Executive Summary: Health Impact Review of HB 1671

Increasing Access to Opioid Antagonists to Prevent Opioid-Related Overdose Deaths

Evidence indicates that HB 1671 has potential to increase the number of opioid antagonist rescue kits that are distributed and administered and in turn decrease health complications and deaths from opioid overdose and decrease health disparities.

BILL INFORMATION

Sponsors: Representatives Walkinshaw, Griffey, Cody, Smith, Peterson, Magendanz, Riccelli, Stanford, Appleton, Robinson, Tharinger, Jinkins

Summary of Bill:

- Authorizes practitioners to prescribe, distribute, and deliver opioid antagonists directly, through standing order, or collaborative drug therapy agreement to first responders, pharmacists, and other entities or individuals at risk of experiencing or witnessing an opioid-related overdose.

HEALTH IMPACT REVIEW

Summary of Findings:
This health impact review found the following evidence regarding the provisions in HB 1671:

- Strong evidence that allowing practitioners to prescribe, distribute, and deliver opioid antagonists directly, through standing order, or collaborative drug therapy agreement to first responders, pharmacists, and other individuals or entities will likely result in opioid antagonists being more frequently distributed and administered.
- Very strong evidence that opioid antagonists being more frequently distributed and administered will likely decrease health complications and deaths from opioid overdose.
- A fair amount of evidence that decreased health complications and deaths from opioid overdose will likely decrease health disparities.

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Health Impact Review of HB 1671

Increasing Access to Opioid Antagonists to Prevent Opioid-Related Overdose Deaths

February 5, 2015

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Acknowledgement

We would like to thank Amy Poel, Epidemiologist with the Washington State Department of Health, for analyzing and providing state vital statistics data. We also wish to thank Dr. Caleb J. Banta-Green, Senior Research Scientist with the Alcohol and Drug Abuse Institute and Affiliate Associate Professor with the University of Washington School Of Public Health, for providing consultation for this review.

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Introduction and Methods

A health impact review is an analysis of how a proposed legislative or budgetary change will likely impact health and health disparities in Washington state (RCW 43.20.285). For the purpose of this review 'health disparities' have been defined as the differences in disease, death, and other adverse health conditions that exist between populations (RCW 43.20.270). This document provides summaries of the evidence analyzed by State Board of Health staff during the health impact review of House Bill 1671 (HB 1671).

Staff analyzed the content of HB 1671 and created a logic model depicting possible pathways leading from the provisions of the bill to health outcomes. We consulted with stakeholders and conducted objective reviews of the literature for each pathway using databases including PubMed and Google Scholar. Naloxone is the opioid antagonist most frequently referenced in the scientific literature, therefore the terms "naloxone" and "opioid antagonist" have both been used throughout this review.

The following pages provide a detailed analysis of the bill including the logic model, summaries of evidence, and annotated references. The logic model is presented both in text and through a flowchart (Figure 1). The logic model includes information on the strength of the evidence for each relationship. The strength-of-evidence has been defined using the following criteria:

- **Not well researched:** the literature review yielded few if any studies or only yielded studies that were poorly designed or executed or had high risk of bias.
- **A fair amount of evidence:** the literature review yielded several studies supporting the association, but a large body of evidence was not established; or the review yielded a large body of evidence but findings were inconsistent with only a slightly larger percent of the studies supporting the association; or the research did not incorporate the most robust study designs or execution or had a higher than average risk of bias.
- **Strong evidence:** the literature review yielded a large body of evidence on the relationship (a vast majority of which supported the association) but the body of evidence did contain some contradictory findings or studies that did not incorporate the most robust study designs or execution or had a higher than average risk of bias; or there were too few studies to reach the rigor of 'very strong evidence'; or some combination of these.
- **Very strong evidence:** the literature review yielded a very large body of robust evidence supporting the association with few if any contradictory findings. The evidence indicates that the scientific community largely accepts the existence of the association.

Staff made modifications to these criteria at the start of the 2015 legislative session beginning January 12, 2015. Therefore strength-of-evidence rankings may not be comparable between reviews completed before and those completed after this date.

This review was subject to time constraints, which influenced the scope of work for this review. The annotated references are only a representation of the evidence and provide examples of current research. In some cases only a few review articles or meta-analyses are referenced. One article may cite or provide analysis of dozens of other articles. Therefore the number of references included in the bibliography does not necessarily reflect the strength-of-evidence. In addition, some articles provide evidence for more than one research question so they are referenced multiple times.

Analysis of HB 1671 and the Scientific Evidence

Summary of HB 1671

Authorizes practitioners to prescribe, distribute, and deliver opioid antagonists directly, through standing order, or collaborative drug therapy agreement to first responders, pharmacists, and other entities or individuals at risk of experiencing or witnessing an opioid-related overdose.

