

Reducing Fatal Opioid Overdose: Prevention, Treatment and Harm Reduction Strategies

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The opioid overdose epidemic is a major threat to the public’s health, resulting in the development and implementation of a variety of strategies to reduce fatal overdose [1-3]. Many strategies are focused on primary prevention and increased access to effective treatment, although the past decade has seen an exponential increase in harm reduction initiatives. To maximize identification of opportunities for intervention, initiatives focusing on prevention, access to effective treatment, and harm reduction are examined independently, although considerable overlap exists. Particular attention is given to harm reduction approaches, as increased public and political will have facilitated widespread implementation of several initiatives, including increased distribution of naloxone and policy changes designed to increase bystander assistance during a witnessed overdose [4-7].

INTRODUCTION

The Opioid Epidemic

Opioid use, abuse, and overdose collectively constitute one of the most significant and ongoing threats to the public’s health in this country [3,8]. In the past 2 decades, unparalleled access to prescription opioids such as hydrocodone, oxycodone, and fentanyl has led to a full-scale epidemic [9]. Fatal opioid overdose does not discriminate. It takes the lives of our nation’s wealthiest and poorest inhabitants and is blind to race, education, and social status. Between 1999 and 2010, fatal opioid overdoses quadrupled from 4,030 deaths in 1999 to more than

16,000 in 2010 [1,2]. In 2008, as deaths from accidental poisonings outpaced those from motor vehicle collisions for the first time in more than 3 decades, opioid pain relievers were involved in 73.8 percent of those deaths [10,11]. The Centers for Disease Control and Prevention (CDC†) has reported that for every unintentional overdose death related to an opioid analgesic, nine people are admitted for substance abuse treatment, 35 visit emergency departments, 161 report drug abuse or dependence, and 461 report nonmedical uses of opioid analgesics [9].

The opioid epidemic has affected the lives of countless families and has garnered the attention of many public health officials, harm reduction organizations, health

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†Abbreviations: CDC, Centers for Disease Control and Prevention; JCAHO, Joint Commission on the Accreditation of Healthcare Organizations; VA, Veteran Affairs; OME, oral morphine equivalents; PMP, Prescription Monitoring Program; NIH, National Institutes of Health; SAMHSA, Substance Abuse and Mental Health Services Administration; MAT, medication-assisted treatment; BNI, Brief Negotiated Interview; SBIRT, Screening, Brief Intervention and Referral to Treatment; ACGME, Accreditation Counsel for Graduate Medical Education; NIDA, National Institute of Drug Abuse; EMS, emergency medical services; EMTs, emergency medical technicians; ONDCP, Office of National Drug Control Policy; DEA, Drug Enforcement Administration; STIR, Screening, Treatment Initiation and Referral to Treatment; ED, Emergency Department; OEND, opioid education and naloxone distribution; FDA, Food and Drug Administration; ONDCP, Office of National Drug Control Policy.

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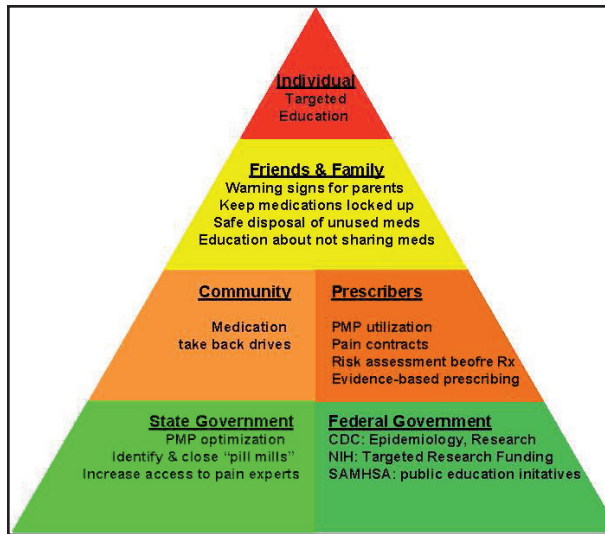


Figure 1. Opportunities to reduce overdose risk through primary prevention. There are multiple access points for primary prevention initiatives on an individual, friends and family, community, prescriber, and government level. Abbreviations: Prescription Monitoring Program (PMP), Prescription (Rx), Center for Disease Control (CDC), National Institute of Health (NIH), Substance Abuse and Mental Health Services Administration (SAMHSA).

care professionals, and policy makers. There have been significant strides in developing initiatives to decrease fatal opioid overdose, most of which fall into three broad areas: 1) primary prevention; 2) increasing access to effective treatment; and 3) harm reduction strategies, including wide distribution of naloxone and legislation to increase medical and bystander assistance during an overdose [2,5,12]. In each of these three broad areas, there are opportunities for interventions on the individual, friends and family, community, health care provider, state, and federal levels (Figure 1). While recognizing the important role of prevention and treatment on reducing overdose fatalities, the primary focus of this review will be evaluating the role of harm reduction strategies and initiatives to consider how they can inform the implementation of more comprehensive harm reduction solutions.

