical makeup of OxyContin was altered and many users turned to heroin or synthetic opioids to get a better high.¹¹

In terms of racial groups, the group hit the hardest by opioid overdose has been, by far, non hispanic whites, with 19.4 deaths per 100,000 people as of 2017, whereas Hispanics only saw 6.8 deaths per 100,000 people that year.⁴⁰ The trend since the turn of the 21st century has been that opioid overdose death rates have increased for every race, but the rate of increase for non-Hispanic whites has been the greatest, such that the gap between non-Hispanic whites and Hispanics increases every year (Figure 8). The trend for the black population was very similar to that of the Hispanic population through 2012, but from then on, the rate of increase for blacks took a steep upturn. In 2018, there were 14 deaths per 100,000 people in the black population, which is just above the midpoint between the rate for Hispanics (7.5)and non-Hispanic whites (18.6) that year.⁴⁰ One explanation for the sudden change in the trend for the black population is that they were more severely effected by the onset of the most recent stage of the opioid crisis, the explosion of synthetic opioids. This explosion coincided precisely with the sudden increase in opioid-related deaths in the black population starting in 2013. This explanation is also strongly supported by CDC data, which shows that from 2017-2018, the black population actually had an even higher rate of increase in rate of synthetic opioid (excluding methadone) related deaths (22%) than the non-hispanic white population did (6%).⁴¹ Furthermore, 2010-2015 CDC data from Florida, which has the second-highest black population count of all states, shows that the rate of synthetic opioid related deaths increased for blacks during that period while it mostly decreased for whites.⁴² Another piece of evidence for this is that the highest concentration of opioid overdoses for blacks between 2013-2017 was right around the geographical epicenter of the synthetic opioid explosion, in Ohio.⁴⁰



Figure 8. Opioid Overdose Deaths Per 100,000 People by Race/Ethnicity: 1999-2018⁴³

Another essential demographic determinant to take into account in evaluating the opioid crisis is socioeconomic status. In a recent study, a "blue-collar" index, which was designed to measure the extent to which a population is made up of blue-collar workers, was found to correlate positively with most types of opioid overdose death.³⁴ Another recent study showed that over 40% of people who died of opioid overdose in the U.S. between 2008 and 2015 were unemployed, while the national unemployment rate didn't rise above 10% during that time period.⁴⁵ It is difficult to ascertain whether this indicates that opioid addiction leads to unemployment, unemployment leads to opioid addiction, both, or neither. However, it was determined that unemployed people are at higher risk for opioid overdose.⁴⁵

Socioeconomic status can also impact which class of opioids a population is most likely to access. For example, because prescription opioids require expensive doctor visits and renewal of prescriptions for costly pharmaceutical drugs, there is a close relationship between socioeconomic status and opioid prescribing.⁴⁶ Additionally, there is precedent for socioeconomic bias in doctors' prescribing practices, as patients with a higher socioeconomic

Note: The most significant deviation from the overall trend displayed in the graph is the rate of change in deaths per 100,000 people for whites from 2017-2018. The rate went from having a high positive slope to having an almost equally negative slope.

status are more likely to be prescribed opioids than clinically similar patients of lower socioeconomic status.⁴⁶ While the quantity of available literature and data about socioeconomic determinants for opioid overdose in the United States is extremely limited, the data that does exist strongly indicates that lower income levels correlate with higher rates of opioid overdose.⁴⁷ Importantly though, this trend is much more prominent for heroin overdose deaths than it is for prescription overdose deaths. This is likely due to the same reason expressed above, that populations with lower income face numerous barriers in trying to get prescription opioids, so while they often turn to other opioids, they do suffer less from prescriptionopioid-related deaths. With this basic background in the demographics of the opioid crisis, the availability of naloxone and sociodemographic disparities therein can be better contextualized and understood.