Health impact of HB 1671

Evidence indicates that HB 1671 has potential to increase the number of opioid antagonist rescue kits that are distributed and administered and in turn decrease health complications and deaths from opioid overdose and decrease health disparities.

Pathways to health impacts

There is strong evidence that allowing practitioners to prescribe, distribute, and deliver opioid antagonists directly, through standing order, or collaborative drug therapy agreement to first responders, pharmacists, and other individuals or entities will likely result in opioid antagonists being more frequently distributed and administered.[1-7] There is very strong evidence that naloxone effectively reverses opioid drug overdoses.[3,4,6-9] In addition evidence indicates that naloxone can be administered safely and effectively by overdose witnesses such as Emergency Medical Technicians (EMT), police officers, friends, family, and other bystanders.[2-7,10,11] There is a fair amount of evidence that decreasing adverse effects from opioid overdose would decrease health disparities by race/ethnicity.[6,12-15]

Magnitude of impact

There is evidence that HB 1671 will likely result in distribution and use of a large number of naloxone rescue kits.[1-7] Data indicate that there are high rates of fatal opioid overdoses in Washington state, with an average of 611 opioid related overdose deaths each year between 2011 and 2013.[15] There is also evidence that naloxone is highly effective, reversing between 72% and 100% of opioid overdoses when administered.[3,4,6-9] Therefore if opioid antagonists were made universally available in Washington we could expect these kits to save the lives of an estimated 440-611 people per year. This assumes complete availability, so this estimate is a best-case scenario. However these mortality data also only capture fatal overdose deaths and do not consider the large number of individuals who are likely victims of non-fatal opioid overdoses each year in Washington, but who may experience serious negative health effects resulting from extended drug-induced central nervous system and respiratory depression.[8,9,16] Therefore, HB 1671 has potential to save a large number of lives and to prevent other serious adverse health outcomes.

Logic Model

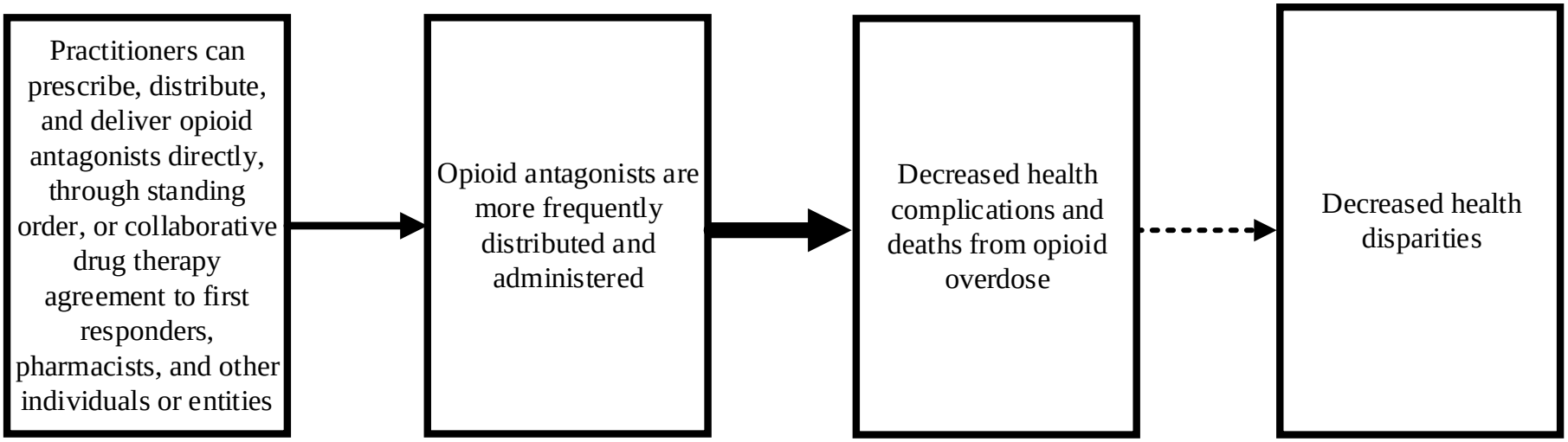
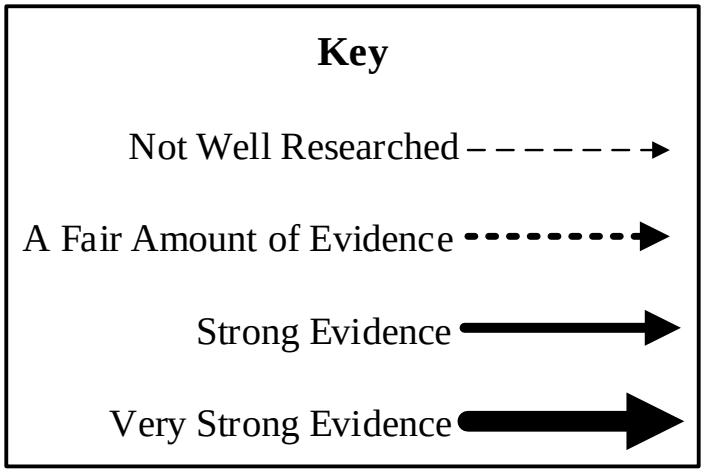