Increased Opioid Prescribing

Opioid prescriptions in the United States have increased in the past 25 years from 76 million in 1991 to nearly 207 million in 2013 [6]. The rapid rise in the rates of prescribed opioids has been influenced by myriad factors: a focus on inadequate pain management by physicians; new pain management standards from the Joint Commission on the Accreditation of Healthcare Organizations (JCAHO); aggressive marketing practices by pharmaceutical companies; and an increasing emphasis in medicine on patient satisfaction metrics [14,15]. With increased attention to pain as the “fifth vital sign” and professional society guidelines based on risk-benefit analysis by expert consensus rather than high quality research studies, many health care providers embraced chronic opioid

therapy for management of non-malignant chronic pain [16-21]. Other factors related to increased opioid prescriptions for chronic pain include ongoing safety concerns about non-steroidal inflammatory medications and lack of patient access to pain management specialists or alternative therapies for chronic pain management [22-24]. A recent guideline developed by the Physicians for Responsible Opioid Prescribing concludes that although opioids are effective for short term use, the evidence of long-term efficacy of opioids for treating non-malignant pain is “limited and of low quality” [25].

Types of Opioid Use

It can be helpful to think about “types” of opioid use, as each category may have unique risk factors for overdose and opportunities for intervention. Although oversimplified, one method of classification includes medical opioid users, non-medical prescription opioid users, heroin users, and those who combine opioid use with alcohol or other drugs, such as benzodiazepines.

Medical opioid users take opioid pain relievers exactly as prescribed by their physicians for the purposes of pain relief, without taking extra doses of medication for pain relief or pleasurable effect [16]. Importantly, despite strict adherence to instructions, patients taking high doses of opioid pain relievers as prescribed are not protected from fatal overdose [26,27]. One study reported a dose-dependent increase in likelihood of opioid overdose. They reported a 3.7-fold increase in overdose at 50 mg of prescribed oral morphine equivalents (OME) per day and 8.9-fold increase in those with more than 100 mg OME per day in comparison to the 0-20 mg OME per day group [27]. This effect is highlighted by a case-cohort study of Veterans Affairs (VA) patients, which concluded that the risk of overdose death was directly related to the maximum prescribed dose of opioid medication, particularly when prescribed more than 100 mg OME per day [26].

Non-medical opioid use is defined as the use of illicit, prescription or over-the-counter drugs in a manner other than directed by a physician [13,28]. Identification of the source of non-medical opioid use can help guide effective interventions, such as educational campaigns against sharing medications and medication take back events. A recent analysis of a national health survey found that the majority of past year occasional non-medical opioid users (< 2.5 days per month) reported obtaining the drug for free from a friend or relative, in contrast to the one in four participants who endorsed heavy use (>16 days per month) [28]. They also found that heavy medical users were less likely than occasional users to steal opioids from a friend or relative, more likely to receive prescriptions from multiple health care providers, and more likely to buy opioids from friends, family members, and drug dealers [28].

An increase in new heroin initiates with a history of non-medical prescription opioid abuse has been reported [3,29,30]. Past year heroin use rates in this population increased from 62 per 1,000 individuals in 2002-2004 to 95

per 1,000 in 2010-2012 [31]. Moreover, individuals endorsing past year non-medical use of opioids were the only demographic with increased rates of past year heroin use over that time period [31]. This trend is highlighted in a retrospective mixed-methods analysis of national data on 2,797 patients entering substance abuse treatment, which found that 75.2 percent of heroin users report non-medical use of prescription opioids prior to heroin use [29]. Study participants endorsed increased accessibility and significantly lower cost as factors that influenced heroin usage [29]. This study also highlights the shift of the heroin epidemic out of urban centers, with 75.2 percent of participants living in less urban areas [32].

Although prescription opioids cause more fatal overdoses than heroin, there has been an alarming increase in both heroin use and overdose fatalities. Between 1999 and 2010, deaths from prescription opioid overdose quadrupled to 6.0 deaths per 100,000, with heroin overdoses doubling to 1.0 per 100,000 [31]. Possibly because of numerous interventions to reduce prescription drug abuse at that time, prescription drug overdoses decreased slightly from 6.0 to 5.6 per 100,000 between 2010 and 2012 [31]. Of concern, though, is that fatal heroin overdoses doubled again during that time, which may reflect increased heroin use in the face of decreased access to prescription opioids [31].