Naloxone as an Opioid Receptor Antagonist

When an opioid enters the body, it binds to opioid receptors throughout the central nervous system and peripheral tissues, resulting in an analgesic effect by inhibiting neurotransmitter release to the postsynaptic neuron.⁴⁹ This results in the blocking of pain signals being sent via neurotransmitters to the brain. As a result, a person who takes opioids feels less pain. Additionally, opioids inhibit the activity of GABA (gamma-aminobutyric acid) neurotransmitters.⁴⁹ When GABA binds to neuron receptors, it opens ion channels, facilitating an influx of negatively charged ions, creating an inhibitory effect.⁴⁹ As such, GABA minimizes the release of dopamine. Thus, inhibiting GABA release results in the release of a large amount of dopamine⁴⁹. This causes the addictive feeling that draws many recreational opioid users into lifelong opioid habits.⁴⁹ Another impact of opioids is that breathing, coughing, sneezing and other bodily processes are significantly suppressed.⁵⁰ For many, this creates a relaxing feeling, supplementing the positive physical and psychological effects of dopamine.⁵¹ Overdose takes place when the opioid receptors reach a certain threshold of saturation which causes the breathing to slow down increasingly until it comes to a halt, which can be fatal⁵². One popular method used to overturn the effect of overdose is oxygen administration. By administering 100% oxygen into the respiratory pathway, the little breathing that the person is still doing will take in a greater concentration of oxygen and blood oxygen levels can be raised to normal levels.⁵³² However, oxygen tanks are not always readily available and this method of treatment is generally reserved for hospitals and at safe-injection sites in other countries. Another concern with this approach is that if the body's breathing rate is too slow, even saturated oxygen won't be enough to raise the oxygen concentration in the bloodstream to safe levels. Therefore, the more trusted and more portable treatment is the administration of naloxone.

Naloxone, first approved by the FDA for use against opioid overdose in 1971, is a highly competitive opioid receptor antagonist. When it enters the system, it binds to opioid receptors, knocking the opioids off the receptors and blocking them from reattaching (Figure 9). Because naloxone has a greater affinity for the opioid receptor than the opioids do, naloxone is able to take the place of the opioid on the receptor quickly. The effect is immediate but transient, lasting at most 180 minutes. If the effect of the opioid has not yet worn off by that time and the concentration of opioid ligands at the opioid receptors is still dangerous-ly high, another dose must be given, often in conjunction with oxygen treatment. Sometimes, the standard dose of naloxone ligands is high enough to replace the opioid ligands on the receptor.⁵³

There are two ways which naloxone can be administered and they have been used interchangeably in recent years. Most often, naloxone is administered intravenously and as soon as it enters the bloodstream, it knocks opioid ligands off the opioid receptors all over the body. Another method of administration which has been used increasingly in recent years is nasal spray. When naloxone is given nasally, it is immediately absorbed through nasal mucosa and into the bloodstream quite near the brain, without having to pass through the rest of the body first. Disarming the opioid receptors in the arms, torso and legs is not essential to save a person's life. Instead, it is only necessary to block the receptors in the brain, which cause respiratory suppression upon opioid binding. For this reason, the naloxone market has become increasingly saturated with nasal alternatives to the intravenous option⁵⁴. The nasally administered drug is preferable for many due to the inconvenience and discomfort often associated with needles. Further, many people don't know how to give an injection, which quickly limits the pool of people who can save a person experiencing an overdose. On the other hand, anyone can give a nasal spray, so this form of the medication empowers a much larger force with the capability to overturn an overdose. Therefore, by increasing the prevalence of nasally administered naloxone, the odds of someone who is capable of using a naloxone agent being nearby the overdosing individual are much higher. This benefit would effectively improve outcomes for individuals who experience opioid overdoses.⁵⁵ Using the intranasal device also precludes any delays in gaining vascular entry, which is a common issue for frequent intravenous opioid users.⁵⁶ Importantly, there is also an auto-injecting naloxone administration device, which makes it easier to administer naloxone intravenously.⁵⁷ However, it is not as popular as the manual intravenous option or the nasal spray, possibly because it is much more expensive, as a pack of two can cost up to \$4500.³³

When comparing the two types of naloxone, an essential term to discuss is bioavailability. Bioavailability refers to the relative amount of the substance which is available for use inside the body.⁵⁸ While use of the nasal spray certainly increases the population of people who are able to administer naloxone as opposed to intravenous means, it has been shown that the bioavailability of naloxone in the essential areas of the brain after a intranasal dose (51.9%) is just over half of what it is after an intravenous dose (98.3%).⁵⁹ Evidently, the mechanism of absorption through nasal pathways is less effective than intravenous mechanisms and the intravenous dose provides a greater degree of relative bioavailability.