Figure 1
Increasing Access to Opioid Antagonists to Prevent Opioid-Related Overdose Deaths
HB 1671



Summaries of Findings

Will allowing practitioners to prescribe, distribute, and deliver opioid antagonists directly, through standing order, or collaborative drug therapy agreement to first responders, pharmacists, and other individuals or entities result in opioid antagonists being more frequently distributed and administered?

There is strong evidence that programs and individuals with the authority and ability to distribute opioid antagonists distribute large amounts of naloxone and that these naloxone kits are frequently used to respond to opioid overdose.[3-7] Evidence indicates that at least one barrier to distributing naloxone is the need for practitioners to individually prescribe each naloxone kit.[3] Therefore, giving practitioners explicit authority to prescribe, distribute, and deliver opioid antagonists through standing order or collaborative drug therapy agreement will likely help minimize this current barrier. The American Medical Association has issued policies and public statements endorsing legislation to increase the availability of naloxone to patients, first responders, and bystanders indicating that at least some practitioners are likely to use the authority to prescribe opioid antagonists.[1] Dr. Caleb Banta-Green, PhD, MPH, MSW, Senior Research Scientist with the Alcohol and Drug Abuse Institute and Affiliate Associate Professor with the University of Washington School of Public Health, also indicated that practitioners in Washington state would likely use this authority to write these orders. Dr. Banta-Green has extensive experience across Washington working with prescribers and pharmacists on overdose prevention and response including dispensing naloxone (Banta-Green, personal communication, February 2015).

Evidence also indicates that non-medical witnesses to drug overdoses have demonstrated a willingness to administer naloxone.[6] This is further supported by the large number of bystanders who seek naloxone refills and report that they administered naloxone in response to an opioid overdose.[3-7] Drug users and their friends and family, emergency medical personnel, and police officers frequently witness opioid overdoses.[2-4] This indicates that increasing access to opioid antagonists for these individuals and the providers that serve them has great potential to ensure that these bystanders can respond to overdoses. A survey conducted in Seattle by Banta-Green et al. found that 93% of surveyed police officers and 100% of surveyed paramedics had witnessed an opioid overdose in their careers.[2]

Magnitude of impact

A 2010 national survey found programs that provide naloxone reported distributing an average of over 800 vials per program in the previous 12 months. Cumulatively these programs distributed naloxone to 53,032 people between 1996 and 2010 and received reports of a cumulative 10,171 overdose reversals from naloxone.[3] The literature indicates that somewhere between 9% and nearly 50% of distributed naloxone kits are reportedly used to reverse opioid overdoses.[3,6,7] Reports indicate that naloxone administrations have been effective for 72-100% of the overdoses.[4,6,7,9]

Emergency Medical Service (EMS) medical directors where given authority to write standing orders to Emergency Medical Technicians (EMT) to administer naloxone in Boston, Massachusetts in 2012. In 2013 Boston EMS responded to 1,207 overdose calls and EMTs

administered naloxone in 458 cases. A similar trend was observed in Revere, Massachusetts with firefighters who administered naloxone 114 times between 2010 and 2013. In this same time period, police officers who were given authority to carry and administer naloxone administered naloxone 201 times.[5] Between 2011 and 2013 in Washington state 1,176 individuals died of prescription opioid overdose and 658 individuals died of non-prescription opioid overdose. These rates have been steadily increasing since 1995, from an age-adjusted death rate for all opioids of about 3/100,000 in 1995 to over 8/100,000 in 2013.[15]

Therefore if opioid antagonists were made universally available in Washington we could expect these kits to save the lives of an estimated 440-611 people per year (based on the efficacy of naloxone). This assumes complete availability, so this estimate is a best-case scenario. However these mortality data also only capture fatal overdose deaths and do not consider the large number of individuals who are likely victims of non-fatal opioid overdoses each year in Washington, but who may experience serious negative health effects resulting from extended drug-induced central nervous system and respiratory depression.[8,9,16] Therefore, HB 1671 as potential to save a large number of lives and to prevent other serious adverse health outcomes.

Will opioid antagonists being more frequently distributed and administered decrease health complications and deaths from opioid overdose?

