A Way Forward

How Naloxone Saves Lives from Opioid Overdose

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Introduction

As we enter the new decade, few have any sense of optimism that we will be leaving the opioid epidemic behind us. A perfect storm of factors have coalesced over the past two decades which has placed an incredible strain on the healthcare system. Unfortunately, despite monumental efforts to combat opioid overdose, the number of overdoses has only plateaued. Overall opioid overdoses seem to have stabilized, declining 4.1% in 2018, but overdoses from fentanyl, cocaine, and methamphetamines continue to plague the country.1 Young and old, rich and poor, educated and less informed have all been affected.

Naloxone has steadily gained popularity since its invention because of its unique ability to counteract toxicity, neurological impairment, and the respiratory depressive effects of opioids. Naloxone has successfully reversed respiratory depression in countless opioid overdoses in thousands of patients and has allowed them to have a second chance at life. It is well established that a critical component of reducing overdose mortality is increasing access to naloxone among three important groups—patients with chronic pain at risk for overdose, patients with substance use disorders (SUDs) and/or opioid use disorders (OUDs), and to the community overall, to help reverse overdoses emergently.

Ensuring ready access to naloxone is one of SAMHSA’s Five Strategies to Prevent Overt re Deaths.2 All 50 states and the District of Columbia have implemented legislation to increase access to naloxone by allowing distribution by pharmacists, simplifying the process of obtaining naloxone, and increasing distribution to friends and families of individuals at risk for overdose. Many states have established standing orders, issued by the State Department of Health for the public rather than an individual, that allows pharmacists to dispense naloxone to anyone at risk. In 46 states, Good Samaritan laws have been implemented that protect bystanders and individuals from arrest or prosecution for administering naloxone in good faith. As a result, the number of naloxone prescriptions dispensed by retail pharmacies increased 106% from 2017 to 2018.3 While this increase is substantial, it is important to note that the national 2018 data produced a ratio of only one naloxone prescription per 69 high-dose opioid prescriptions with as much as a twenty-five fold variation across US counties. The lowest percent of naloxone prescriptions from retail pharmacies occurred primarily in rural counties—areas that have been especially devastated by the opioid crisis.3

Statement from the Surgeon General

I, Surgeon General of the United States Public Health Service, VADM Jerome Adams, am emphasizing the importance of the overdose-reversing drug naloxone. For patients currently taking high doses of opioids as prescribed for pain, individuals misusing prescription opioids, individuals using illicit opioids such as heroin or fentanyl, healthcare practitioners, family and friends of people who have an opioid use disorder, and community members who come into contact with people at risk for opioid overdose, knowing how to use naloxone and keeping it within reach can save a life.
On April 5, 2018, the Surgeon General issued a public advisory to raise awareness among health care providers and the public about the importance of increasing the availability and access to naloxone. While the statements of the Surgeon General and changes in legislation have improved dispensing and access, there is significant variation in the levels of awareness of naloxone among different at-risk populations. A key at-risk population is the large number of medical patients who are receiving high dose oral morphine milligram equivalent (MME) prescriptions for pain. Some of these patients might not be aware of their risk for overdose and/or of the beneficial effects of naloxone as a potential option for emergency treatment. Among this group are elderly patients heavily reliant on their health care provider (HCP) to counsel them about risks and prescribe any necessary medication. Yet, HCPs report low levels of knowledge and self-efficacy in counseling patients about overdose and naloxone.

Strategies for increasing access must be thoughtfully developed and employed. Some have advocated for an over-the-counter strategy, whereas others have suggested maintaining at-risk individuals within the healthcare system by keeping HCPs involved in managing SUDs as chronic diseases in a non-stigmatizing way. This approach will require patient and family education on the medical need for naloxone.

Access models, including over-the-counter availability, must be critically examined to prevent any negative impact of unintended consequences from strategies for the distribution of naloxone. Prescriptions of naloxone to patients with commercial insurance or Medicaid may require little or no out-of-pocket expense. In April 2019, the Centers for Medicare and Medicaid Services (CMS) encouraged sponsors of Medicare Part D plan to lower cost-sharing for naloxone in 2020. These reimbursement options would become unavailable with over-the-counter distribution strategies if appropriate actions are not taken to support patients who need naloxone desperately.

This special Expert Panel was convened to discuss that point of view and consider current trends in opioid use as well as prevailing attitudes towards the subject of naloxone availability. Root causes of opioid misuse, OUD, and overdose were assessed. Naloxone utilization was discussed in the context of socioeconomic factors, access to care, educational initiatives, neurobiological models, and regulatory policies, and interventions. Models of care were reviewed and data were presented that show just how much work will be necessary to educate health care providers and patients alike about the benefits of at-home use of naloxone for reversal of opioid toxicity including overdose and life-threatening respiratory depression. It is clear that barriers to health care provider prescribing and distribution of naloxone in the community exist. However, overcoming these barriers will save many lives.

The Expert Panel agreed that naloxone availability without a prescription may have unintended consequences and negatively impact naloxone access. A number of varied factors from differences between patients with OUD, the elderly, pain, and patients with psychiatric disorders, to loss of insurance coverage were discussed in detail. For example, patients may be less likely or able to shoulder a greater burden of cost versus low co-pays, or in some cases, no co-pays when covered under a typical pharmacy benefit. This white paper reviews the data used by the panelists to establish their positions and sets up recommendations for the way forward.
Background

“I think the current opioid crisis is extremely complicated given the fact that opioids have been on the planet forever, and even synthetic opioids such as methadone have been around for more than 70 years. So what makes these past 20 to 30 years different and has led to the crisis that we’re facing right now? I think it is multifactorial with many good intentions leading to some very bad outcomes producing the opioid crisis we have now.”

- Teresa Rummans, MD

How Did We Get Here?

As reviewed by Rummans and her group at the Mayo Clinic, the unprecedented increase in opioid-related overdoses and mortality has escalated exponentially, infiltrating all segments and strata of American society while concurrently overwhelming our healthcare system and befuddling policymakers. In a historical context, the current opioid crisis in the United States is not the first opioid-related crisis in the country. The crisis has brought opioid overdoses, OUDs, children left without parents, a growing burden on the foster care system, increased medical consequences, and infectious disease with no end in sight. As pointed out by Cicero, the prescription opioid crisis was quickly followed by a heroin use epidemic, and is now a fentanyl and synthetic opioid crisis where experts see more primary fentanyl use disorders. The Centers for Disease Control and Prevention (CDC) reported over 28,000 U.S. deaths in 2017 related to synthetic opioids (other than methadone), more than any other opioid. The impact has been so widespread that most Americans know someone who has overdosed, and consequences are not relegated only to the people struggling with a SUD or OUD and dying, but also to their friends and family, and our society. The evidence is overwhelming and confirmed by the unprecedented three years of declining life expectancy in the United States. This decline in life expectancy is attributed to deaths of despair, depression-suicide, alcohol and drug abuse, opioid, and cocaine overdoses, and to the natural progression of substance use disorders.

The current opioid crisis, as reviewed by Professor Rummans, was triggered, in part, by making pain the 5th vital sign, through the use of patient satisfaction surveys to evaluate and reimburse hospitals and physician pain providers. To comply with the newly imposed, subjective standards of “quality care” as described by the Institute of Medicine (IOM) in 2001 patient self-rating of current pain levels resulted in widespread cognitive dissonance by many providers regarding the risk of opioids to justify their utility, especially for non-malignant pain. In retrospect, it was a predictable “disaster in the making” that can be traced back to the late 1990s. Like all Black Swan events, the pattern of contributing factors is clear, but only after it seems too late. Even now, experts have only begun to recognize the lack of breakthrough pain research, lack of non-opioid pain pipeline, and a dearth of options for many patients in pain. The increase in overdose mortality among all demographic groups has healthcare officials wondering how the most technologically advanced nation on the planet could be losing ground regarding the health and longevity of its citizens, particularly following a two decade trend of extending life.
Fentanyl and Synthetics-4th Phase of the OUD Epidemic$^{13,14}$