Figure 9. Naloxone Mechanism of Action⁶⁰



Note: When the opioids are bound to the opioid receptors, a cascade resulting in the lifting of GABA restrictions on dopamine release is initiated. This cascade also results in the slowing or termination of transmission of pain signals. Naloxone is a competitive antagonist which kicks the opioid off the receptor. The green receptors pictured are a part of the central nervous system.

Naloxone Availability: Socioeconomic Determinants

Given the complexity of the opioid crisis and all of its components, it is not surprising that naloxone access is inconsistent throughout the country. Naloxone access is impacted by laws, policies, prices, socioeconomic factors, geographic factors and demographics. One of the most staggering determinants of naloxone access is household income. Households which bring in \$20,000 per year (approximately \$4000 per year more than average annual full time minimum wage salary and \$7500 above the national poverty line for households of one person⁶¹) or more were four times more likely to have access to naloxone than households with lower income levels.⁶² This would seem to indicate that a higher income and socioeconomic status correlates with greater naloxone access. However, this is not always the case. Surprisingly, people who inject drugs who were recently homeless are almost three times more likely to have access to naloxone.⁶³ Additionally, people who are unemployed are actually more likely to have naloxone access.⁶² There is currently no singular, clear explana-

tion for these findings. It is likely that in households which bring in over \$20,000 per year, there is a higher chance that there is enough money to be spent on naloxone. However, people who are homeless or unemployed are much more likely to participate in street-level naloxone training and distribution programs, which might make them more likely than average to have access to naloxone. Another significant impact of socioeconomic status is related to the price of naloxone. It has been found that intranasal naloxone can be up to twenty⁶⁴ times more expensive than intravenously administered naloxone. This puts people of lower socioeconomic status at an immediate disadvantage in the case of an overdose event. While many people receive naloxone through free distribution programs, there no available data relating to the relative ratio of store-bought naloxone to naloxone given out for free through distribution programs. As elaborated upon above, one of the most significant upsides of the nasal drug is that there is a much larger population of people who could use it properly than there would be for an intravenous drug. Accordingly, in a town with lower income levels, it is less likely that the more expensive intranasal agent is widely possessed. As a result, in the case of an overdose event, it is much less likely that there would be anyone nearby to administer naloxone to the overdosing individual. Even if overall naloxone access levels in towns with lower income levels matched those in towns with higher income levels, there is a strong chance that the naloxone in the town with lower income levels would be mostly the intravenously administered model. Because fewer people are capable of administering the intravenous model properly, it is less likely that someone capable of administering naloxone would find the overdosing individual in time to save his or her life. Naloxone has been deregulated in recent years, making it more easily accessible in most states from a purely legal standpoint. However, its price has also continuously increased, making it increasingly difficult to access for people in lower socioeconomic classes despite the legal deregulation.⁶⁴ Further, towns with lower income are less likely to have the local government funding to run extensive naloxone campaigns, which have been hugely successful. One West Virginia study found that after naloxone campaigns were aggressively pushed in one area in 2017, EMS responders received 40% fewer calls for overdoses in that area in 2018.⁶⁵ It seems likely that naloxone use precluded the need for EMS in many of those cases.

Naloxone Availability: Geographic Determinants

Naloxone access also varies significantly by geographical region. One study in Detroit found that whereas 41.9% of people who inject drugs had access to naloxone in rural and suburban areas, only 18.3% had access in urban areas.⁶² One likely explanation for this discrepancy is that people in urban areas don't feel as great a need to have naloxone because they are much closer to medical assistance and can always call first responders in case of an overdose. Help is always nearby in the city, whereas opioid users in suburban and rural areas know that first responders would take longer to reach them⁶⁶ and are also less likely to have the proper equipment and medications⁶⁷ and therefore, the need for naloxone access is greater. Alternatively, it is possible that naloxone distribution programs are either more prevalent or more successful in rural and suburban areas, or at least in those targeted in this study.