There is very strong evidence that naloxone effectively reverses opioid drug overdoses. This has been demonstrated in animal trials, human clinical trials, and field experience.[3,4,6-9] This indicates that opioid antagonists are effective both in decreasing deaths from overdoses and minimizing other adverse health effects associated with overdose. Adverse health effects of nonfatal opioid overdoses are extensive and include: build-up of fluid in the lungs (oedema), pneumonia, heart issues (arrhythmia, acute cardiomyopathy, haemoglobinaemia), dissolution of muscle cells, kidney failure, inadequate oxygen to the brain, and cognitive impairment.[16]

In addition evidence indicates that naloxone can be administered safely and effectively by overdose witnesses such as EMTs, police officers, friends, family, and other bystanders.[2-7,10,11] One study found that nonmedical individuals likely to witness an overdose who were given a brief training (15-120 minutes) in a variety of settings including in private homes, on the street, and in needle exchange programs were as skilled as medical experts trained in overdose recognition and treatment both in recognizing hypothetical overdose scenarios and instances when naloxone should be administered. Untrained individuals were less likely than trained individuals to accurately identify these scenarios but even the untrained participants had a relatively strong ability to identify overdose symptoms and when naloxone should be administered.[11] Dr. Banta-Green indicated that the programs in Washington state that currently distribute naloxone provide training on how to prevent, recognize, and intervene in an overdose including calling 911 and how to administer naloxone (Banta-Green, personal communication, February 2015). Evidence indicates that this is true for programs across the country.[6] A second retrospective study of actual responses in the field found that formally trained bystanders and untrained individuals were just as likely to properly administer naloxone. The authors indicate that "untrained individuals" received the kits from their social networks and that they often also received training on how to use the kits from these same individuals.[10]

Will decreased health complications and deaths from opioid overdose decrease health disparities?

There is a fair amount of evidence that decreasing adverse effects from opioid overdose would decrease health disparities by race/ethnicity.[6,12-15] Washington state vital statistics data indicate that American Indian/Alaska Native (AI/AN) populations are significantly more likely to be victims of fatal opioid overdose than any other racial/ethnic group. This is true for both prescription and non-prescription opioids.[15] These data also show that AI/ANs have significantly higher death rates than most other subpopulations.[14] This indicates that decreasing the disproportionate negative impact of opioid overdoses could help decrease racial/ethnic disparities both for opioid overdose fatalities and for death rates in general. However it is not clear from the evidence if naloxone and other opioid antagonists are accessed equitably by all racial/ethnic subpopulations when made available. One program in California reported the racial/ethnic demographics of the participants who accessed naloxone and found that 61% self-reported as Caucasian, 15% as African American, 7% as Latino, 2% as Asian/Pacific Islander, 2% as Native American, 3% as more than one race/ethnicity, and 3% as "other." The authors did not indicate if this is reflective of the at-risk population or the service area population and these data also do not indicate who is being rescued by these emergency kits. However this information does indicate that individuals from diverse racial/ethnic backgrounds are accessing this resource.[6]

Nationally researchers have found that populations that face health disparities, such as individuals who are unstably housed, are at greater risk of death from opioid overdose and are more likely to access naloxone through distribution programs.[6] Due to time limitations and a lack of readily available data for Washington state we did not evaluate the potential impacts that this bill could have on disparities by, for example, housing status, educational attainment, or income.

Annotated References

1. American Medical Association webpage. http://www.ama-assn.org/ama/pub/news/news/2014/2014-04-07-naxolene-product-approval.page. Accessed February 3, 2015.

The American Medical Association has issued policies and public statements endorsing legislation to increase the availability of naloxone to patients, first responders, and bystanders.

2. Banta-Green CJ, Beletsky L, Schoeppe JA, Coffin PO, Kuszler PC. Police officers' and paramedics' experiences with overdose and their knowledge and opinions of Washington state's drug overdose-naloxone-good samaritan law. *Journal of urban health : bulletin of the New York Academy of Medicine.* 2013;90(6):1102-1111.

Banta-Green et al. surveyed police officers (n=251) and paramedics (n=28) in Seattle, Washington following the passage of 2010 state legislation (RCW 69.50.315) that increased availability of naloxone and provided immunity from drug possession charges for overdose victims and bystanders who seek medical aid. Researchers conducted self-administered written surveys with officers in the fall of 2011 in-person at staff meetings ("roll calls"). The researchers attended each shift time once in each of the five precincts in Seattle to conduct the surveys. There was a 97% response rate among officers present at roll calls and respondents represented 50% of the patrol officers in Seattle. During the same time the authors surveyed paramedics at a single staff meeting. Half of the paramedics in Seattle were surveyed. Ninety-three percent of surveyed officers had been at an opioid overdose in their careers and 64% had attended one in the past year. All of the surveyed paramedics had been at an opioid overdose in their career and 89% had been at an opioid overdose in the previous year. Only 16% of officers and 7% of paramedics were aware of the 2010 law—but only a very small percent of overdoes victims (1%) or bystanders (1%) had been arrested at the officers' most recent overdose encounter.

