Title

Modeling of overdose and naloxone distribution in the setting of fentanyl compared to heroin

Authors

Coffin, Phillip O
Maya, Sigal
Kahn, James G

Publication Date

2022-07-01

DOI

10.1016/j.drugalcdep.2022.109478

Peer reviewed

HHS Public Access

Author manuscript

Drug Alcohol Depend. Author manuscript; available in PMC 2023 July 01.

Published in final edited form as:

Drug Alcohol Depend. 2022 July 01; 236: 109478. doi:10.1016/j.drugalcdep.2022.109478.

Modeling of overdose and naloxone distribution in the setting of fentanyl compared to heroin

Phillip O. Coffin, MD[a,b],

Sigal Maya, MS[b],

James G. Kahn, MD MPH[b]

[a]San Francisco Department of Public Health, 25 Van Ness Ave Suite 500, San Francisco CA 94102

[b]University of California San Francisco

Abstract

Background: Fentanyl has replaced most other non-prescribed opioids in much of North America. There is controversy over whether a hypothetical reduced efficacy of naloxone in reversing fentanyl is a major contributor to the coincident rising overdose mortality.

Methods: We modified an existing Markov decision analytic model of heroin overdose and naloxone distribution to account for known risks of fentanyl by adjusting overdose risk, the likelihood of death in the event of overdose, and the proportion of cases in which available naloxone was administered in time to prevent death. We assumed near-universal survival when naloxone was administered promptly for heroin or fentanyl overdose, but allowed that to decline in sensitivity analyses for fentanyl. We varied the proportion of use that was fentanyl and adjusted the modified parameters accordingly to estimate mortality as the dominant opioid shifted.

Results: Absent naloxone, the annual overdose death rate was 1.0% and 4.1% for heroin and fentanyl, respectively. With naloxone reaching 80% of those at risk, the overdose death rate was 0.7% and 3.6% for heroin and fentanyl, respectively, representing reductions of 26.4% and 12.0%. Monte Carlo simulations resulted in overdose mortality with fentanyl of 3.3-5.2% without naloxone and 2.6-4.9% with naloxone, with 95% certainty. Positing reduced efficacy for naloxone in reversing fentanyl resulted in 3.6% of fentanyl overdose deaths being prevented by naloxone.

Conclusions: Heightened risk for overdose and subsequent death, alongside the time-sensitive need for naloxone administration, fully account for increased mortality when fentanyl replaces heroin, assuming optimal pharmacologic efficacy of naloxone.

Keywords

heroin; fentanyl; overdose; naloxone; modeling

Corresponding author: Phillip O. Coffin: San Francisco Department of Public Health, 25 Van Ness Ave Suite 500, San Francisco CA 94102, Tel: +1-415-554-8176, Fax: +1-415-554-4363, pcoffin@gmail.com; phillip.coffin@sfpdh.org.

INTRODUCTION

Fentanyl has replaced heroin and opioid analgesics as the dominant non-prescribed opioid in many regions of North America.(Ciccarone, 2021) For example, fentanyl accounted for 6.7% of opioid overdose deaths in San Francisco in 2014 and 89% in 2020.(Coffin et al., 2021) This transition was associated with an increase from 127 to 584 opioid overdose deaths.(Coffin et al., 2021) This profound increase in mortality raises concerns about the viability of prevention programming.

Naloxone provision, a major tool in overdose mortality prevention,(Doe-Simkins et al., 2009; Enteen et al., 2010; Green et al., 2008; Maxwell et al., 2006; Paone et al., 2010; Piper et al., 2008; Sporer and Kral, 2007; Walley, 2012) may not be as effective at preventing mortality in the setting of fentanyl compared to heroin. Some investigators have suggested that standard naloxone dosing does not reverse fentanyl overdose, citing as evidence retrospective studies of naloxone doses used by emergency medical services (EMS) showing that, for example, multiple naloxone doses were used in 15.0% of cases in 2013 and 21.4% in 2016.(Geiger et al., 2020) In contrast, an analysis of pre-hospital and emergency department naloxone use in 2017 and 2018 showed no difference in the median dose of naloxone required for successful reversal by the presence or absence of fentanyl,(Carpenter et al., 2020) and an analysis of overdose survivors recruited from an emergency department found no association between fentanyl blood concentration and the dose of naloxone required for reversal.(Krotulski et al., 2021) Similarly, in Pittsburgh, PA, while the proportion of opioid overdose deaths attributed to fentanyl rose from 3.5% to 68.7%, the mean number of doses of naloxone administered by lay persons did not change (from 1.62 [SD 0.83] to 1.52 [SD 0.75]).(Bell et al., 2019)