Fentanyl is approximately 100 times more potent than morphine and 50 times more potent than heroin. Breathing can stop after use of just two milligrams of fentanyl. That’s about as much as trace amounts of table salt. Synthetic opioids like fentanyl accounted for 3,000 deaths in 2013—by 2018, they accounted for over 30,000.$^{13}$ The ease of production in unregulated sectors of the Chinese and Mexican economies is difficult for U.S. authorities to curb or eliminate. The internet promotes novel strategies for synthesizing the substance, spreading its production across many labs; suppliers use the U.S. Postal Service for distribution; and e-commerce helps to get the drug from manufacturers to U.S. consumers for fentanyl transactions. This report observes that for only $10 through the postal system, suppliers can ship a 1-kg parcel from China to the United States. Pardo et al find that, “however bad the synthetic opioid problem is now, it is likely to get worse before it gets better.” Using a large variety of sources, including data on mortality, drug seizures, expert interviews, and a wide array of research on drug epidemics and markets, the report places the fentanyl crisis in historical context and maps its current trajectory.$^{13}$

Our Possible Fentanyl Futures

The three waves of the current opioid crisis followed: prescription opioids, heroin, and synthetic opioids.$^{14}$ Now we have a synthetic or even a primary fentanyl epidemic. It is not likely to just go away. Drug cartels can make fentanyl all over the world at a very low cost. One of the key findings from the report by Pardo and colleagues is that fentanyl’s death toll doesn’t grow because of new consumers, but because it replaces less deadly opioids among individuals with OUD.$^{13}$ An arresting statistic from the report is that if, in 2017, other parts of the United States had synthetic opioid fatalities at even half the rate of New England’s, there would have been approximately 9,000 more drug deaths. In the future, it is possible that synthetic opioids may become a standard part of substance use in the United States, or that it may get overtaken by another, faster-growing methamphetamine or cocaine epidemic.$^{13}$ In a recent publication in *Science*, researchers examined drug overdose deaths and unintentional drug poisonings in the United States. They demonstrated that while drug overdoses may look like they come and go, in reality, they grow year after year. From 1979 through 2016 they grew exponentially along a remarkably smooth trajectory.$^{15}$

Severity of the Problem

These disturbing trends point to a complex web of causation involving nearly all aspects of how we live. Case and Deaton (2015) documented all case mortality in the United States from 1998 to 2013.$^{16}$ What they discovered was not expected or predicted by anyone. Morbidity and mortality among those who were previously thought of as a robust and healthy age cohort, that is, middle-aged white persons, were in fact, very unhealthy and dying prematurely. The study revealed that increased morbidity was namely due to chronic pain, SUDs, depression, liver disease, cardiometabolic disease, obesity, suicide and overall difficulties in daily living. The high mortality of this age cohort is associated with SUDs, accidental overdose, cardiovascular disease, overdose with suicidal wish or intent, and suicide. The authors referred to this shocking mortality as “Deaths of Despair” and a contributing factor to the declining life expectancy in the United States.$^{16}$
Evidence-based Medications for Addiction Treatment (MAT)

We know that nearly all opioid overdoses can be reversed by naloxone, and that OUD can be successfully treated with evidence-based, patient-centered treatments of adequate duration and intensity. The latter long-term solution cannot occur without the former acute, life-preserving intervention. Reversing an overdose again and again is not a logical public health response to OUD overdose. This seems logical to their loved ones, health providers, and experts. But, accepting evidence-based MAT and other treatment does not automatically happen. The use of the overdose as a teachable moment, supplemented by peer and professional interventionists can promote transition from near death and overdose to buprenorphine or methadone treatment.

Individuals who use illicit opioids have a different experience and motivation for using drugs, therefore the acceptance regarding the utility and value of overdose reversal agents differ than for those who are prescribed opioids for pain. The individual using illicit opioids realizes that an overdose is possible and may believe he/she has taken the necessary precautions to minimize their risk. In contrast, an older person prescribed opioids for pain or an athlete who has just had a serious injury may not consider overdose a possibility. Thus, experts who focus on reducing overdose deaths have argued that increased access to optimal, individualized treatment including MAT such as buprenorphine, buprenorphine/naloxone, naltrexone, or methadone are essential modalities. While MAT may not seem like a primary treatment modality for opioid overdose, the experts agree that it is a safe and effective treatment modality for reducing recidivism and repeat overdose.

In the current opioid overdose epidemic, whose roots have been studied and reviewed previously by Cicero and Rummans, MATs have been shown to be safe and effective, reducing overdose in those patients who are treatment adherent. Unfortunately, approximately 50% or more patients drop out of treatment prematurely. Moreover, new data suggests that overdose risk continues long after patients successfully complete treatment with buprenorphine. Overdose reversal is largely determined by the availability of naloxone at the place and the time that overdose occurs and the willingness and capacity for someone to administer naloxone. Yet we cannot know, with any degree of certainty, where or when a potentially fatal opioid overdose will occur. Improving naloxone availability is the best chance of saving lives from overdose.

After a nonfatal overdose, connecting individuals across the spectrum to a multimodal treatment facility and management plan that includes MAT is essential to positive outcomes. Yet, linkage to treatment is often lacking. Physician health programs, employee assistance, and court-directed treatment have done a better job at this through use of supervision, contingency management, and even coercion. This is essential to treatment adherence and outcomes, but is very difficult work. In a very recent study of 3,606 adolescents and young adults, aged 13-22, who survived an opioid overdose, an NIH-funded team found that less than 2% of the young people received MAT. Alinsky and colleagues found that less than 20% received a diagnosis of OUD and 68% did not receive treatment of any kind for their OUD. Linkage to behavioral services occurred in only 29.3%, and only 1.9% received one of the FDA-approved MATs. Linkage to treatment after an overdose requires continued support and supervision.

It is obvious, logical, and well-reasoned to increase naloxone availability in emergency
departments, ambulances, and among emergency medical technicians (EMTs), as they routinely encounter opioid overdose. However, improving naloxone access at other points of care where overdose risk is likely, remains a challenge. A good place to start is by encouraging all patients with OUD to carry naloxone, for their loved ones to carry naloxone, and for their homes to have naloxone nearby in the bedroom or bathroom. Panelists went so far as to say that current and past OUD patients, as well as their loved ones, are a high-risk of overdose group and should have naloxone nearby at all times.

**At-Risk Patient Populations**

Getting naloxone to high-risk patients and their loved ones is an important public health initiative. However, patients with OUD and SUD are not the only groups at high risk for overdose. Much progress has been made in understanding the demographics and other behavioral characteristics of opioid overdose patients. In research by Rose et al, two groups of decedents from opioid overdose were identified. The first group was described as predominantly Caucasian males with OUD as a principal diagnosis, but were also abusing other intoxicants and therefore diagnosed with co-occurring SUD. The second group of decedents were defined as nonproblematic opioid users with a diagnosis of chronic pain and mental illness. The health records indicated they had been seen by surgical, pain, and other subspecialty providers. As opioids are safe and effective and not likely to be replaced anytime soon, these patients with chronic pain are an important at-risk group. Relief of pain augments the anti-stress and anti-anxiety effects of opioids making long-term use problematic. For these reasons, opioid exposure in patients with concurrent psychiatric disease can be risky. The panelists noted that at least two, and possibly three distinct populations at risk for opioid overdose need specific strategies and policies for naloxone access, distribution, and interventions. Professional education to encourage naloxone within existing practice guidelines should be devised to reduce overdose among these groups.

One size does not fit all, and one strategy is unlikely to be enough for every group. A multimodal approach is needed. In patients with chronic pain treated with high doses of opioids daily, concurrent use of benzodiazepines, sedatives, and medical comorbidities heighten risk of overdose. In a recent study, researchers evaluating risk of overdose death among 2.2 million people in North Carolina related to high-dose opioid use noted, “Much of the risk at higher doses appears to be associated with co-prescribed benzodiazepines. It is critical to account for overlapping prescriptions, and justifies taking a person-time approach to MME calculation with intent-to-treat principles.”