3. Centers for Disease Control and Prevention. *Morbidity and Mortality Weekly Report February 17, 2013: Community-Based Opioid Overdose Prevention Programs Providing Naloxone — United States, 2010.* 2012.

This Morbidity and Mortality Weekly report indicates that in 2010 the Harm Reduction Coalition surveyed 50 programs in the United States known to distribute naloxone. Forty-eight programs representing 188 local programs completed the survey (96% response rate). The first opioid overdose program began distributing naloxone in 1996—since this date the respondent programs reported training and delivering naloxone to a cumulative 53,032 people (average per program 1,104.8) and receiving reports of a cumulative 10,171 overdose reversals from naloxone (average per program 211.9). In the previous 12 months the programs reported distributing 38,860 naloxone vials (average per program 809.6). Depending on the indicator, between 22 and 29 of these programs were able to use program data to supply these numbers while the other programs provided estimates. The authors cite evidence that drug users frequently witness drug overdoses. Over 40% of the programs reported problems obtaining naloxone in the months leading up to the survey. Cited barriers include the cost of naloxone and the inability of suppliers to fill orders for reasons such as not having a medical provider to either order naloxone from suppliers or prescribe naloxone to users.

4. Clark AK, Wilder CM, Winstanley EL. A systematic review of community opioid overdose prevention and naloxone distribution programs. *Journal of addiction medicine.* May-Jun 2014;8(3):153-163.

Clark et al. conducted a systematic review of the literature on the state and effectiveness of opioid overdose prevention programs (OOPP). The authors indicate that naloxone is a Food and Drug Administration approved medication with "well established efficacy and safety" and cite four studies to support this assertion. Nineteen peer-reviewed articles met their inclusion criteria. A majority of the program participants across all studies which reported each demographic were white (61/4%) and male (68.3%). One program reported serving primarily African American participants. Nearly 80% of all participants reported witnessing an overdose during their lifetime. The OOPPs curriculum usually included several components including how to recognize an overdose and how to administer naloxone. These trainings varied in length from 10 to 60 minutes. The authors found that naloxone was used successfully by participants in 18 of the 19 studies for a total of 1,949 naloxone administrations across 18 programs. These studies reported a survival rate following administration from 83-100% with eleven studies reporting 100% survival rate. The studies which found the lowest rates of survival had the greatest number of unknown overdose outcomes. Authors of one study found that naloxone was not used in any of the witnessed overdoses for which they had data. Nine studies reported adverse outcomes following administration of naloxone including vomiting, problems with the naloxone syringe, and rarely seizures (4 total cases reported). Five studies compared the rate of EMS notification pre-and post-training and the results were mixed with two studies finding an increase in notification, two finding a decrease, and one finding no change. The authors cite evidence indicating that EMS is rarely contacted following an overdose even without the availability of bystander-administered naloxone. The authors rated the quality of the studies and found that the published studies were of "fair" quality because the quantitative studies used self-report and did not use randomization. They do note that the well-established efficacy of naloxone may make randomized studies unethical. The study quality scores ranged from 4 to 7 (average 6.1) out of a possible 8. The authors gave seven of these studies a quality rating of 7 out of 8 with a point being deducted for lack of randomization.

5. Davis CS, Ruiz S, Glynn P, Picariello G, Walley AY. Expanded access to naloxone among firefighters, police officers, and emergency medical technicians in Massachusetts. *Am J Public Health.* Aug 2014;104(8):e7-9.

Davis et al. indicate that in 2012 the Massachusetts Office of Emergency Medical Services began allowing EMS medical directors to write standing order to EMTs to administer intranasal naloxone without a waiver. In 2013 Boston EMS service responded to 1207 overdose calls and EMTs administered naloxone in 458 cases. They found that serious adverse reactions were uncommon. In 2010 firefighters in Revere, Massachusetts were trained and permitted to administer naloxone. Between 2010 and 2013 these firefighters administered naloxone 114 times. Police officers in Quincy, Massachusetts were trained and given authority to administer naloxone. In three years these police officers administer naloxone 201 times.

6. Enteen L, Bauer J, McLean R, et al. Overdose prevention and naloxone prescription for opioid users in San Francisco. *Journal of urban health : bulletin of the New York Academy of Medicine.* Dec 2010;87(6):931-941.