Fentanyl is far more potent, lipophilic, and fast-acting than other opioids. The risk of overdose when using fentanyl, based on data from the Sydney, Australia, safe injection facility, is estimated to be 9.17 times greater than opioid analgesics and 2.32 times greater than heroin.(Latimer et al., 2016) In addition, overdose from fentanyl is believed to be far more likely to result in death. This is in part due to its greater potency, and in part to the speed at which overdose occurs.(Somerville et al., 2017) In contrast to heroin overdose, which generally results in onset of respiratory depression and eventual arrest over 30-60 minutes,(Sporer et al., 1996) this progression happens within minutes for fentanyl, sometimes prior to removal of the needle from the decedent's arm.(Somerville et al., 2017) Once cardiac arrest has occurred, overdose survival and the utility of reversing the opioid effect is limited, and negligible without advanced cardiac life support.(Sporer et al., 1996) These distinctions imply that there is a much narrower window of time during which layperson intervention is effective for fentanyl compared to heroin overdose. However, modeling of the impact of evidence-based interventions on overdose is currently based on heroin.

The first model ever to estimate the heroin overdose, overdose mortality, and the impact of naloxone provision was published in *Annals of Internal Medicine* in 2013.(Coffin and Sullivan, 2013a) We sought to adjust this model, which has served as the basis for multiple

subsequent models (Coffin and Sullivan, 2013b; Langham et al., 2018; Uyei et al., 2017), to account for the influx of fentanyl in communities across North America.

METHODS

We adapted our previously published model, which is described in detail elsewhere.(Coffin and Sullivan, 2013a) Briefly, the model consisted of a Markov model with an integrated decision analytic model built in Microsoft Excel 2010™ (Redmond, WA) estimating costs and QALYs from a societal perspective, with annual transitions, standard background mortality, and 3% annual discounting. The model followed people from 21 years of age, the average age of initiating heroin use in the U.S.(2010) Detailed input parameters and their justifications can be found in the original manuscript, with instantaneous rates transformed into probabilities. The original model was iteratively calibrated to be consistent with conservative estimates of overdose, mortality, naloxone usage, and drug use cessation from epidemiologic studies,(Bohnert et al., 2009; Centers for Disease Control and Prevention, 2012; Coffin et al., 2003; Coffin et al., 2007; Darke et al., 2011; Darke et al., 1996a, b; Doe-Simkins et al., 2009; Evans et al., 2012; Galea et al., 2006; Gossop et al., 1996; Hakansson et al., 2008; Hser et al., 2001; Jenkins et al., 2011; Maxwell et al., 2006; Ochoa et al., 2005; Piper et al., 2008; Stoove et al., 2009; Strang et al., 2008; Tobin et al., 2009; Vlahov et al., 1991; Vlahov et al., 2008; Wagner et al., 2010; Wampler et al., 2011; Wu et al., 2011; Zador et al., 1996) following methods guidance from Stout et al.(Stout et al., 2009)

We modified three parameters to account for the transition to fentanyl. First, we multiplied the risk of overdose by 2.3 to account for the heightened risk for overdose when people knowingly inject fentanyl compared to heroin at safe injection sites.(Latimer et al., 2016) Second, we doubled the risk of death in the event of a fentanyl overdose, based on data finding that when patients arrive in the ED with fentanyl overdose, they are twice as likely to require advanced respiratory support compared to heroin or other opioid analgesics.(Fox et al., 2018) Third, we reduced by half the likelihood that naloxone would be administered in time to reverse a fentanyl overdose, given the rapidity of fentanyl overdose and progression to cardiac arrest compared to heroin.(Somerville et al., 2017; Sporer et al., 1996) Importantly, we also modified the efficacy of naloxone such that the likelihood of overdose survival was the same for fentanyl or heroin (99.97%) if naloxone was administered soon enough.

We determined absolute and relative overdose death rates with and without naloxone distribution; we did not update or evaluate cost-effectiveness.