Individuals with a psychiatric disorder co-morbid with sexual, physical and emotional trauma including post-traumatic stress disorder (PTSD), major depression, and anxiety disorders are also at higher risk of overdose. In these patients, the opioids’ reinforcing effects and mood altering effects may provide some relief from psychiatric distress. It is important not to forget many patients with underlying psychiatric disorders and chronic pain are at higher risk for suicide. In this situation the overdose is not “accidental” but the unfortunate outcome of planned self-harm. Treatment of co-occurring psychiatric conditions is not always recognized nor recommended among treatment providers for SUDs. For example, untreated or undertreated depression among those receiving care for SUDs are associated with relapse and suicide by overdose. Therefore, continuing education about better recognition and treatment of co-occurring psychiatric disease among patients with OUD is an obvious target for getting naloxone into the hands of this at-risk patient group.
**Intentional vs. Accidental Overdose**

The expert panel noted that suicide might very well be a root cause of more opioid overdoses than the data suggest. Chronic self-administration of opioids, while initially used for euphoria may result in depression, anhedonia, and suicidal thinking. An “intentional” suicide attempt by fatal drug overdose refers to an individual seeking to overdose to end his/her life. This may sound straightforward enough, but the issue is much more nuanced, and relates to how we understand and respond to the opioid overdose epidemic. If all overdoses are considered “accidental” until proven otherwise, we may be missing higher rates of suicide and depression, and different approaches to prevention, identification, and treatment.

The Directors of the National Institute of Mental Health (NIMH) and National Institute on Drug Abuse (NIDA) recently reviewed the literature linking overdose and suicide.\(^{33}\) Up to 30% of all accidental overdoses are suicides. They observed that, controlling for other conditions, suicidal thoughts are 40% to 50% higher among individuals misusing prescription opioids, and that, “people with a prescription OUD were also twice as likely to attempt suicide as individuals who did not misuse prescription opioids.”\(^{33}\)

In psychiatry, suicide may be easy to identify with a post-mortem history constructed by survivors and caregivers and analysis of the intent, plan and a note. Others are more subtle and the panel referred to these as more passive suicidality. Most experts believe that death certificates underestimate opioid and other overdoses as well as suicide. Oquendo and Volkow suggest that a declining motivation to live can range “from engagement in increasingly risky behavior despite a lack of conscious suicidal intent, to frank suicidal ideation and intent.”\(^{34}\)

More recently, Harvard researchers confirmed this hypothesis by interviewing survivors of opioid overdoses.\(^{35}\) An astounding 58.5% of participants said that they had at least some desire to die before their most recent opioid overdose, and only 41.5% said that they did not want to die. This is quite remarkable considering the assumption that all overdoses were accidental until recent work began to look deeper at the association between depression and overdose. 36% of participants stated that they had a strong desire to die. 21% reported “I definitely wanted to die.” 30.2% believed it was “not at all likely” they would overdose. 13.2% stated that an overdose was “extremely likely”. This study also found that among 92% of participants heroin or fentanyl was the drug of choice.\(^{35}\) While more study is necessary, it is clear that patients with SUD and OUD have undiagnosed and untreated depression and anhedonia which further complicates efforts to save their lives and link these individuals to treatment.

Most of what we used to think of as the leading causes of death have been decreasing. Suicide is now more than twice as common as homicide in the United States.\(^{34}\) Longtime, established patterns of mortality are radically changing. For instance, there are now more deaths from self-harm than from diabetes\(^{36}\) Yet, inadequate attention has been paid to deaths by overdoses, suicide, and addiction. In a recent study, investigators revealed the connection between opioid-related overdoses and the spectrum of suicidal motivation.\(^{37}\) To wit, the expert panel consensus is clear: mortality from accidents and injury in the United States are the primary default cause-of-death assignment when the cause is not clear. Accidental deaths are too often misclassified as suicides by overdose.\(^{38}\)

**Prevalence and Trends**

OUD and SUDs have exacted a significant toll on U.S. society, and none more costly than the loss of human life and the sorrow and
suffering by the individual’s family and loved ones after a senseless overdose death, but also
the many more persons struggling for many years with substance use. The socioeconomic
costs are staggering, plus the overwhelming burden on our health care system. There are no
easy answers as concerned healthcare providers and policy makers struggle to wrestle with the
unrelenting, complicated, and in some areas, growing problem. While it is certainly true that
most opioid overdoses have other drugs in their blood at the time of death, and most people
with SUDs use multiple substances, we will focus here on the opioid use, overdose, and OUD
epidemics. Naturally, cocaine and methamphetamine fatal overdoses may be fentanyl over-
doses in disguise. Illicit drugs are not pharmaceuticals approved by the FDA. Rather, the fact
that they are illicit means that heroin, cocaine, or other drugs may have fentanyl added as an
adulterant. This synthetic phase of the current overdose epidemic indicates to the panelists
that naloxone should be available and administered whether the patient or other informants
say the overdose was something other than an opioid. What can we do to prevent overdoses
and improve treatment for opioid overdose, OUDs and SUDs?

The Neurobiology of
Addiction and Opioids

Opioid use disorders are secondary to bi-
ological mechanisms that impact various
interconnected brain systems that form the
functional neuroanatomy of brain reward
pathways in the mammalian brain. In what
follows, we provide a brief synopsis of reward
circuitries involved in OUDs.

The development of OUDs in animal models
and humans is dependent on interactions
of interconnected brain reward regions that
include the nucleus accumbens, dorsal stri-
atum, prefrontal cortex (PFC), and dorsal striatum, among others. These brain regions
receive dopaminergic projections from the
ventral tegmental area (VTA) and the sub-
stantia nigra pars compacta (SNpc). The
dorsal striatum is known to be involved in
the mediation of habitual drug taking behav-
iors. On the other hand, the PFC is involved
in drug seeking, reinstatement of drug
seeking, and other complex cognitive behav-
iors including decision-making in relation
to drug taking behaviors. The strength of
rewarding behaviors is dependent on specific
interactions between the nucleus accumbens
and hippocampus. It is important to note
that these brain regions contain high concen-
trations of opioid receptors that are called
mu, delta, and kappa receptors. Specifically,
Mansour et al. (1987) reported large concen-
trations of mu and delta opioid receptors
in the frontal cortex and dorsal striatum of
rats. The dorsal striatum also contains high
concentration of kappa opioid receptors. mRNAs that code for these receptors are also
found in those brain regions. Mu receptors
are the most important receptors as far as the
therapeutic effects and the abuse potential
of opioid drugs are concerned. PET studies
using radio-labeled opioid drugs have also
identified mu opioid receptors in human brain
regions. Post-mortem studies have reported
decreased expression of mu opioid receptors
in the striatum and PFC of heroin users. Human studies have also documented abnor-
malities in these regions of humans who
suffer from SUDs.

Of direct relevance to the topic of this white
paper, opioid receptors are located in brain
regions including the nucleus parabrachialis
medialis and ventrolateral medulla that control respiration, pupillary responses to light in the midbrain, and pain pathways in the spinal cord. Over the clinical course of opioid abuse, patients will develop tolerance and other molecular abnormalities in all these systems with moderate-to-high concentrations of opioid receptors. Overdoses of opioids impact mu receptors in all those brain regions and result in miosis, respiratory depression, and hypoxia.

**Brief Overview of Opioid Use Disorder**

Through the pioneering work of a handful of scientists and physicians, many of which have contributed to this paper, we have a far better understanding of the etiology and pathophysiology of addictive disease than even 5 years ago. Yet, knowledge alone, and in the hands of only a fraction of health care professionals and policy makers has done little to stem the tide of OUD in the United States.

What is not well understood by many primary care physicians and most specialties outside of addiction medicine, is that while self-administration of opioids is dangerous and addicting, opioids are safe and effective when administered to the appropriate patients. However, taking medication as prescribed can lead to important neuroadaptation to brain regions involved in reward-processing and motivational salience. Sadly, we don't fully understand who is at most risk for the development of OUD after opioid exposures. In the future we might have genetic markers of risk, but for now we only have behavioral factors to consider when evaluating a person's level of risk. What does the person bring to the opioid challenge? Exposure to opioids after a tonsillectomy increases abuse and OUD risk. This shows the logical roles that age and time of exposure play in risk of abuse. PTSD, early exposure to opioids, sexual or physical trauma, and several candidate genes may make some people more vulnerable than others, but it is clear that opioid overdose and OUD can and do happen independently of genetic and epigenetic risks. Genes related to OUD have been discovered and their role in increasing the risk for OUD is supported through transcriptome analysis (the volume of messenger RNA molecules).

The co-occurring expression of neuropsychiatric conditions with OUD is common. Genetically or epigenetically vulnerable persons using opioids are at greater risk and quickly manifest as OUD once exposed.