The higher prevalence of naloxone in more rural areas might also be a response to a greater need. During the first wave of the current opioid crisis, between 1999 and 2004, the drug overdose mortality rate rose 159% in rural counties and just 54% in metropolitan counties during that same period.⁶⁸ Despite the fact that there is a much greater prevalence of naloxone access in rural areas, as well as a greater burden of opioid overdoses per 100,000 persons, the odds of naloxone use by emergency medical responders in rural areas is barely greater than it is in urban areas (Figure 10). While the authors who published that data argued that it indicates that increasing naloxone use in rural areas could save many lives, this seems to be a premature assumption. Because naloxone access is already so much more prevalent in rural areas, it is likely that the rate of EMS providers administering naloxone is lower than expected because people who live in rural areas are using their own naloxone, rather than relying on the slow-responding EMS providers to bring it to them.⁶⁹ On the other hand, urban residents who are much less likely to have access to naloxone on their own choose to rely on EMS providers. Interestingly, while the rate of overdose mortality for suburban areas was about midway between that of urban and rural areas, the rate of naloxone usage was highest for suburban areas. In order to develop a better understanding of how the geographical determinants of naloxone access and use tie together, further research would be necessary. It

would be useful to have data that reflects overall naloxone use as opposed to just naloxone used by EMS providers, which is only a fraction of all naloxone used in some areas. For example, a study involving opioid users in rural Alaska found that participants rarely called 911 following an overdose. Almost all of the participants preferred to use naloxone on their own. There was a palpable sense of distrust of anyone associated with law enforcement, as participants felt that upon calling 911, they would be treated as criminals. Even though good samaritan laws protect anyone who calls for medical help in such a scenario as an overdose in Alaska, participants didn't truly believe they would be provided immunity upon calling 911.⁶⁹ This clearly demonstrates that the lower numbers of naloxone use by EMS providers in the above study does not necessarily indicate anything about the amount of naloxone use overall. Evidently, people who use opioids in rural areas tend to distrust EMS providers more and tend to have personal naloxone kits more often, thus they are significantly more likely to treat themselves with naloxone, or have a family member treat them, as opposed to calling for help.

Figure 10. Overdose Rates and Odds of Naloxone Administration by EMS Providers by Level of Urbanicity, 2012³⁴



Note: The mostly linear, solid line indicates that the rate of opioid death per 100,000 persons increases as rurality increases and urbanicity decreases. The dip in the dotted line shows that naloxone is not being used nearly as much as expected in rural areas

Classes of opioids

A study done in a Chicago hospital surveyed one hundred patients who were identified by their care providers as frequent opioid users.⁷⁰ Of the patients who injected opioids, an impressive 76% had heard of naloxone and 39% had access to it at some point. At the same time, of opioid users who had no history of injecting opioids only 32% had heard of naloxone and a shocking 2% had access to it at some point. This enormous discrepancy is difficult to fully account for, but the authors of the study suggested that it had to do with the source of naloxone kits. Everyone in their study who reported having access to naloxone at some point got it from a distribution program of sorts, not from a pharmacy or a doctor. Therefore, they explained, it is likely that people who inject opioids are more likely to participate in community programs where naloxone would be distributed, such as needle-exchange programs. The fact that none of the participants in the survey received naloxone from a pharmacy also highlights the importance of co-prescribing. An increasingly popular practice, doctors who prescribe opioids are now co-prescribing naloxone alongside the opioid, to minimize the risk of overdose death. The significance of this practice is that if it is implemented broadly and properly, an entire class of opioids can be nearly eliminated from the crosshairs of this crisis. If naloxone is co-prescribed for all who pick up opioids at pharmacies, it can be assured that every prescription opioid user at least has access to naloxone. This would likely make a significant dent in the mortality rates for opioid overdose, because it is believed that only 2% of people who use opioids non-intravenously have access to naloxone.⁷⁰

Pharmaceutical Naloxone Distribution

In 2014, new legislation was passed in California which gave pharmacies the option to sell naloxone over the counter without requiring a prescription. A study found that 71% of pharmacies carried naloxone.³² Interestingly more than half of those were CVS pharmacies, which seem to almost always have naloxone in stock, as confirmed in several studies.^{32 34} Sadly, despite the encouraging 71% pharmacies that carried naloxone to be sold without a prescription, most pharmacists claimed to have never sold naloxone before.³² Many pharmacists working at pharmacies that had not elected to keep naloxone in stock for over the

counter purchase freely stated that it was because "nobody has asked for it", or because "opioids aren't a problem in this area". Because of attitudes like these, it has been suggested that informational campaigns as to the severity of the opioid crisis and the importance of nalox-one would be helpful.³²

One positive result that emerged from a pharmacy-based study in North Carolina is that there don't seem to be any racial disparities in naloxone availability at pharmacies.⁷¹ While this is an encouraging finding, it is unlikely that this is a widespread phenomenon, as other studies have shown just the opposite. A New Jersey pharmacy based study found a positive correlation between average household income and naloxone availability.³³ While this finding is unfortunate, it is in some ways understandable. With naloxone prices on the rise, people in areas with lower average household income are less likely to be able to afford naloxone at a pharmacy and are more likely to turn to street-level distribution programs instead.