Model:

The model, described in detail in the original manuscript,(Coffin and Sullivan, 2013a, b) ran for 64 years by which time most people in the population were deceased. The Markov model consisted of the following states: heroin/fentanyl use, discontinued use, nonfatal or fatal overdose, and death for other reasons.(Sporer and Kral, 2007) Based on data that the primary risk factor for opioid overdose is a prior overdose,(Coffin et al., 2007) data regarding the annual and lifetime rates of overdose,(Coffin et al., 2007; Darke et al., 1996a;

Darke et al., 2007; Gossop et al., 1996; Hakansson et al., 2008; Havens et al., 2011; Jenkins et al., 2011; Milloy et al., 2008; Ochoa et al., 2005) and the risk of subsequent fatal overdose,(Darke et al., 2011; Stoove et al., 2009) the original model was calibrated to demonstrate a peak in overdose death in the fourth decade of life.(Coffin et al., 2003; Zador et al., 1996) This required assuming a relatively low rate of first time overdose that declined with age(Darke et al., 2007) but increased after the first overdose and again after the second.(Coffin et al., 2007; Darke et al., 2007; Jenkins et al., 2011; Milloy et al., 2008; Ochoa et al., 2005; Sporer, 1999) To adjust the model to fentanyl, we multiplied the risk of each phase of overdose by 2.315789 for the base case analysis, not to exceed 1.0.(Latimer et al., 2016) This adjustment was increased and decreased by 50% for the upper and lower limit values.

The decision analytic model processed the overdose event. If an overdose event were witnessed, emergency medical services (EMS) might be called, resulting in probabilities that the event would produce survival or death. In the setting of naloxone distribution, additional layers included if naloxone had been provided to the person, if it was available at the event, and if it was administered prior to cardiac arrest. The rate of naloxone administration prior to cardiac arrest, 80% in the original model, was reduced to 40% for fentanyl due to the rapid progression of fentanyl compared to heroin overdose. The rate of death for an overdose without intervention, 8.2% in the original model, was doubled for fentanyl.(Fox et al., 2018) The increased likelihood of survival after EMS was assumed to be unchanged from the original model.[4,5,18–22] For the fentanyl model, however, we adjusted the increased likelihood of survival if naloxone was administered to match the likelihood of survival from the heroin model (i.e., per the original model, 91.8% of persons would survive a first-time heroin overdose without intervention and 99.97% would survive with either EMS activation or naloxone; with 100% fentanyl saturation, 83.6% would survive a first-time fentanyl overdose without intervention, 91.0% would survive with EMS activation but no bystander naloxone, and 99.97% would survive with naloxone administration).

The final modification to the model was to estimate the proportion of opioid use that was fentanyl. The model assumed a baseline of 100% heroin use. To estimate the proportion of use that was fentanyl, we used the proportion of opioid deaths attributed to fentanyl (a readily-available measure in most communities). Because the risk of overdose and overdose death due to fentanyl is greater than those due to heroin, we assumed that there was a non-linear relationship between prevalence of fentanyl use and the proportion of overdose deaths due to fentanyl (e.g., if just 5% of overdose deaths were due to fentanyl, vanishingly few people were using fentanyl, whereas if 90% of overdose deaths were due to fentanyl, most people at-risk were using fentanyl). We iteratively selected the square of the proportion of opioid overdose deaths due to fentanyl as the proportion of use that was fentanyl as that was close to the increased risk of overdose from fentanyl and generated an change in the mortality rate that was most consistent with empiric data(Coffin et al., 2021; Paone et al., 2017); we also conducted sensitivity analyses using exponents of 1.5 and 2.5. We then multiplied this value by the adjustments to risk of overdose, risk of death from overdose, and proportion of overdoses in which naloxone is administered in time, to generate scenarios ranging from 100% heroin to 100% fentanyl use in a community.

Outcomes:

Outcomes included the rates of non-fatal and fatal overdose, and the proportion of overdose deaths prevented by naloxone distribution. We report results ranging from the original model focused on heroin, up to 100% fentanyl use.

Uncertainty:

To test the impact of the novel fentanyl parameters, we conducted deterministic sensitivity analyses by eliminating each individual fentanyl adjustment. In addition, to model the assumption that naloxone is less efficacious in reversing fentanyl overdose compared to heroin overdose, we reduced the relative increase in survival when naloxone was administered to match that for heroin (resulting in a lower 91.0% surviving a first-time fentanyl overdose after naloxone administration). We also conducted a probabilistic sensitivity analysis to address the uncertainty around the novel fentanyl parameters. Proportion of opioid deaths due to fentanyl, relative increase in overdose frequency with fentanyl, relative reduction in overdose survival without intervention for fentanyl, reduction in naloxone use prior to cardiac arrest for fentanyl, and relative increase in survival with naloxone were varied at once in a Monte Carlo simulation with 1,000 iterations. This analysis was also conducted with three other scenarios: 20% naloxone coverage, and the high and low exponential relationships between the proportion of opioid deaths that were due to fentanyl and the proportion of use that was fentanyl.