**The common and predictable disease sequelae often include:**

- Increased tolerance
- Progressive anhedonia, in which previously rewarding activities are no longer rewarding
- A narrowing of interests
- Mental preoccupation with obtaining and consuming a drug
- Compulsive drug seeking behavior
- Persistent, chronic pathological drug taking
- A loss of behavioral control in which one's behavior becomes incongruent with one's values and moral beliefs
- Repeated harmful consequences, e.g., familial, occupational/educational, legal, and social
- Failed attempts to mediate or discontinue drug use
- Increased emotional lability and despair
- Increased maladaptive, risky or dangerous behavior
- Drug and dose specific medical complications, accidents, and injury
- Suicidal ideation
We are not yet able to predict, whether by genomic testing or other means, in which patients with OUD would do best on what treatment. When asked if there would be a way to tell in advance of giving someone opioids whether they had a genetic abnormality or an opioid deficiency syndrome, Dr. Cadet stated, “There are some studies that suggest there is a single nuclear polymorphism that can predict whether somebody is going to become more of a heroin addict. And there is one SNP—if you make an animal susceptible to opiate addiction, you can show that by inserting the SNP in their genome, you can decrease the expression of the mu opioid receptors and that makes the animal give themselves more drug. You could predict that the patients who have low receptors to start with might be more likely to go on to develop a heroin use disorder.”

**Treatment**

We do know what treatment is and what works. A recent study has shown that treatment of OUD also reduces overdoses. Expanding Medicaid rolls under the Affordable Care Act may have saved as many as 8,132 people from fatal opioid overdoses, virtually all involving heroin and fentanyl. MATs work to reduce recidivism, improve retention, and reduce overdose.

Expanding access to buprenorphine is important to meeting the needs of patients with OUD, but government regulations requiring a DATA waiver to prescribe have limited utilization. A survey of recently waived clinicians found that only 13.1% were prescribing at or near their patient limit. Most patients with OUD benefit from psychotherapeutic modalities, peer and group support, and ongoing recovery counseling and coaching. MATs should be readily available and legislators may also reconsider the “methadone only in clinics” laws and regulations. Samet calls for allowing methadone dispensing in pharmacies and prescriptions in primary care. This would be a promising and positive development.

There is no silver bullet. Particular treatment options each have their place for different patients, requiring a carefully targeted and individualized approach. Medical professionals should give close attention to patients’ concerns about treatment locations and their broader social support networks. Without patient and provider collaborative care, OUD treatment outcomes are poor at best. Patients with OUD, as outlined in the DSM-5 criteria, should be screened for medical comorbidities such as infectious diseases, physical trauma, heart, kidney, pancreatic and lung disease. It is common for individuals with OUD to smoke and have other SUDs such as alcohol use disorder. Rarely do patients with OUD have a primary care provider or get routine evaluations, examinations, vaccinations, or regular lab testing to monitor their health. If routine healthcare is ignored, both acute and chronic conditions worsen, compromising overall health and shortening their lives. This has been documented among those who are adherent to their MAT regimen and following their treatment plan.

Approximately 11% of U.S. adults report daily pain, and an estimated 5 to 8 million patients with chronic pain use long-term opioids to manage their pain, putting them at risk for developing OUD. Dr. Stanos participated in a recent consensus panel report that acknowledged the challenges of diagnosing incipient OUD in patients with chronic pain, but emphasized the need to consider an OUD diagnosis and initiate MAT treatment in alignment with CDC recommendations when warranted. A subset of patients with chronic pain and comorbid SUD face additional barriers to access to MAT and naloxone because of stigmatization of both chronic pain and SUD.
Medical professionals should always consider the efficacy of long-acting injectable buprenorphine for patients who meet criteria, and long-acting injectable naltrexone treatment for patients with high contingency management, a monitor or internal motivation and high external support. Accordingly, among patients in need of a tapering or detoxification plan to safely transition to buprenorphine, it is critical that the physician advise the procurement of naloxone rescue kits for patients, their families, friends, and loved ones.

As Kleber suggested before us, looking at all options and all diagnoses for patients who relapse or experience a recurrence of symptoms is a critical step in devising a treatment plan that minimizes the risk of relapse and overdose. We point out that the current challenges of the drug overdose epidemic and high prevalence of poorly managed chronic pain offers us a chance to change our overall approach to OUD and SUD treatment. It is clearly not an either-or proposition.

### The Quagmire of Chronic and Intractable Pain Management

Chronic pain has been broadly described as pain that typically lasts greater than three months or past the time of normal tissue healing. Chronic pain can be the result of an underlying medical condition, injury, or arise from medical treatment, inflammation, or an unknown cause. Estimates of the prevalence of chronic pain vary. At present, the best available evidence suggests that between 20% and 30% of the U.S. adult population suffers from chronic pain and is increasing. Prescribing opioid analgesics for pain management—particularly for the management of chronic noncancer pain has increased more than four-fold in the United States since the mid-1990’s through 2012. The increased availability of prescribed opioids to patients and non-pain patients in the community was multifactorial. Groups included patients prescribed opioids for acute and chronic pain, excessive and unused medication prescribed in the perioperative and dental settings, diverted opioid from medical clinics, and egregious illegal prescribing by so-called “pill mills” contributed not only to opioid misuse, but development of OUD and upsurges in opioid-related overdose deaths. These concerns prompted a critical review and promulgation of various state and scientific guidelines into the CDC-sponsored opioid management guideline in 2016, Guideline for Prescribing Opioids for Chronic Pain. Twelve core recommendations included guidance that clinicians should use caution when initiating opioids (new starts) at any dosage, should carefully reassess evidence of individual benefits and risks when considering increase dosage to > 50 MME per day, and should avoid increasing dosage to > 90 MME per day or carefully justify a decision to titrate dosage to > 90 MME/day. For those patients already managed on chronic opioid therapy, the CDC recommended reassessing an individual patient’s risk-benefit profile and consider compassionate patient-centered
tapering when risks of continued opioid therapy outweigh benefits. The Guideline importantly advised evaluation of risk factors for opioid-related harms and recommended prescribing naloxone when the following specified risk factors for overdose were present:

**Risk Factors for Overdose**

- Patient history of overdose or substance use disorder
- Any patient prescribed an opioid dose of $\geq 50$ MME per day
- The concurrent use of benzodiazepines and opioid therapy for chronic pain patients.\(^{72}\)

The Guideline also discussed the importance of individually re-assessing, in a compassionate patient-centered manner, those patients already receiving chronic opioid therapy and consider tapering if harms or adverse effects outweigh benefits. The Guideline was adopted broadly and contributed to the trend of reduction in opioid prescribing. But with the rapid uptake came unintended consequences resulting in restrictive practices that are inconsistent with the Guideline and go beyond the recommendations.\(^{73}\) A consensus panel report (which included Dr. Stanos) highlighted the inconsistencies that include inflexible dosing, duration, thresholds that encourage hard upper limits of dosing, and rapid tapering of opioids, resulting in patients who had been appropriately prescribed opioids now faced with stigma and discrimination and are often dismissed from practices with no alternative pharmacological treatment approaches for them and their pain management.\(^{63}\) Safe prescribing for pain in alignment with the CDC guideline, is possible and most experts believe that blaming the patient with pain or the pain expert at this time in the epidemic is not justified.

Dr. Gebke, a family medicine chairman and physician who leads 50 practices with approximately 250 providers, shared his experience with changing attitudes of providers, “We have seen across Indiana, as in many states, that many of the pill mills have been shut down. As those offices are closed, patients are displaced, often through no fault of their own and they are on very high doses of medication and need to be followed somewhere. Unfortunately, they’re looked at as lesser people that physicians don’t want to take care of because of this problem.”

Patients suffering from chronic pain may use opioids as part of their individualized treatment plan. In appropriately monitored patients, opioids may be an effective tool to help maintain or improve their quality of life and level of function. Although these individuals are physically dependent on opioids, they are not “addicted” or meet criteria for opioid use disorder. Understanding how to better or more safely use opioids not only for chronic pain, but for acute pain and perioperative pain, will help to decrease opioid related morbidity and mortality, including opioid overdoses.