The Biology of an Opioid Overdose

The pathophysiology and acute medical management of an opioid overdose is similar irrespective of whether the opioid that was taken was legally prescribed or illegally bought on the street. Heroin and prescription opioids such as oxycodone, hydrocodone, codeine, fentanyl, and morphine are opioid receptor agonists [1,33]. They can effectively modify the perception of pain by binding to opioid receptors in pain pathways within the brain and spinal cord [33]. Additionally, opioids can bind to opioid receptors in the dopaminergic reward pathway of the brain to produce euphoria and modify neuronal reward circuitry connections [33,34]. Opioid binding also causes other effects such as pupillary constriction and decreased gastric motility. In the setting of larger overdoses, respiratory depression can occur, limiting adequate oxygenation of blood, which reduces oxygen availability to the brain and heart, leading to unresponsiveness, anoxia, cyanosis, and death [34]. This respiratory depression, which is reversible until death occurs, can take 1 to 3 hours and can be reversed with the pharmacological antidote naloxone, which displaces opioids from the opioid receptor and blocks the binding of additional opioids for 20 to 90 minutes [35-38]. Thus, naloxone binding prevents opioid receptor activation. Some prescription opioids have a longer duration of effect than naloxone and their ingestion increases the risk that respiratory depression may recur and additional naloxone may be required [34]. This is one reason that immediate transport to the Emergency Department (ED) is advised if naloxone is administered outside of the hospital.

Non-fatal opioid overdose has been associated with a number of complications, including anoxic brain injury, pulmonary edema, acute respiratory distress syndrome, hypothermia, rhabdomyolysis, renal failure, compartment syndrome, liver failure, seizures, and traumatic injury [34]. More often than not, though, overdose patients often completely recover with limited morbidity and frequently refuse acute medical care [34]. This was demonstrated in a 2003 case series of 998 individuals with non-fatal opioid overdose who refused ED transfer after naloxone resuscitation in the field and did not experience fatal overdose within the next 12 hours [39].

PRIMARY PREVENTION

Decreasing the number of individuals who abuse opioids is an intuitively reasonable approach to reducing fatal overdoses. This end can be achieved by reducing the number of new opioid abusers and by increasing engagement of current users in effective specialized treatment programs. As the opioid epidemic has grown, public health officials, health care professionals, community organizations, law enforcement, and legislators have initiated a variety of strategies to reduce the number of individuals at risk for fatal overdose. Many of these strategies employ educational interventions for primary prevention and target high-risk individuals, such as teens and those with a history of substance abuse disorders, although evidence for the impact of this approach is limited [40]. Other initiatives focus on close contacts, such as family, and on the importance of not sharing prescribed opioids, keeping them locked up, and safely disposing of unused medications. Large quantities of medications have been recovered during local and nationwide medication take-back drives that range from an anonymous mail-in program in Maine to a biweekly collection by pharmacists in parks, police stations, and other public spaces in Florida [36,41,42]. In addition, the Drug Enforcement Administration (DEA) has conducted nine country-wide medication take-back days since 2010, in which pharmacies and hospitals are able to accept and collect unused medications, resulting in the collection of 2,411 tons of controlled medications [43]. While the success in collecting medications can be documented, the actual impact on substance abuse and overdose rates is unknown. The co-occurrence of many educational initiatives and interventions across communities makes it particularly challenging to demonstrate the impact of an isolated program [36].

Other educational initiatives target health care providers and include efforts to increase prescriber use of pain contracts, urine drug testing, and routine use of prescription monitoring programs (PMPs) before initiating new opioid prescriptions [25,36,44]. Forty-nine states currently have some version of a prescription monitoring program, although low numbers of prescriber registration and infrequent PMP use has been reported in many states [41,45,46]. Furthermore, there are no data showing that

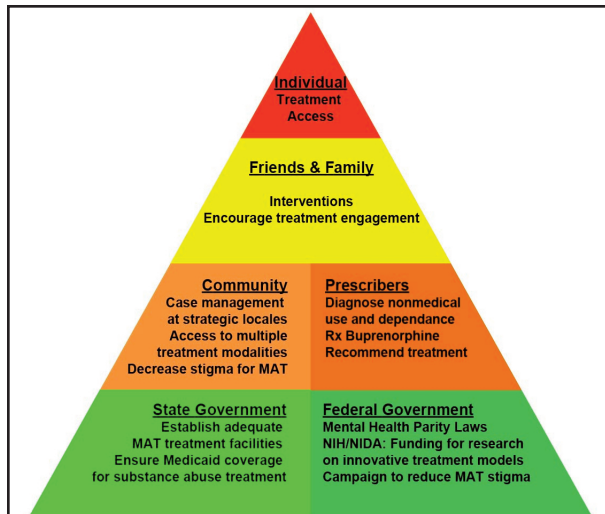


Figure 2. Opportunities to reduce overdose risk by increasing treatment engagement. There are multiple access points for initiatives on an individual, friends and family, community, prescriber, and government level. Medication-assisted treatment augments counseling and behavioral therapies with medications, such as methadone or buprenorphine. Abbreviations: Prescription (Rx), Treatment (Tx), National Institute of Health (NIH), National Institute of Drug Abuse (NIDA), Medication-Assisted Treatment (MAT).