RESULTS

In the absence of naloxone, the model predicted an average rate of overdose per year of 12.3% for heroin and 25.0% for fentanyl, with an overdose death rate among persons actively using opioids of 0.97% for heroin and 4.09% for fentanyl. The age at which people actively using were most likely to die from an overdose was 47 years for heroin and 36 years for fentanyl. The likelihood of survival in the event of an unwitnessed overdose declined from 89.9% for heroin to 81.6% for fentanyl. When EMS was contacted, average survival was 97.9% for heroin and 88.9% for fentanyl. When naloxone was administered in time, average survival was 97.9% in all scenarios, as we assumed naloxone was equally effective for heroin and fentanyl.

In the setting of 80% coverage with naloxone, the annual rate of overdose death rate declined 26.4% (to 0.71%) for heroin, and 12.0% (to 3.60%) for fentanyl (see Figure 1). The reduction in overdose mortality was proportional to naloxone coverage, such that a program that reached 100% of people would reduce overdose death by 33.7% for heroin and 15.7% for fentanyl, and a program that reached 20% of people would reduce overdose death by 6.2% for heroin and 2.7% for fentanyl. A community without naloxone programming that transitioned from all heroin to all fentanyl use could expect a 4.2-fold increase in opioid overdose mortality. A community with naloxone programming could expect a 4.2-fold increase if there was 20% coverage, a 5.1-fold increase with 80% coverage, and a 5.4-fold increase with 100% coverage.

Sensitivity Analyses:

On deterministic sensitivity analyses, we individually eliminated fentanyl adjustments and report the increase in opioid overdose mortality from 100% heroin to 100% fentanyl use. If the frequency of overdose with fentanyl were the same as the frequency of overdose with heroin, there would be only a 1.6-fold increase in mortality. If fentanyl overdose did not result in a higher rate of death than heroin overdose, mortality would increase 2.7-fold. In the setting of 80% naloxone coverage, if naloxone was administered prior to cardiac arrest as frequently for fentanyl as for heroin, there would a be 4.1-fold increase in mortality. If naloxone administered prior to cardiac arrest resulted in the same proportional increase in survival for fentanyl as for heroin (i.e., a lower overall likelihood of survival), there would be a 5.6-fold increase in mortality.

The upper and lower limits of the overdose risk adjustment for fentanyl and the risk of death from fentanyl overdose without intervention generated estimates of annual fentanyl overdose mortality from 3.5-4.8% (Figure 2).

Evaluating the impact of modified parameters on the proportion of opioid overdose deaths prevented with naloxone, the increase in overdose risk from fentanyl had minimal impact, however the relative reduction in survival for fentanyl overdose was more substantial, resulting in a range from 4.1-18.9% of deaths being prevented. Similarly, the ability to administer naloxone prior to cardiac arrest had a significant influence, resulting in a range from 5.5-19.6% of deaths being prevented (i.e., if naloxone could be administered prior to cardiac arrest as often for fentanyl as for heroin, the annual fentanyl overdose death rate would be as low as 3.29%). Finally, we assumed at baseline that timely naloxone administration resulted in successful reversal of nearly all fentanyl overdoses; assuming a lower effectiveness of naloxone resulted in as little as 3.6% of deaths being prevented (Figure 3) and a corresponding 5.6-fold increase in opioid overdose mortality with the transition from heroin to fentanyl.

In probabilistic sensitivity analysis varying all fentanyl adjustment parameters, as well as the efficacy of naloxone for fentanyl reversal, at once in a Monte Carlo simulation with 1,000 iterations, increasing fentanyl saturation in the community led to a non-linear increase in the annual opioid death rate, regardless of naloxone availability (Figure 4). In the context of 100% fentanyl, the overdose death rate would be 3.3-5.2% without naloxone and 2.6-4.9% with naloxone with 95% certainty. In the context of 50% fentanyl, these rates would be 1.6-2.3% and 1.3-2.1%, respectively. The same analysis resulted in a range from 2.7-23.8% of overdose deaths prevented with 80% naloxone coverage, with 95% certainty. The upper range would result in a 4.4-fold increase in mortality with the transition from heroin to fentanyl.