“The Guideline does not endorse mandated or abrupt dose reduction or discontinuation, as these actions can result in patient harm. The Guideline includes recommendations for clinicians to work with patients to taper or reduce dosage only when patient harm outweighs patient benefit of opioid therapy. The recommendation on high-dose prescribing focuses on initiation. The Guideline offers different recommendations for patients already on opioid dosages greater than or equal to 90 MME.”

Robert Redfield, MD – Director, CDC
One major potential catalyst to change clinical practice has been the emergence of naloxone as a rescue medication for patients with OUD at risk of overdose. As with other major paradigm shifts in medicine, the availability of naloxone presents a beneficial disruptive innovation around which new systems of care may be assembled and deployed. Better insights have been needed to understand who is at risk and why; how to raise awareness of risk amongst users and their network; what socioeconomic pressures are increasing the risk of overdose; and what other demographic factors may play a role in the future. Panelists addressed these questions, putting a fine point on emerging data about the availability of naloxone.

**Mechanism of Action of Naloxone**

Naloxone hydrochloride is a synthetic N-allyl derivative of oxymorphone. Classically, it is thought of as purely a narcotic nonselective antagonist exerting its effect through competitive inhibition at the $\mu > \delta > \kappa$ opiate receptors. It reverses the cardiovascular and respiratory depression caused by opioid overdoses and essentially is a relatively safe and useful diagnostic and therapeutic agent. However, it is worth mentioning that other mechanisms of action may be clinically relevant as well. For example, there is ample evidence that opioids are immunosuppressive and predispose patients to sepsis and invasion of the brain by HIV virus. Antagonism of this effect by naloxone may be clinically protective. The (+) isomer of naloxone has been shown experimentally to exert effects at the toll-like receptor 4 (TLR4). Antagonism of this receptor by naloxone reverses neuropathic pain and reduces opioid and cocaine reward and reinforcement. Naloxone has been shown experimentally to reduce inflammation by suppressing cytokine expression. Finally, a relatively new path of inflammation has been identified that involves activation of nuclear factor-kappaB (NF-κB). Naloxone has demonstrated the inhibition of endotoxin-induced up-regulation by this system by antagonizing L-type calcium channels and, to a lesser extent, the $\mu$-opioid receptors.

It is important to factor in these additional mechanisms of action because much of what happens to patients at high-risk of opioid overdose is secondary damage. A patient who survives overdose faces the prospects of other medical conditions like anoxic brain injury, sepsis, heart valve damage, cardiac arrhythmia, pneumonia, abscesses, hormone dysregulation, and the effects of malnutrition. These all contribute to prolonged hospital stays in the intensive care environment, which can be fraught with secondary risk. When considering the trajectory of a survivor of overdose, it is beneficial to consider that naloxone is more than a critical link in the chain of rescue, but it may also play a role in positioning the patient for a better long-term outcome.

**Naloxone – Can Save Lives if People are Educated to Carry and Use it**
Improving Our Understanding of Populations At-Risk for Overdose

It is notoriously difficult to estimate the risk of overdose from opioids, in part because our understanding of the extent of the problem has been limited. Dr. Fuehrlein presented new data (Figure 1) showing that official estimates of heroin use are grossly underestimated. In 2010, the National Survey on Drug Use and Health (NSDUH) estimated that there were 60,000 active heroin users in the United States. However, this projection well missed the mark according to work done by Caulkins in 2005 and Midgette in 2019. They relied upon multiple sources of data (including urinalyses from the Arrestee Drug Abuse Monitoring Program) to develop real estimates showing Daily or Near Daily use of heroin may affect as many as 3 million individuals.88,89 This fifty-fold difference is hard to comprehend, but this discrepancy may explain why the epidemic presented as something of a surprise and why we have been challenged to organize the resources needed to catch up and counter the epidemic. Although sophisticated machine-learning techniques are now being deployed to improve surveillance, as a nation, we were “caught unaware” of the massive nature of this problem until it became obvious.

Adding to the challenge is the variable presentation of overdose for different demographic groups. Dr. Baron discussed cases illustrating elite athletes who broke a femur and did not feel at risk of overdose or any untoward effects. Older people prescribed opioids or opioids plus benzodiazepines may be considered by the CDC and their HCP to be at high risk, but do not see themselves at risk by virtue of their lack of drug misuse or interest in taking their pain medications to get high. Among 209,947 adults aged at least 65-years-old insured through an AARP Medicare Supplement Plan (excluding cancer or hospice patients) found that 57% had a prescription for opioids. 28% had opioids plus one CNS prescription (benzodiazepines, gabapentinoids, muscle relaxants, hypnotics, antipsychotics). 15% had opioids plus two or more CNS prescriptions. Approximately 60% of concurrent medications were ordered by the same prescriber, most often a primary care physician.90 In other examples, an older patient with cognitive impairment and a patient with sleep apnea are both at risk of an overdose, but for different reasons.

Opioid dose variability may be a risk factor for overdose. In a nested case-control study of 228 patients who experienced an overdose, Glanz et al found that high dose variability of greater than 27.2 MME was associated with a
significantly increased risk of overdose compared with low dose variability.\textsuperscript{91}

Practicing in a psychiatric emergency department (ED), Dr. Fuehrlein shared the well-established protocol for a patient with OUD who presents to the ED. That patient receives education about OUD, naloxone, and harm reduction. The patient is also provided access to naloxone upon discharge. On the other hand, if an older patient on opioids, without OUD, but physically dependent (150 MME per day) presents to the ED because of an event and on the advice of their primary care physician, the protocol is not so clear.

Prediction in individuals is not the same as a prediction at the population level. This is only confounded by the heterogeneous approach and lack of standardization of care. Furthermore, more overdose deaths result from OUD/SUD and illicit use than from legitimate prescription use. Panelists agreed—one policy does not fit all. We have to look at this in a more holistic approach.

There currently exists a significant opportunity to make a major difference in the lives of patients who are prescribed opioids and may be at-risk for overdose. A survey conducted by Clear Perspectives of three at-risk populations (Figure 2) strikingly revealed that only one third of patients receiving opioid prescriptions are actually aware that naloxone can be used at home for reversal. Even among those considered high risk for overdose, only 44% were aware that naloxone can be used at home (Figure 3).\textsuperscript{92}

Less than one quarter of all opioid users in the survey were ever offered naloxone, and only one third of patients who meet CDC at-risk criteria were offered naloxone for at-home use in case of overdose.\textsuperscript{92}

This low level of awareness is troubling and speaks to several factors that are hampering more wide-spread co-prescription of naloxone. Educational interventions to both patients and prescribers are necessary to improve provider-patient communication about the risk for overdose, signs/symptoms of overdose, and informing patients that naloxone is available for use by them or a loved one at home. Panelists presented their experience that social stigma plays a significant role by interfering with proper communications from providers to their patients.

As a short-acting agent temporarily reversing the effects of opioids, naloxone gives a person with OUD a second chance—an opportunity to receive treatment. As a result of the Surgeon General’s, CDC, and other campaigns to improve naloxone access, retail pharmacies
increased naloxone dispensing from 2012 to 2018, but the gap remains between high dose opioid prescriptions and co-prescribed naloxone.\textsuperscript{3}

Stigma surrounds OUD and overdose prevention. It can be likened to the early days of antidepressants when patients often expressed that they felt stigmatized at the pharmacy when they heard “Mr. Jones, your Elavil is ready”. Stigma kept many depressed patients from filling much needed prescriptions. But, in this case, is it stigma plus the lack of pharmacist and HCP education? It is tough to pinpoint a cause for these data by Guy and colleagues. Is filling a prescription for naloxone a taboo? Is the prescriber’s reluctance to address the risks of high-dose opioid prescribing to be blamed on shame and stigma? No one knows for sure. The CDC and Surgeon General of the United States encourage us to improve naloxone access at the local level, including prescribing and pharmacy dispensing. But, patients who ultimately overdose are very different. Those with OUD or SUDs need treatment. Rather than focus on intervention and MAT treatments here, we have focused on naloxone. This perspective makes sense because of the interventions available for OUDs. Naloxone, when available and given in an overdose, really saves lives. Unfortunately, the lowest rates of naloxone dispensing are in the areas with the highest opioid overdose rate. We are now in the third phase of the opioid epidemic, with opioids giving way to heroin and now fentanyl. Individuals who overdose often overdose again, and many patients treated in substance use programs or health care providers’ offices with MATs, relapse.