PMPs effectively identify individuals who have opioid use disorders [46]. Nonetheless, evidence exists that PMP use does change prescriber behavior, and many states are pursuing mandatory PMP registration and use for physicians [47,48].

On a state level, efforts to decrease non-medical opioid use have included establishing and optimizing prescription monitoring programs, closing down “pill mills,” and increasing access to pain experts [49,50]. On a national level, the CDC, DEA, National Institutes of Health (NIH), and Substance Abuse and Mental Health Services Administration (SAMHSA) provide funding for research, coordinate medication take-back drives, and conduct national educational campaigns to raise awareness, including SAMHSA’s recent development of an opioid overdose tool kit with sections for patients, families, and medical providers [9,51].

INCREASING ACCESS TO EFFECTIVE TREATMENT

Increasing access to effective treatment is another important strategy to decrease the disease burden associated with the opioid epidemic. Briefly, we will provide some background on medication-assisted treatment (MAT) modalities, as they remain underutilized despite evidence that this approach improves health and social outcomes [52-54]. MAT includes the use of a medication, such as methadone or buprenorphine, to augment traditional counseling and behavioral therapies for the treatment of opioid addiction. Methadone and buprenorphine reduce

craving and withdrawal symptoms [33]. Differences in regulatory and pragmatic factors determine patient access to these treatments [52,53,55]. Frequently, medication-assisted treatment is not locally available due to cost or availability of local providers [52,56]. Additional challenges include stigma associated with medication-assisted treatment, concerns about diversion, and a general aversion to substance abuse treatment clinics being located in one’s community [55,57,58]. Medication-assisted treatment has been demonstrated to improve outcomes, including frequency of opioid use, HIV transmission, criminal activity, and mortality [53,54,59-63]. Widespread access to these treatments is an important component of stemming the disease burden associated with the opioid epidemic.

A less established approach includes modifying techniques that have been successful at reducing harmful alcohol use for use in patients with opioid abuse and dependence [64,65]. Screening, Brief Intervention, and Referral to Treatment (SBIRT) and the Brief Negotiation Interview (BNI) include a structured discussion in which patients reflect on the connection between substance use and negative consequences and reasons to change behavior in his or her life [66,67]. Furthermore, they are engaged in developing a plan to mitigate harmful substance use [66,67]. One modification of these techniques, Screening, Treatment Initiation and Referral to Treatment (STIR), incorporates initiation of treatment into the index health care visit and has shown promise in recent ED-based studies for tobacco and opioid dependence [65,68,69]. A recent randomized controlled trial for opioid dependence reported decreased opioid use and increased treatment engagement at 30 days in patients with ED-initiated buprenorphine followed by 10 weeks of primary care-based buprenorphine treatment and medical management in comparison to a standard referral or BNI with facilitated referral to a specialized treatment center [65]. Although further studies are needed, this represents a paradigm shift in which emergency physicians initiate treatment and refer patients much as they would patients with other chronic diseases such as asthma, diabetes, and hypertension.

As illustrated for primary prevention, there are multiple distinct opportunities for interventions to increase engagement in effective treatment for opioid abuse (Figure 2). On an individual level, targeted educational initiatives and referral to treatment may be used to increase treatment engagement. Close contacts such as friends and family also may play a role in encouraging patients with opioid use disorders to seek and continue to engage in treatment. Communities and states can work to improve known deficits in local treatment services, with particular attention to those that offer medication-assisted treatment [3,56]. Communities, states, and the medical community can work to increase the general knowledge of the biologic underpinnings of addiction, which would facilitate the treatment of addiction as a disease rather than a moral

failure [33,70]. The American Board of Addiction Medicine recently has become an American College of Graduate Medical Education (ACGME)-accredited subspecialty, which will increase specialized training opportunities and the incorporation of addiction-specific teaching in general medical training [71]. On a national level, the U.S. Department of Health and Human Services, which oversees many governmental research, health care, and evaluation agencies, can continue to make opioid overdose prevention a priority, as it did in early 2015 when it announced dedicated funding to increase 1) health care provider training and resources, 2) increasing use of naloxone, and 3) expand the use of MAT [8].