Enteen et al. cite three studies which indicate that EMS is called in fewer than half of overdose events. The authors also highlight evidence that intravenous drug users often make attempts to revive overdose victims without calling EMS and demonstrate a willingness to administer naloxone during an overdose if it was made available. Programs that administer naloxone typically provide overdose response education and training on how to administer naloxone. The authors also cite findings from four studies in the United States of programs that distribute and train individuals to administer naloxone. The findings indicate that nearly half of the individuals provided with naloxone indicated having used the reversal drug in the previous 3 to 6 months with 74-100% of these individuals reporting reversal. One additional study with a longer-term follow-up in Chicago found that 9% of individuals provided with naloxone had administered the opioid antagonist while a long-term study in Massachusetts found that 19% of individuals provided with naloxone administered the opioid antagonist. Enteen et al. evaluated the Drug Overdose Prevention and Education (DOPE) Project run by the San Francisco Department of Public Health to train and distribute naloxone to populations at high risk for overdose. Trainings typically last between 10 and 30 minutes. Participants in the program were asked to complete a brief questionnaire following training and all participants who received naloxone refills were asked to complete an additional questionnaire. Between 2003 and 2009 the DOPE Project prescribed naloxone to 1,942 individuals with the number of new individuals increasing steadily each year. Seventy-five percent of participants reported their race/ethnicity (61% Caucasian, 15% African American, 7% Latino, 2% Asian/Pacific Islander, 2% Native American, 3% more than one race/ethnicity, 3% other). The authors do not indicate if this is reflective of the at-risk population or the service area population in general. Eighty-eight percent of participants reported their housing status with 59% reporting being homeless or unstably housed. Previous studies in San Francisco have found unstably housed individuals to be at increased risk of opioid overdose death. The program provided 1,020 refills, 399 (40%) of which were provided after participants reported using naloxone to respond to an overdose. Participants reported that 89% of overdose events were reversed with an additional 3% of overdose outcomes being unknown to the administrator. Four victim deaths were reported, and in three of these cases the victim had been unconscious for an indeterminate amount of time. Adverse effects following naloxone use were rarely reported and included vomiting, discomfort, anger, and seizures (3 cases). The authors note the limitations of this study include reliance on self-report, a lack of ability to know how many of the participants administered naloxone since the evaluation only captured those who returned for a refill, and that those with positive experiences may have been more likely to return for a refill.

7. Walley AY, Xuan Z, Hackman HH, et al. Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: Interrupted time series analysis. *BMJ (Clinical research ed.)*. 2013;346:f174.

Walley et al. conducted a time series analysis to determine the impact of naloxone training and distribution programs on opioid-related use of acute care hospitals (using state inpatient hospital and outpatient emergency department discharge data) and overdose deaths (using state vital statistics data). They included 19 communities in Massachusetts with five or more opioid related unintentional or undetermined intentional deaths in each year from 2004 to 2006. Between 2006 and 2009 eight local public health agencies began providing overdose education and nasal naloxone distribution (OEND). These programs provided OEND to potential overdose bystanders under a standing order from the OEND medical director. Potential "bystanders"

included opioid users, social service agency staff, family, and friends of opioid users. The training took from 10 to 60 minutes and was tailored to the knowledge and needs of the participants. The OEND program collected questionnaire data at enrollment and whenever an enrollee requested a refill. In their analysis the authors controlled for a number of potential confounding factors including community level demographics, other treatment programs in the community, and health systems changes. Between September 2006 and December 2009 OEND programs in Massachusetts enrolled 4,857 individuals and 545 naloxone rescue attempts were reported. In the 19 communities included in the study 2,912 individuals were enrolled and 327 rescue attempts were made. They found that naloxone was successful in 150 out of 153 attempts (98% success rate). The authors do not clarify why they are using 153 as the denominator rather than 327 when calculating success rate. For the three unsuccessful attempts EMS was contacted and the victims survived. The authors found that opioid related deaths were reduced significantly in those communities that implemented OEND compared to those that did not implement these programs. They found no statistically significant association between program implementation and opioid related acute care hospital utilization.

8. Dahan A, Aarts L, Smith TW. Incidence, reversal, and prevention of opioid-induced respiratory depression. *Anesthesiology.* 2010;112(1):226-238.
Dahan et al. provide a review of the evidence on naloxone efficacy and dosage. The authors cite a large number of studies indicating that naloxone has been shown to effectively and rapidly reverse respiratory depression induced by opioids. This relationship has been found in human and animal trials. They note that the extent and the duration of the reversal are dependent on many factors such as the opioid used, the opioid dose, and mode of administration. The evidence provided by Dahan et al. indicate that naloxone is more effective for some opioid overdoses than for others and that opioids with high receptor affinity require greater naloxone concentrations or a continuous infusion of naloxone in order to be fully effective compared with an opioid with lower receptor affinity.