When addressing the barriers patients with OUD face in accessing naloxone, Jessica Hulsey Nickel boiled it down to stigma, implementation challenges, and reaching patients who need naloxone most. From a policy perspective, she proposed six strategic priorities for ending SUD as a major health problem.

### 6 Strategic Priorities for Ending SUD

1. End stigma
2. Help patients and families in crisis
3. Prevent addiction and intervene quicker
4. Improve treatment
5. Foster innovation
6. Respond to addiction through education

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### Awareness Does Not Necessarily Mitigate Risk

Patients with OUD or SUD are at high risk for overdose when using drugs recreationally. In patients who die from an overdose, there is a significant degree of overlap between prescribed and illicit opioids. It is not intuitive or logical that users would place themselves at such grave risk, but it turns out that this very risky behavior is part of what they crave.\textsuperscript{53}

Unfortunately, these are the people at the greatest risk of overdose and would benefit the most by having naloxone available. Awareness of naloxone, then, does not necessarily mitigate risk, particularly amongst those with unwarranted overconfidence in their ability to manage their dosing. This cognitive bias is an example of the Dunning-Kruger Effect, which describes how people with low levels of expertise are more likely to exhibit a disproportionate lack of insight into their ignorance. The panel
shared the data of user “responsibility” which indicated that the people in greatest need are the least likely to seek rescue solution.

Denial also plays an important role. Data from a 2019 survey of opioid users in the United States revealed that more than two thirds of the patients taking opioids who meet CDC at-risk criteria believed that they had little to no risk of an opioid overdose.\(^9^2\)

However, these patients do not exist in a vacuum and often have family or friends who care for them and are aware of their risky behavior. These advocates would be ideal candidates to stock naloxone as they often are the first responders on the occasion of an overdose. A proper risk stratification scheme, then, ideally would make it easier to identify these advocates and enable them to be equipped to intervene with naloxone.

One of the biggest challenges is raising awareness. Many parents, for example, are unaware that their children are high-risk users. Denial may act as a powerful reason why so many parents are unwilling to attend events designed to raise awareness. Unfortunately, all too many parents do not seek out information because of the stigma attached to the subject or simply because they couldn’t fathom their children being affected.\(^9^4\)

## Overdose Competencies

The widespread acceptance of naloxone faces many barriers to acceptance. Beyond a lack of knowledge, attitudes, opinions, and stigma are interfering with acceptance and availability.

The diverse palette of people using opioids, whether prescribed or not, creates a challenge when it comes to assessing knowledge of overdose risks, mitigations, and treatments.\(^9^5\) Socio-economic factors, education level, cognitive status, demographic factors, and cultural norms all play a role in how people perceive and handle these very powerful agents.

The panel agreed that it is important to “medicalize” overdose. Encouraging treatment after a near-death event cannot be overestimated as a treatment for the SUD related cause of the overdose. There are certain basic principles about the function of opioids that are easy to grasp: respiratory depression, loss of inhibition, impaired cognition, interaction with other medications, and decreased employability. These principles cannot be assessed easily with forced-choice answers, but they can be taught in a no-nonsense way that illuminates consequences.

With the presence of ubiquitous online social media, tools may be developed that not only assess awareness of overdose risk but also assess awareness of rescue treatments. Well-designed competency assessments could theoretically be tied back to educational opportunities that present easily digested information directed at the consumer level.\(^9^2\)

Dr. Baron explained that what is taught by the teacher is often less important than what is learned by the learner. To wit, any assessment of competency should include not only a query of knowledge but also beliefs, opinions, and attitudes, which constitute the “affective component,” a fundamental necessity for change.
This is essential, as changing attitudes requires more than facts. Emotional resonance and empathy followed by emotional investment and commitment to see one's salient objective realized is an effective approach to initiate behavior. Accordingly, messages must be properly tailored and customized to speak to "target populations" if we are to overcome the stigma attached to opioid use, as well as increasing access to and using naloxone. “But it’s just for junkies” is the narrative that must be overcome with truth, non-judgmental language, and listening to the community in order to “earn the right to be heard.” The only way to overcome the mountain ahead is to coalesce communities into agents of life saving change.

Dr. Baron suggests that athletes are much less likely to accept a prescription of naloxone, as they may see it as a sign of weakness. Conversely, athletes, respond well to Cognitive Behavioral Therapy and positive messages that prevent them from feeling “flawed” or defective. Their need to maintain a specific “invincible” mindset predisposes them to avoid asking for help. They tend to pursue a “resilient” attitude in which, in their domain, asking for help represents a loss of control. The degree to which they have a reliable support system and effective coping skills may determine their willingness to reach out for solutions that may be helpful. For that reason, the panel advocates making naloxone available not only for athletes to carry on their person but also in the locker room, in locker cabinets, and training facilities.

Patients with chronic pain without SUD are similar to athletes in that they may harbor preconceived notions of the role of naloxone. They may be wary of the stigma linking naloxone to SUD patients and thus want to avoid accidentally telegraphing a signal to their network that they may be opioid-dependent, as many are treated as such at their pharmacies. Thus, there is much work to be done to create positive messages, free of judgment, that help to destroy stereotypes and eliminate stigma.

While trying to improve access to naloxone and overdose reversal, the panel emphasized that expansion of coverage for OUD treatment must go hand in hand with expanded access to naloxone. Recent studies have looked at the effects of Medicaid expansion, which gave millions of low-income adults access to health insurance. Medicaid expansion was made optional in a 2012 Supreme Court ruling, and only 32 states and Washington, D.C., had opted to expand by the study period (with the total increasing to 37 in the past few years). Improved access to MAT for OUD was linked to a reduction in opioid overdose death rates. Counties in states that expanded Medicaid under the ACA by 2017 were compared to counties in states that didn’t expand Medicaid, accounting for variables like demographic and policy differences. The researchers found that Medicaid expansion counties had a 6% lower rate in opioid overdose deaths than non-expansion counties. The decline was mostly due to an 11% lower rate of deaths involving heroin and a 10% lower rate for deaths linked to synthetic opioids.

**Risk Stratification**

Panel members agreed that people who use opioids are highly diverse in their presentation, characteristics, and motivations. Painting all of them with a broad brush does little to serve the objective of reducing untimely deaths from overdose. Instead, it is desirable to be able to characterize patients according to various factors that predict which patients are at high risk of overdose. Such insight is highly desirable because it could potentially save many lives.
However, panel members expressed concern that we could be missing many subtle and nuanced factors, due to the way we indiscriminately look at opioid users. The fact is that nearly all opioid users and many of their doctors are under intense scrutiny as a result of opioid medications. Thus, a deeper dive is warranted to develop a better, more accurate understanding of who is using opiates as prescribed, as opposed to illicitly; who is likely to transition from prescribed use to illicit use; and who is at high risk of death. The panel noted that there are well-defined demographic characteristics and risk factors that are identifiable and predictive of bad outcomes. These should be utilized in a formal risk stratification rubric.

The panel pointed out that among those who use prescription opioids for pain, the vast majority use them as prescribed. However, some patients are at greater risk of overdose than others. Among those who are involved in illicit use, some of them started out with prescription medications then found themselves facing a difficult decision when denied further refills. The option of opioid withdrawal is daunting to most and often so unpleasant that illicit opioids seems a reasonable option for them. Other opioid consumers start illicitly using for recreational purposes and matriculate from one agent to another, often “running towards the fire” when they hear of other users dying from overdoses due to powerful batches.

Thus, a worthy stratification scheme would serve two important functions. On the one hand, it would appropriately identify those patients at high risk of accidental or intentional overdose, enabling appropriate interventions to save their lives, including the use of naloxone. On the other hand, such a scheme, when done well, has the potential to also allow those patients at low risk to continue to benefit from appropriate opioid prescribing without the stigma or risk of being cut off inappropriately. Overall, morbidity and mortality would be reduced for both patient populations.

Where to Begin?