HARM REDUCTION STRATEGIES

The alignment of public and political will has led to an exponential increase in harm reduction initiatives to curb fatal opioid overdose, representing a fundamental shift from previous approaches that favored the criminalization of drug use [4,8]. The philosophy of harm reduction has roots in the public health approach. It does not endorse drug use, but accepts drug use as a reality and focuses on reducing its harmful consequences, including death, HIV, hepatitis C, criminal activity, and incarceration [70,72]. There are multiple opportunities for harm reduction strategies to minimize the morbidity and mortality associated with opioid abuse and dependence, including targeted overdose education, naloxone distribution, and policies to increase bystander assistance in the case of an overdose (Figure 3).

Individuals at particularly elevated risk for fatal overdose include those prescribed more than 100 mg per day of oral morphine equivalents with a personal history of overdose; those recently released from a controlled environment such as jail and inpatient substance abuse treatments; and those who mix opioid use with alcohol, benzodiazepines, or other drugs [13,26,36,51,73]. Emergency Departments frequently provide care for patients at high risk of opioid overdose, providing a unique access point to patient populations that may not otherwise access a health care venue for targeted overdose risk assessment, counseling, and naloxone distribution [74-76]. An ED-based program that included opioid education and naloxone distribution (OEND) demonstrated that the intervention was logistically feasible in Emergency Departments and that high-risk populations were receptive to the intervention [75]. Prisons provide another access point to individuals at high risk for overdose, with astoundingly high rates of fatal drug overdoses reported in the first few weeks of release from incarceration [77-79]. For example, a retrospective cohort analysis of more than 30,000 prisoners released between 1999 and 2003 in Washington State reported a relative risk of death from drug overdose of 129 during the first 2 weeks post-incarceration compared to other state residents [77]. Currently, there are programs both in the United States and abroad

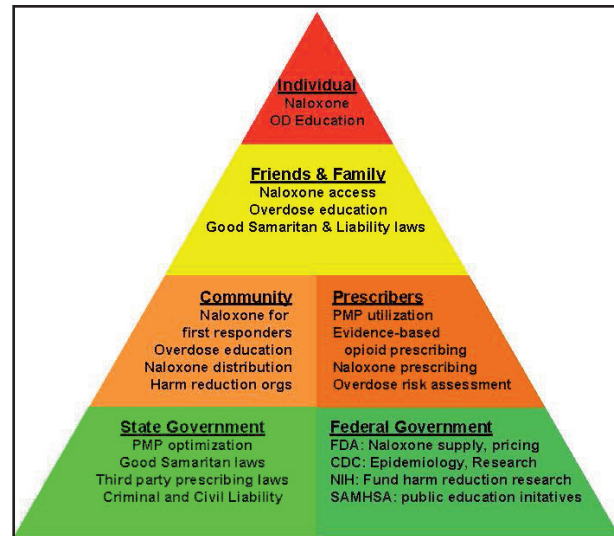


Figure 3. Opportunities to reduce overdose risk through harm reduction strategies. There are multiple access points for initiatives on an individual, friends and family, community, prescriber, and government level. Abbreviations: Food and Drug Administration (FDA); Overdose (OD); Prescription Monitoring Program (PMP), National Institute of Health (NIH), Substance Abuse and Mental Health Services Administration (SAMHSA).

evaluating the impact of providing overdose education and naloxone distribution for high-risk prisoners prior to release in an effort to curb overdose deaths, although no preliminary data is yet available [72,80].

Many harm reduction organizations have incorporated naloxone distribution into their scope of services. The logic behind naloxone take-home programs is that when it comes to reversing an opioid overdose, time matters. It has been well reported that many overdoses are witnessed by individuals who would be willing to intervene and provide assistance [35,73,81]. Naloxone is an opioid antagonist, which means that it displaces opioids from opioid receptors and prevents additional opioid from binding. Naloxone rapidly reverses the effect of opioids, including analgesia and respiratory depression, and lasts 20 to 90 minutes, allowing individuals to access medical care. Naloxone administration by intranasal and intramuscular administration has been shown to be safe and effective with minimal training [37,82,83]. Naloxone has been used for in-hospital opioid reversal for more than 40 years, and although rare side effects have been reported, it has an excellent safety profile [38,84].