Legal Determinants

Adoption of naloxone access laws was shown to lower the national rate of overdose deaths by 9-11%.⁷² However, it has been shown several times that more lax naloxone access laws actually result in more opioid related hospitalizations and a more severe mortality rate for opioid overdose.^{31 72} While this seems counterintuitive, one explanation proposed by the authors of the study was is that naloxone saves the lives of many people who would've otherwise died on the scene of the overdose. Therefore, many people who would have died without naloxone are now being admitted to hospitals for opioid overdose, following the administration of naloxone.³¹ Another proposed explanation for this is that increased naloxone prevalence gives opioid users a greater degree of confidence in their drug use and mitigates their fear of overdose, which results in them using larger amounts of more potent opioids, causing more hospitalizations.

Naloxone access laws come in many different permutations (Figure 11). This is another factor which complicates the already complex web of determinants and disparities that make up the opioid crisis. Because each state has its own variation of naloxone access policies which were not implemented synchronously, comparing studies done in two different states, or even in one state but at two different times, necessitates taking a deeper look at how the policies may have impacted the data collected and conclusions reached. A recent study pointed out that the complication doesn't stop there, as the policies implemented in one state also impact neighboring states.³¹ This demonstrates just how complex the issue of naloxone access is and how difficult it is to compare data between studies given the various legal contexts which each state presents.

Figure 11. Provisions of Naloxone Access Laws in U.S.

- **Provision 1:** Having immunity from criminal prosecution for prescribing, dispensing, or distributing Naloxone to a layperson for prescribers.
- **Provision 2:** Having immunity from civil liability for prescribing, dispensing, or distributing Naloxone to a layperson for prescribers.
- **Provision 3:** Having immunity from professional sanctions for prescribing, dispensing, or distributing Naloxone to a layperson for prescribers.
- **Provision 4:** Having immunity from criminal prosecution for prescribing, dispensing, or distributing Naloxone to a layperson for dispensers.
- **Provision 5:** Having immunity from civil liability for prescribing, dispensing, or distributing Naloxone to a layperson for dispensers.
- **Provision 6:** Having immunity from professional sanctions for prescribing, dispensing, or distributing Naloxone to a layperson for dispensers.
- Provision 7: Prescribers are allowed to provide Naloxone to third parties.
- **Provision 8:** Pharmacists are allowed to dispense or distribute without a patient-specific prescription from another medical professional.
- **Provision 9:** Immunity from criminal liability when administering Naloxone for a Layperson.

Provision 10: Immunity from civil liability when administering Naloxone for a layperson.

Provision 11: Removing criminal liability for possession of Naloxone.¹⁸

Note: Citizens are often affected by not just one provision, but multiple provisions and different formulations. This can come about when one state implements several different provisions over time, or when citizens live near the border between states, they can be impacted by the laws on each side of the state border.

Conclusion

As emphasized throughout, because there are so many factors to take into account in analyzing this crisis, it is difficult to verify any conclusions or definitive measures that must be taken. Rather, the more reasonable approach is to try to address programs on a more local level. Each community struggling with opioid-related issues faces unique challenges that are unlikely to completely parallel neighboring communities. Because of the umbrella term "opioids", many different drugs are grouped together as one problem. While the physiological or pharmacological mechanism of prescription OxyContin and injected fentanyl might be more or less the same, the practical pathways towards mitigating overdose deaths can be very different. For example, prevention of overprescription of opioids can be controlled more easily by prosecuting doctors and Pharma companies guilty of contributing to overprescription and instituting new regulations which prevent overprescription. On the other hand, cutting down the United States' supply of synthetic opioids led FDA agents on a legally complex international investigation involving hundreds of empty offices and factories across China.³ It is important to recognize just how disparate the sources of various types of opioids are, because it would be ill-advised to appoint a single team to monitor domestic overprescribing and international fentanyl rings. At the same time, harm reduction practices address all classes of opioids with relative equality. Naloxone overturns an opioid overdose regardless of the class of opioid used. If each county were to focus on its own local opioid crisis, more specific and targeted plans of action can be developed and likely produce more efficient and efficacious results.

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