There are numerous entry points in which to initiate interventional strategies that slow, hinder, or reduce the pain, suffering and mortality resulting from the drug epidemic in the United States. However, the shocking mortality rate associated with illicit and prescription opioid abuse is of highest priority. Accordingly, the best, most timely and cost-effective intervention for preventing acute opioid overdose mortality is increasing the availability and administration of naloxone. Why? Because the favorable efficacy and safety profile of this medication is well established in the scientific literature and undisputed among addiction and emergency medicine professionals regarding the lifesaving effect of naloxone on those experiencing respiratory distress due to the effects of opioid overdose. Yet “how” to get naloxone in the hands of those who are in a position to intervene and are willing to administer it to a person who has overdosed remains unsettled. Expanding access to naloxone is not a straightforward one size fits all proposition. There are numerous pros and cons that can potentially inhibit or increase access and administration of this life-saving drug. The purpose of this paper is to synthesize and summarize the best available evidence by some of the leading scientific experts on neurobiology, addiction medicine, psychiatry, primary care and academic medical institutions in hopes of making naloxone accessible in order to save lives. As with other
major paradigm shifts in medicine, the availability of naloxone presents a beneficial disruptive innovation around which new systems of care may be assembled and deployed. Better insights have been needed to understand who is at risk and why; how to raise awareness of risk amongst users and their network; what socioeconomic pressures are increasing the risk of overdose; and what other demographic factors may play a role in the future. Panelists addressed these questions, putting a fine point on emerging data about the availability of naloxone.

Progress has been Made in Naloxone Access, but Not Nearly Enough

A central issue was how to best improve access to naloxone. Nine states (Arizona, California, Florida, New Mexico, Ohio, Rhode Island, Vermont, Virginia, and Washington) have implemented legislation requiring naloxone co-prescribing with high risk opioids. Dr. Gebke provided the panel with his experience throughout Indiana and Dr. Fuehrlein with the Veterans Administration demonstrating that naloxone access was not a question of cost and access was nearly universal. What was missing was a true understanding of risk and interventions directed at going to the pharmacy or carrying naloxone. Expanding state-level policies requiring naloxone co-prescribing to high-risk patients may have large effects on clinical practice. Additional research is needed to improve the understanding of patient and clinician barriers to naloxone and determine the benefits and cost-effectiveness of naloxone co-prescribing. Clinicians, pharmacists, and the patients on an opioid regimen should be educated about naloxone and the importance of co-prescribing. Health systems could easily pursue proactive approaches such as implementing co-prescribing prompts into electronic health records and at point of purchase.

Naloxone distribution programs include community education and provide naloxone administration kits to opioid users, their friends and families, and any willing person who may be in a position to rescue someone during opioid overdose. From a purely economic cost benefit analysis the argument for naloxone is sound.
Argument for Naloxone

- A naloxone distribution program in Massachusetts reduced opioid overdose deaths, without increasing opioid use, by an estimated 11% in the nineteen communities that implemented the program.\textsuperscript{99}
- A large-scale national study showed that opioid overdose deaths decreased by 14% in states after they enacted naloxone access laws.\textsuperscript{100}
- Statistical modeling analysis suggests that increased naloxone distribution among emergency personnel and laypersons could reduce opioid overdose mortality by 21%.\textsuperscript{101}
- States that adopted naloxone legislation saw fatal opioid overdoses fall by an average of 27% during the second year following passage and 34% in subsequent years, according to a study published in \textit{JAMA Internal Medicine}.\textsuperscript{102}
- Researchers found that laws encouraging the distribution of naloxone—but stop short of allowing direct dispensing by pharmacists—did little to reduce opioid-related overdose deaths.

There are a handful of states that have naloxone distribution programs. New York and California are two examples that have implemented best practices in public policies and distribution networks to provide naloxone to first responders, city and county departments of health, and correction facilities (Figure 4).

All the expert panelists with clinical experience have known many patients who have overdosed numerous times and miraculously lived. Many times it seems like OUD should be considered like other fatal diseases.\textsuperscript{103} However, some of these patients eventually went on to, and successfully completed treatment, and now live happy, fulfilling lives, free from the shackles of OUD. No one ever knows for sure who will make it and remain in recovery, or who will relapse and die. Naloxone doesn't discriminate. It saves the lives of rich and poor, old and young, black and white. Naloxone may save the same person 20 times before something changes in them or their circumstances and against all odds, they received the help they needed and live in recovery. It would be better if the first time they overdosed, we had intervention systems in place to link them to treatment. But, it is a gratifying experience to meet and individual in recovery years later and hear how lucky they were and feel as they turned their lives around to become productive, contributing citizens.

Naloxone: In Search of a Public Health Model

The panel discussed several effective public health models to conceptualize logical approaches to naloxone distribution and encourage filling prescriptions and carrying naloxone. For example, should naloxone be thought of like cardioversion with equipment strategically located in public places, airports and hospitals? Yes, the panel agreed. Should it be more universally applied to adults, like CPR training for cardiac arrest or Heimlich for choking? The panel found that proposal to be an extremely unlikely model for opioid overdose response. Another model discussed was drug or food allergy. Parents with a child who has a drug or food allergy, carry an EpiPen\textsuperscript{®} and when possible, so do their loved ones. It is commonly found on crash carts, as well. If we
use the example of the EpiPen®, who should carry naloxone? This made sense to the panelists for people with OUDs, SUDs, and their loved ones.

Panelists did not think it was logical to give every American naloxone and encourage each and every one of them to carry naloxone, and refill it when it expired. While the CPR or Heimlich model might be popular, they do not necessitate additional cost or obtaining a refill. Getting naloxone in the right places and in the right hands is the challenge. In hospitals and EDs, naloxone is typically on crash carts and available like cardioversion. Naloxone should be readily available in any drug rehabilitation or treatment facility, and in the homes and possession of individuals with OUD/SUDs and their loved ones. Reducing stigma and encouraging family members, friends and neighbors of persons with OUD to see themselves as potential life-saving agents, in an army of other life-saving agents who are trained, aligned and coalesced against the common enemy, opioid dependence, and not against the suffering person. This simple paradigm shift could save many thousands of lives each year.

The panel noted that the challenge of getting naloxone to be considered as an important rescue medication by elder pain patients, athletes, and others determined to be at high-risk by CDC guidelines has proven more daunting than predicted. Healthcare provider-patient education and motivational enhancement is the most likely way to change the mindset of these patients groups. It should also be carried by CDC recommended patients with pain, at the bedside of elder patients taking opioids for pain, and in senior communities. Their loved ones and care takers should understand opioid reversal if they see them obtunded, breathing shallowly, and in distress.

**Unintended Consequences of Unsupervised Dispensing**

We are in a new and extremely dangerous phase in the opioid epidemic. Fentanyls and other manufactured drugs are primary drugs of abuse and also added to heroin. Developing prevention, intervention, and treatment approaches for the current problems are difficult and complicated. As noted by Dr. Rummans, good intentions can lead to very bad outcomes. Today, we find another, similar advocacy initiative brewing in the position of widely distributing naloxone without a prescription. The panelists could not find data or studies to support this hypothesis. Many thought it was emotionally compelling and difficult to not endorse to show that you are doing everything that you can in such an OUD crisis. They agree that improving access is critical, but that access can only be improved by identifying the patient subgroups and messages or strategies needed by each for maximizing access and utilization. Supporters of simply changing naloxone to over-the-counter (OTC) argue that the enormity of the epidemic demands a proportionate response and claim that a move to OTC status would stem the tide of damage. They claim that “Naloxone is often unavailable when and where it is most needed,” and that “Naloxone's prescription-only status is a barrier to access.”

Panelists did not dispute the first point. Indeed, Dr. Stanos supported this with disquieting data showing that more than three quarters
of opioid deaths occur outside of a clinical setting, yet only 5% of people prescribed opioids receive a co-prescription of naloxone. However, the panel diverged from the advocacy position and argued that naloxone should only be dispensed with a prescription for a variety of reasons.