The first naloxone distribution program in the United States began in Chicago. In 1996, the Chicago Recovery Alliance program started distributing naloxone through a mobile van-based harm reduction program and in the subsequent decade delivered naloxone to 10,211 people with 1,011 reported overdoses reversals [85,86]. The movement for take-home naloxone continued to gain momentum, driven almost entirely by harm reduction advocates, friends and families of lost loved ones, and policymakers concerned about the rising rates of overdose in their com-

munities [72,87]. A Harm Reduction Coalition survey showed that as of 2010, 188 local naloxone programs in 15 states and the District of Columbia had distributed naloxone to 53,032 individuals and received reports of 10,171 drug overdose reversals [9]. By June 2014, 644 local programs in 30 states and Washington, D.C. were responsible for the distribution of 152,283 naloxone kits and 26,453 overdose reversals [5].

Efforts also have been made to increase naloxone access to all levels of Emergency Medical Services (EMS) personnel including Emergency Medical Technicians (EMTs) and First Responders. First Responders include law enforcement officers, firefighters, and other public servants who have completed basic but not EMT-level training. This trend was driven by the fact that nationwide, EMTs outnumber paramedics 3:1 and the number of first responders far exceeds both EMTs and paramedics [84]. Increasing the pool of individuals carrying naloxone increases the likelihood that the first person to arrive at an overdose is capable of initiating naloxone reversal. One study estimated that using EMTs to administer naloxone could reduce time for intranasal naloxone delivery between 5.7 and 10.2 minutes, which has the potential to significantly reduce the mortality and morbidity associated with opioid overdose [88]. As of 2013, 14 states allowed EMTs and three states had enabled first responders to carry and administer naloxone [89]. In April 2014, New York Attorney General Eric Schneiderman announced the "Community Overdose Program," a statewide program to train and equip law enforcement agencies with naloxone [90]. This and other formative initiatives paved the way for a nationwide trend, given the Office of National Drug Control Policy's (ONDCP) statement that naloxone "is a life saving overdose reversal drug which we believe should be in the patrol cars of every law enforcement professional across the nation" [91].

Interestingly, this movement has occurred largely outside of the medical community, with the exception of a small number of health care providers with specific training or interest in substance abuse. In part, this effect may be driven by challenges specific to prescribing naloxone, including the failure of local pharmacies to stock naloxone, uncertainty about insurance coverage, and difficulties integrating naloxone specific-education into an already time-limited clinical setting [23,92]. Likely, though, there are other factors at play. In 2006, a voluntary, anonymous national survey of 588 physicians found that less than 25 percent of physicians were aware of naloxone prescription as an intervention to reduce overdose [93,94]. This study also reported that more than half of these physicians would not consider prescribing naloxone and that negative attitudes toward intravenous drug users, pessimism in treating drug abuse, and fear of social or professional disapproval were associated with not considering naloxone prescription [94]. In part, inadequate addiction-specific education in medical school and post-graduate training may be a fault, perhaps compounded by

limited exposure to individuals who have successfully recovered from opioid use disorders [71,93,95]. To address this problem, additional substance abuse-specific education is indicated across the continuum of medical education. This education should emphasize evidence-based opioid prescribing, consideration of naloxone prescription for high-risk patients and other strategies and other strategies to prevent opioid overdose [51].

One example of a multi-faceted community-initiated overdose prevention program that included targeted prescriber education is Project Lazarus in Wilkes County, North Carolina. In 2007, Project Lazarus began training local physicians to use an overdose risk assessment tool. If a patient was deemed to be at-risk, he or she watched a 20-minute training video on recognizing and responding to overdose and were prescribed naloxone, to be collected at a pre-specified community pharmacy [36]. Overdose risk assessment was coupled with other initiatives, including town hall meetings, promotion of prescription monitoring program (PMP) use, a new buprenorphine-based treatment clinic, and new prescribing policies in the local Emergency Department and hospital. Additionally, a program involving "academic detailing," a concept borrowed from the pharmaceutical industry to influence prescribing habits, was employed. From 2008 to 2010, they provided one-on-one prescriber education on evidence-based opioid prescribing, which corresponded to a decrease from 80 percent to 10 percent of individuals with fatal overdoses having an active prescription for opioids from a Wilkes county physician [36]. Preliminary unadjusted data from Wilkes County demonstrated that the overdose rate dropped from 43 per 100,000 in 2008 to 29 per 100,000 in 2010, which authors suggest may be related to these community-based overdose prevention efforts, although a definitive causal link cannot be determined [36].

Given physician reluctance to prescribe naloxone and an overall excellent safety profile, several states have moved to alternative models, including collaborative practice agreements and behind-the-counter models. For example, since 2007, Massachusetts has had a standing order from the Department of Public Health to distribute naloxone kits without requiring additional physician approval. Since 2012, anyone can walk into a Rhode Island Walgreens pharmacy to obtain a naloxone kit without a prescription, based on a collaborative practice agreement supported by a single physician [96,97]. As of December 2014, 27 states have passed legislation that allows "third-party prescription," which means that physicians can prescribe naloxone to parents, family, and anyone who is concerned that they may one day find their loved one unconscious from an overdose [7].