Assuming 20% naloxone coverage (see Supplement Figure 1) and 100% fentanyl, the overdose death rate would be 3.1-5.2% with 95% certainty, with the mean estimate of 4.2% corresponding to a 2.3% reduction in overdose mortality compared to no naloxone. Assuming the rate of fentanyl use was equal to the proportion of opioid deaths due to fentanyl to the power of 1.5, the increase in the overdose death rate was more linear, such that, in the setting of 50% fentanyl and no naloxone, the overdose death rate would be

1.8-2.7% (mean 2.3%) with 95% certainty (see Supplement Figure 2). Assuming the rate of fentanyl use was equal to the proportion of opioid deaths due to fentanyl to the power of 2.5, the increase in the overdose death rate was more upward sloping, such that, in the setting of 50% fentanyl and no naloxone, the overdose death rate would be 1.5-2.0% (mean 1.7%) with 95% certainty (see Supplement Figure 3).

DISCUSSION

Modifying an established heroin overdose and naloxone distribution model to fentanyl predicted a several-fold increase in the number of opioid overdose deaths experienced as fentanyl came to be involved in 100% of opioid overdose deaths. Adjusting only three parameters to increase risk for overdose and subsequent mortality, and to reduce the rate of naloxone administration prior to cardiac arrest, readily accounts for the dramatic increase in overdose death and apparent reduced effectiveness of naloxone distribution in reducing opioid overdose mortality. As an empiric example, as San Francisco transitioned from opioid overdose deaths due to heroin and prescription opioids in 2014 to 89% of deaths due to fentanyl in 2020, opioid overdose deaths increased from 127 to 584, a 4.6-fold increase. (Coffin et al., 2021) Assuming San Francisco has 80% naloxone coverage, the model would have predicted a 4.3-fold increase. Unfortunately, replacement of other opioids with fentanyl consistently resulted in a several-fold increase in opioid overdose mortality that would not be averted with a bystander-administered reversal agent, regardless of reach or effectiveness.

Simple adjustments to an established model elucidated several unique aspects of opioid overdose epidemiology in the setting of fentanyl. Assuming a stable number of at-risk persons who initiate use at the same age as during the heroin era, the age at which people who were actively using were most likely to die shifted 11 years younger when fentanyl came to dominate the market. Thus, at least some of the shift to younger opioid overdose decedents may be due to the higher risk nature of fentanyl, rather than a new cohort of youth using fentanyl. In addition, the number of overdose events was nearly three-fourths greater in the setting of fentanyl compared to heroin, supporting the observed increase in opioid overdose events and reported naloxone reversals.(Coffin et al., 2021)

Importantly, these predictions assumed that naloxone was pharmacologically as effective for fentanyl overdose as it was for heroin overdose – i.e., naloxone administered prior to cardiac arrest resulted in near-universal survival. Reducing the efficacy of naloxone to reverse overdose in the setting of fentanyl, as some have suggested to account for rising mortality, would be associated with a 5.6-fold increase in overdose mortality as a community shifted from heroin to fentanyl, exceeding observed data.(Coffin et al., 2021; Paone et al., 2017) If we also assumed naloxone was administered prior to cardiac arrest as often for fentanyl as for heroin, overdose mortality increased just 4.1-fold with the transition to fentanyl, corresponding to prevention of 19.6% of overdose deaths from naloxone programming. These results suggest that interventions allowing immediate administration of naloxone in the setting of a fentanyl overdose – such as safe consumption spaces or technology that automatically administers naloxone in the setting of hypoxia – could save a significant number of lives. Novel naloxone formulations or alternative opioid reversal agents, in

contrast, would not be expected to have an outsized impact on the overdose epidemic, as they remain limited by the inherent nature of bystander reversal interventions.