9. Robinson A, Wermeling DP. Intranasal naloxone administration for treatment of opioid overdose. *American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists.* 2014;71(24):2129-2135.Robinson et al. provide a review of the literary evidence on the efficacy of intranasal naloxone. The authors summarize two studies which found low adverse events associated with naloxone administration (both intramuscular and intranasal) following an overdose although minor adverse effects such as agitation, sweating, vomiting, headaches, and tremor were observed. The authors highlight evidence that naloxone is generally well tolerated and severe negative responses that have been observed, such as cardiac arrhythmias, heart attacks, and seizures generally result from underlying medical problems. Naloxone can also cause abstinence syndrome (withdrawals) in opioid-dependent individuals. The authors indicate that naloxone does not produce physical dependence and thus does not have an abuse potential. They summarize two studies that randomized overdose victims to receive either intramuscular naloxone or intranasal naloxone and found that while intramuscular injections were more effective than nasal applications, both methods of administration were safe and reversed the effects of the opioid overdose in over 72% of the cases. One author of this review is the Chief Executive Officer of a company funded to develop and commercialize a ready-to-use naloxone nasal spray which could introduce a conflict of interest.

10. Doe-Simkins M, Quinn E, Xuan Z, et al. Overdose rescues by trained and untrained participants and change in opioid use among substance-using participants in overdose education and naloxone distribution programs: A retrospective cohort study. *BMC public health.* 2014;14.

Doe-Simkins et al. cite one survey where a minority of respondents who used injection drugs indicated that they would feel comfortable using more heroin after receiving a naloxone kit. The authors then indicate that no studies of Overdose Education and Naloxone Distribution (OEND) programs have demonstrated increased drug use by participants and cite one study which found no change in drug use and two studies which found decreases in drug use following training in OEND. They authors evaluated the difference in witness response to overdose between those trained in the Skills and Knowledge on Overdose Prevention (SKOOP) curriculum (n=295) and those without this training (n=78). Untrained individuals had received the kit through social networks and also received anywhere from no knowledge sharing to extensive knowledge sharing along with the kit. The formal SKOOP training can take between 10 and 60 minutes. The authors conducted a retrospective cohort study using program data from the Massachusetts Opioid Overdose Prevention Pilot program. Participants filled out a questionnaire at enrollment and again if they returned for a naloxone refill. The researchers identified program participants who had used naloxone and who had not been trained by staff. They found that trained individuals and untrained individuals were equally likely to call EMS when witnessing an overdose, although this number was low (about 25%) for both groups. Doe-Simkins et al. also found no significant difference between help seeking, rescue breathing, staying with the victim, or success of naloxone administration by trained versus untrained rescuers. In addition they found no significant overall change in the number of days participants used heroin after being trained and provided with a naloxone kit and indicate that this supports that overdose management and distributing naloxone kits does not lead to increased opioid use.

11. Green TC, Heimer R, Grau LE. Distinguishing signs of opioid overdose and indication for naloxone: An evaluation of six overdose training and naloxone distribution programs in the United States. *Addiction (Abingdon, England).* Jun 2008;103(6):979-989.

Green et al. assessed the knowledge of current and former opioid users who were either trained or untrained in overdose response by six naloxone distribution programs across the United States as well as the knowledge of medical experts. Three of the training programs were new while three were well established. Trainings were brief (ranging from 15 to 120 minutes) and took place in a number of settings including syringe exchange programs, private homes, and on the street. Each site recruited five participants who the program had trained and five who the program had not trained but that were using their other programs (e.g. syringe exchange, drop-in site). Trained participants had, on average, received their training 8 months (range 1-80 months) prior to the evaluation. Participants were provided with 16 scenarios and asked if each was an opioid overdose and if naloxone should be administered. The authors found that, after controlling for demographic and overdose experience factors, potential bystanders who had received training were significantly more likely than untrained bystanders to recognize opioid overdose scenarios accurately and to accurately identify scenarios when naloxone should be used. Trained individuals on average correctly indicated if naloxone should be administered in 13.5 of 16 scenarios while untrained individuals identified this correctly in 11.1 scenarios. The authors note the relatively high opioid overdose symptom knowledge even among untrained participants. Trained bystanders were as skilled as medical experts trained in overdose recognition and

treatment both in recognizing overdose scenarios and instances when naloxone should be administered.

12. Centers for Disease Control and Prevention. ***Morbidity and Mortality Weekly Report November 1, 2011. Vital Signs: Overdoses of Prescription Opioid Pain Relievers--United States, 1999-2008.*** **2011.**The Centers for Disease Control and Prevention analyzed 2008 National Vital Statistics data and found that AI/AN populations had the highest age-adjusted rates of overdose deaths from opioid pain relievers with rates for non-Hispanic white populations being nearly as high. These rates were nearly three times higher than those for black and Hispanic white populations. The authors cite two studies which indicate that these death rates mirror the non-medical and medical use of opioid pain relievers by subpopulations. Vital statistic data is subject to limitations such as misclassification of race/ethnicity and cause of death on death certificates.