On a state level, Good Samaritan and naloxone laws are an important part of preventing fatal overdoses. It has been well documented that bystanders often refrain from calling 911 or seeking medical assistance due to fear of police involvement and criminal liability [38,98]. These

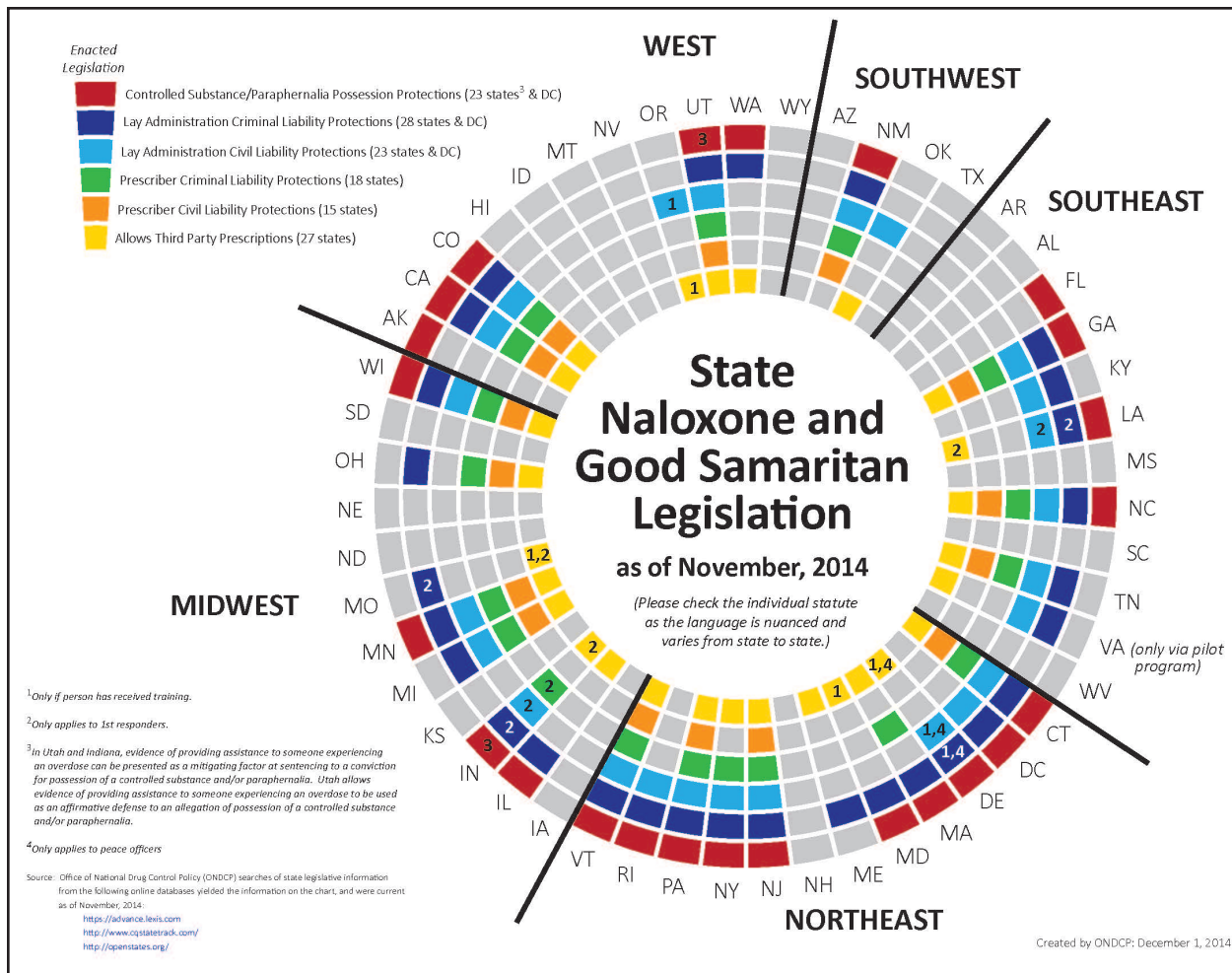


Figure 4. State-by-State Good Samaritan, naloxone liability and third party prescribing laws. Infographic from Office of National Drug Control Policy (ONDCP) website showing which states have passed Good Samaritan, civil and criminal liability protection laws for lay administrator and prescribers, and third party prescribing laws as of December 1, 2014.