### Reasons to Dispense Naloxone with a Prescription

- Dispensing with a prescription does not exclude a physician’s standing order for naloxone from which a pharmacist can dispense naloxone to a patient.
- Data illustrating deficits in risk awareness of overdose preventing the ability to self-select for naloxone.
- An OTC naloxone strategy further removes the patients with a chronic disease from the appropriate diagnosis, management, and care of their health care provider.
- Shifting to OTC could actually have the paradoxical effect of increasing costs to consumers. Currently, naloxone is one of the most well-covered medications in history. One naloxone product has nearly 100% coverage from commercial insurance plans and Federal payors. The majority of patients pay a copay at most to acquire their prescription, averaging around $20 per patient, with many of them paying nothing. Many insurers do not, or like Medicare, cannot cover OTC drugs.
- Under an OTC distribution, it’s expected that the cost of naloxone to the consumer at most distribution outlets would be much higher than the average insurance co-pay, creating a disincentive for purchase without commercial insurance/Medicaid assistance.
- OTC availability still will place the product behind the pharmacy counter, requiring personal identification for purchase. This also is a disincentive and may serve as a barrier for purchase and stigmatize the patient.
- OTC availability may create a disincentive for people at high risk for overdose to seek medical help and further increase their risk on the basis of a false sense of security.
- There is little to no evidence that OTC access currently makes a difference in survival when it is offered in the community. The stigma attached to it may be a barrier for the highest-risk patients, and tailored education for them is likely to have a greater impact and should be the focus of advocacy groups.

### The Way Forward with Naloxone Through Education

In response to the evidence supporting the use of naloxone to prevent opioid overdose mortality, Anne Schuchat, MD, principal deputy director of the CDC stated:

“We are making progress in reducing high-dose opioid prescribing, but there is still too much. And we are seeing significant increases in pharmacy prescriptions for naloxone, but there is much room for improvement.”

Likewise, Robert R. Redfield, MD, Director of the CDC emphasized that access was not enough, public education is needed to engage persons to use Naloxone in order to save a life.

“It is clear from the data that there is still much needed education around the important role naloxone plays in reducing overdose deaths”

Following the Surgeon General’s report the Department of Health and Human Services issued guidelines for health care providers on naloxone prescribing. The following statement provides an excellent analysis and summary on the importance of getting naloxone into as many hands as possible in order to save lives.
The results from several prospective cohort and randomized trials identified the programs associated with higher utilization and efficacy of naloxone intervention. The modalities associated with the best results included structured naloxone training and administration kits to the participants. Participants included both opioid users and concerned others who, as a result, reported significantly greater knowledge of overdose symptoms and improved discernment of when naloxone was indicated. The training resulted in demonstrated superior willingness and competency in administering the drug.\textsuperscript{106,107}

At the community level, the investigation by Bachhuber and colleagues revealed that targeted messaging to increase public support for naloxone intervention was most effective when including both empirically derived factual information about OUD and was delivered in a sympathetic non-judgmental manner. As a result, concerned others reported that they could better empathize with opioid dependent persons and the overwhelming stress on them and on their families. They believed that participation in this program was a significant contribution to their community.\textsuperscript{108} Utilizing a follow-up interval analysis with controls, outcome data revealed significant reduction in opioid overdose mortality in communities that adopted Opioid Education and Naloxone Distribution (OEND) programs when compared to communities without OEND or similar approaches.\textsuperscript{109}

**The HCP-Patient Encounter**

The evidence revealed that the HCP-patient encounter is most likely to result in adherence to using naloxone by discussing opioids and the benefits of naloxone in a non-authoritarian manner.

**Specific recommendations include:**

- Discuss ways to strengthen the provider-patient relationship to support shared decision making in the use of opioids for chronic pain
- Identify potentially negative outcomes that may result from a lack of concordance between provider and patient on opioid therapy
- Identify when to coordinate care with mental health providers and other specialists for patients on opioid therapy
- Discuss ways providers can enhance collaboration with patients to optimize the benefits and minimize the harms from long-term opioid therapy
- When talking to your patients about opioid safety and naloxone, use language that is educational and disarming. For example, “The medication that you are taking is to manage your chronic pain, but must be taken as advised and stored in a safe place. In some situations, an adverse reaction may occur from taking the medication incorrectly causing your breathing to slow or stop. As a standard of care, I recommend that you have a rescue medication at home in the event of an opioid emergency. Would you like to learn about naloxone?”

“To reduce the risk of overdose deaths, the guidance released today reinforces and expands upon prior CDC guidelines. It recommends that clinicians prescribe or co-prescribe (prescribed in conjunction with additional medication) naloxone to individuals at risk for opioid overdose, including, but not limited to; individuals who are on relatively high doses of opioids, take other medications which enhance opioid complications, or have underlying health conditions. By co-prescribing, or prescribing naloxone to at risk individuals, patients and their loved ones could be better equipped for possible complications of overdose, including slowed or stopped breathing. Clinicians should also educate patients and those who are likely to respond to an overdose, including family members and friends, on when and how to use naloxone in its variety of forms.”

- Adm. Brett P. Giroir, MD, assistant secretary for health and senior advisor for opioid policy. December 19, 2018
Education to Reduce the Risk of Overdose

There is a need for greater awareness and education among individuals, families, and health care providers about the risk of major opioid effects from decreased breathing to acute overdose, typically associated with opioid treatment regimens >50 MME.

Risk Established by 2016 CDC Guideline on Opioid Prescribing\(^{72}\):

- Education is also needed to improve awareness of the risk associated when opioids are used with benzodiazepines, gabapentinoids, muscle relaxants, and most CNS agents.
- Health care providers should quantify the risk for their patients and the public.
- Patients in medication transition, e.g., tapering off of opioids or starting a new opioid regimen.
- Risk stratifications should be a part of the pain evaluation.
- When opioid dosage is reduced, a taper slow enough to minimize opioid withdrawal symptoms should be used and based on individual patient goals and concerns. Common tapers involve dose reductions of 5% to 20% every four weeks.\(^{110}\)

Conclusion

The panel reviewed these data and discussed the current needs and challenges.

Recommendations:

- Pain protocols using non-opioids, selective opioid use, and multimodal treatment modalities advance throughout the county. Efforts made by surgeons, dentists, pain specialists, primary care providers, and other health care providers have decreased opioid prescribing for non-malignant pain, but the OUD crisis with overdose continues.
- Develop specific strategies for intervention and to improve awareness of naloxone among all specialized (chronic pain; SUD; psychiatric) at-risk populations.
- OUD risks for the elderly and patients with chronic pain will continue and naloxone awareness, education, and prescribing is prudent to prevent accidental overdose.
- Improve availability and access to naloxone, maintaining at-risk individuals within the healthcare system by keeping HCPs involved in managing substance use disorders (SUDs) as chronic diseases in a non-stigmatizing way.
- Study naloxone prescribing and filling rates for high risk patients, those with OUDs or SUDs, those with pain prescriptions in the dose identified by the CDC, and think about pain in special at-risk populations such co-occurring anxiety, depression, or trauma.
- Medicalize overdose to underscore naloxone rescue as an established treatment modality.
- Keep individuals at risk of overdose in the health care system. Distancing patients from the health care provider by providing access to naloxone OTC further distances patient-centered, holistic care.
- Provide access to naloxone where patients are at greatest risk for overdose—at home. Recruit an army of life-saving agents by strengthening and improving naloxone distribution to patient, family, and loved ones based on best practice models.
- Following an overdose reversal, link the individual to treatment. Expand access to MATs and SUD treatment which can have tremendously positive effects on patient outcomes and overdose. A retrospective analysis of 40,885 individuals with OUD found that treatment with buprenorphine or methadone was associated with reductions in overdose and serious opioid-related acute care.\(^{111}\)
- Start training more addiction medicine physicians and providers, as well as peer counselors, to help facilitate the transition from naloxone reversal to MAT treatment.
- Support EDs and addiction professionals to reduce program turnover and burnout.
- Measure outcomes, especially with targeted high-risk groups. Track the volume of naloxone distributed and correlate with mortality from overdose and share positive results in the pain and OUD/SUD communities.
There are no easy answers to this problem, naloxone is not a panacea.

We are fortunate to have an agent, naloxone, that can reverse heroin overdose and even the more potent fentanyl overdoses.

Naloxone saves lives of those people with OUD/SUD who overdose and those with pain syndromes who overdose. Simply, naloxone provides a second chance whether it is an accidental overdose or if they are intending to die of despair. We need to work together to help everyone understand that an opioid overdose is life-threatening and often fatal. Naloxone reversal should be considered an emergency and treatment of last resort.

Health and Human Services Guide for Clinicians on the Appropriate Dosage Reduction or Discontinuation of Long-term Opioid Analgesic.