13. Northwest Portland Area Indian Health Board. ***American Indian/Alaska Native Community Health Profiles: Washington Substance Abuse.*** **2014.**
The Northwest Portland Area Indian Health Board analyzed Washington state death certificate data for 2006-2010 and corrected for misclassification of AI/AN individuals using the Improving Data & Enhancing Access – Northwest Project. These data indicate that prescription opioid pain relievers contributed to 2.9% of deaths among AI/AN populations and 1.1% of deaths among non-Hispanic white populations. This report does not indicate if these differences are statistically significant.

14. Reed P, Jenks L, Kindig D, Cheng E, Kinne S. ***Health of Washington State Report - Mortality and Life Expectancy.*** **2013.**
Age-adjusted death rates from 2009-2011 Washington state death certificate data indicate that AI/ANs have significantly higher death rates than black, white, Hispanic and Asian populations. This report indicates that death certificates often misclassify race/ethnicity and highlights that death data may underreport for American Indians and Alaska Natives.

15. Washington State Department of Health. ***Vital statistics data.*** **2011-2013.**
Vital statistics data indicate that between 2011 and 2013 in Washington state, 1,176 individuals died of prescription opioid overdose and 658 individuals died of non-prescription opioid overdose. American Indian/Alaska Natives (AI/AN) were significantly more likely than any other racial/ethnic group to be victims of fatal overdoses from both prescription and non-prescription opioids. The AI/AN population had an age-adjusted rate almost three times higher than that for the overall population. The numbers for the Native Hawaiian and Other Pacific Islander population were too low to calculate the rates for both prescription and non-prescription as were the numbers for the Asian population for non-prescription. Rates were calculated per 100,000, age-adjusted for the United States 2000 population. The data also show a steady increase in the number of opioid overdose deaths for all populations between 1995 and 2013 with a larger increase among prescription-related overdose deaths. The rate increased from an age-adjusted death rate for all opioids of 3.3/100,000 (95% CI 2.9-3.8/100,000) in 1995 to 8.6/100,000 (7.9-9.3/100,000) in 2013. It is important to note the potential limitations of death certificate data such as possible misclassification of both race/ethnicity and cause of death. The age-adjusted rates for 2011-2013 were as follows for opioid overdose deaths:

Category	Race	Count	Age-adjusted Rate	Lower CI	Upper CI
Prescription	Total	1176	5.00	4.71	5.30
Prescription	White	1025	6.37	5.97	6.79
Prescription	African American	37	4.98	3.49	7.00
Prescription	AI/AN	44	16.20	11.72	21.92
Prescription	Asian	12	0.77	0.39	1.34
Prescription	NHOPI	2			
Prescription	Multi-race	21	3.71	2.24	5.83
Prescription	Hispanic	34	0.84	0.56	1.21
Prescription	Unknown	1			
Non-Prescription	Total	658	2.85	2.63	3.08
Non-Prescription	White	558	3.79	3.48	4.13
Non-Prescription	African American	27	3.47	2.28	5.19
Non-Prescription	AI/AN	30	10.92	7.33	15.75
Non-Prescription	Asian	3			
Non-Prescription	NHOPI	3			
Non-Prescription	Multi-race	12	1.83	0.91	3.40
Non-Prescription	Hispanic	25	0.68	0.43	1.04
Non-Prescription	Unknown	0			

CI: Confidence Interval
AI/AN: American Indian/Alaska Native
NHOPI: Native Hawaiian and Other Pacific Islander

Rate per 100,000 age-adjusted to U.S. 2000 population; Rates not calculated when counts are fewer than 5. Residents who died outside of Washington excluded.

Only included deaths with underlying cause of death: ICD-10 X40-X49 or where a term to indicate acute was reported and the manner of death was not undetermined.

Morphine and hydromorphone were excluded from prescription category unless it was specifically reported as pharmaceutical or it was the only drug reported and medication use was also reported.

Center for Health Statistics, Washington State Department of Health, February 2, 2015.

16. Warner-Smith M, Darke S, Lynskey M, Hall W. Heroin overdose: Causes and consequences. *Addiction (Abingdon, England).* 2001;96(8):1113-1125.

Warner-Smith et al. provide a review of the literature on heroin overdose including publications on the complications following nonfatal overdose. The negative health effects associated with heroin overdose include: build-up of fluid in the lungs (oedema), pneumonia, heart issues (arrhythmia, acute cardiomyopathy, haemoglobinaemia), dissolution of muscle cells, kidney failure, inadequate oxygen to the brain, and cognitive impairment.