fears have been documented in research surveys and are grounded in case law, with reports of bystanders being arrested for drug possession and charged with murder if they are suspected of supplying the drugs to the victim of a fatal overdose [38]. To address this issue, between 2007 and 2014, 23 states and the District of Columbia have passed legislation with controlled substance and paraphilia possession protections for bystanders acting to help someone experiencing an overdose (Figure 4) [7]. In general, Good Samaritan laws are designed to provide some level of protection from low level-controlled substance possession charges and not for more significant charges such as manufacturing, trafficking, and distribution [12]. Many states have provided mandatory stipulations to receive protection by these laws, including requiring self-identification when calling 911 and waiting on scene for police arrival. Some states require a review of an individuals' criminal record to determine if the bystander is "eligible" for immunity, and in other states such as Utah and Indiana, the protection afforded by the legislation is that "assisting an overdose victim" is a mitigating factor at sentencing [12]. Understanding the effects of these laws on bystander as-

sistance and public perception is important to inform opportunities for improvement and to guide implementation in other states.

After 5 years of discussion and eventual stakeholder buy-in, Washington State passed a "911 Good Samaritan Law" in 2010 [99]. The potential effectiveness of this law was limited in that it did not include funding for public awareness campaigns and no state agency was assigned responsibility for implementation [99]. An initial evaluation, published in November 2011, found that just 16 percent of surveyed law enforcement and one-third of 355 high risk opioid users surveyed at a needle exchange site were aware of the law [6,99]. When these results were shared with law enforcement leadership, it resulted in the development of an educational training video that was widely dispersed [100]. Despite less than perfect implementation, an analysis concluded that no negative outcomes resulted from this misstep and found that once high-risk opioid users were made aware of the law, 88 percent reported that they were more likely to call 911 in future witnessed overdoses [99]. The complicated nature of many existing Good Samaritan laws, combined with their

absolute dependence on successful educational campaigns in order to affect change, highlights the need for careful consideration in the future implementation of these laws. Overall, though, the existence of Good Samaritan laws in nearly half of the country suggests a paradigm shift in the legislative climate and public discourse around reducing fatal overdose.

On a federal level, there are multiple opportunities for intervention to facilitate harm reduction strategies including education, monitoring naloxone cost and supply, strategic reimbursement for clinicians, and targeted research funding. SAMHSA has published an Opioid Overdose Toolkit with targeted education in the sections “facts for community members,” “five essential steps for first responders,” “information for prescribers,” “safety advice for patients and family members,” and “recovering from an overdose” [51]. Also, the CDC regularly reports epidemiological data about overdose, frequently in plain language on their website [13,51]. The Office of National Drug Control Policy (ONDCP) recently has been vocal about its support for increased access to naloxone and has been collaborating with other organizations, including the Harm Reduction Coalition [91]. Experts and advocates have called on the Food and Drug Administration (FDA) to explore alternative formulations and distribution models for naloxone, as well as with monitoring the naloxone supply and significant pricing variations [94,101]. This issue has become particularly relevant as the cost of naloxone doubled over the course of several months during 2014. However, even before this significant price increase, 43.7 percent of the 188 naloxone distribution programs surveyed by the Harm Reduction Coalition in 2010 reported difficulties in obtaining naloxone due to significant increase in the cost of naloxone, inadequate funding, or the inability of suppliers to meet demand [9]. Targeted research to evaluate the effects of these educational initiatives are needed to guide the implementation and of the most effective interventions.

CONCLUSION

The opioid abuse epidemic and its effect on fatal overdose has garnered the attention of individuals, families, communities, health care providers, and policymakers, motivating a critical mass of stakeholders to initiate change. A benefit of communities and states developing their own laws, overdose education programs, and naloxone distribution models is that they provide ample opportunity for impact assessments and empirical research to determine the most effective strategies for implementation. It is encouraging that there has been such diversity of initiatives to prevent fatal overdose, though there are clear areas for further work, including increasing access to medication-assisted treatment, overdose prevention in prisons, improving addiction specific content in medical education and targeted physician/health provider education on evidence-based opioid prescribing and naloxone prescription.

One consequence of a rapid proliferation of overdose prevention programs and health policies is that we still have an evidence gap in determining the most effective and efficient initiatives. Conducting research and methodical evaluations of these interventions is challenging and complex, but critical. Nevertheless, considerable progress has been made, and the harm reductionists are no longer left to fight this battle on their own. Based on the thousands of successful reversals, it seems prudent to continue to support and expand those initiatives. It also seems prudent for prescribers to consider prescribing naloxone to high-risk populations such as those prescribed high doses of opioids, those with a history of a non-fatal opioid overdose, and those recently released from a controlled environment such as prison or inpatient treatment. Reducing the risk for fatal overdose rests on a combination of prevention, treatment, and harm reduction initiatives, and it is critical that we strive to implement these initiatives as quickly and efficiently as possible.

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