Limitations:

This initial effort to adjust an overdose model to the era of fentanyl does not account for several factors. First, the proportion of fentanyl overdose deaths due to unintentional fentanyl exposure may be higher than for heroin, a phenomenon that would require a different approach to capture. Second, we did not consider the variety of fentanyl analogues, which may modify the risk of overdose in complex ways (e.g., due to wide variations in and awareness of potency). Third, we did not consider medications for opioid use disorder treatment, which have also been shown to reduce opioid overdose mortality and would be expected to influence outcomes. Fourth, we assumed no change in the efficacy of EMS in improving survival after overdose. While the delay to EMS arrival may be more likely to reduce survival after fentanyl versus heroin overdose, and thus favor lay naloxone administration, the ability of EMS to perform advanced cardiac life support may offset that difference, resulting in a similar efficacy for each intervention. There are also other factors that influence opioid overdose mortality not considered in this model, such as policing practices and social determinants of health, which reduce the precision of predicted changes in mortality.

In summary, we applied a longstanding model of heroin overdose and naloxone distribution to the emergence of fentanyl. The dramatic increase in mortality as fentanyl enters a community is readily explained by the heightened risk for overdose and risk of death in the event of overdose. The expected increase in overdose mortality was remarkably insensitive to the efficacy of naloxone in reducing the risk of death after fentanyl overdose. While naloxone provision remained an effective intervention to reduce fentanyl overdose mortality, the relative impact was less than for heroin overdose, implying a need to expand programming as broadly as possible, while simultaneously deploying multiple other evidence-based and innovative approaches to prevent overdose or ensure more timely intervention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

Authors report no conflicts of interest, had full access to all of the data in the study, and take responsibility for the integrity of the data and accuracy of the data analysis.

Funding:

This work was supported by National Institutes of Health (grant numbers R01DA045690, 5R37DA015612-170).

References

2010. Substance Abuse and Mental Health Services Administration. Results from the 2009 National Survey on Drug Use and Health: Volume 1. Summary of National Findings. Office of Applied Studies, NSDUH Series H-38A, HHS Publication No. SMA 10-4586. Rockville, MD.

Bassett IV, Walensky RP, 2010. Integrating HIV screening into routine health care in resource-limited settings. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 50 Suppl 3, S77–84. [PubMed: 20397960]

Bell A, Bennett AS, Jones TS, Doe-Simkins M, Williams LD, 2019. Amount of naloxone used to reverse opioid overdoses outside of medical practice in a city with increasing illicitly manufactured fentanyl in illicit drug supply. Subst Abus 40(1), 52–55. [PubMed: 29558283]

Bohnert AS, Tracy M, Galea S, 2009. Circumstances and witness characteristics associated with overdose fatality. Ann Emerg Med 54(4), 618–624. [PubMed: 19540622]

Bohnert AS, Tracy M, Galea S, 2012. Characteristics of drug users who witness many overdoses: implications for overdose prevention. Drug Alcohol Depend 120(1-3), 168–173. [PubMed: 21839588]

Bruneau J, Brogly SB, Tyndall MW, Lamothe F, Franco EL, 2004. Intensity of drug injection as a determinant of sustained injection cessation among chronic drug users: the interface with social factors and service utilization. Addiction 99(6), 727–737. [PubMed: 15139871]

Carpenter J, Murray BP, Atti S, Moran TP, Yancey A, Morgan B, 2020. Naloxone Dosing After Opioid Overdose in the Era of Illicitly Manufactured Fentanyl. J Med Toxicol 16(1), 41–48. [PubMed: 31471760]

Centers for Disease Control and Prevention, 2012. Community-based opioid overdose prevention programs providing naloxone - United States, 2010. MMWR. Morbidity and mortality weekly report 61(6), 101–105. [PubMed: 22337174]

Ciccarone D, 2021. The rise of illicit fentanyls, stimulants and the fourth wave of the opioid overdose crisis. Curr Opin Psychiatry 34(4), 344–350. [PubMed: 33965972]

Coffin PO, Galea S, Ahern J, Leon AC, Vlahov D, Tardiff K, 2003. Opiates, cocaine and alcohol combinations in accidental drug overdose deaths in New York City, 1990-98. Addiction 98(6), 739–747. [PubMed: 12780362]

Coffin PO, McMahan V, Haq N, 2021. San Francisco Annual Report: Substance Use Patterns and Trends through 2020. San Francisco Department of Public Health, San Francisco.

Coffin PO, Sullivan SD, 2013a. Cost-effectiveness of distributing naloxone to heroin users for lay overdose reversal. Ann Intern Med 158, 1–9. [PubMed: 23277895]

Coffin PO, Sullivan SD, 2013b. Cost-effectiveness of distributing naloxone to heroin users for lay overdose reversal in Russian cities. J Med Econ 16(8), 1051–1060. [PubMed: 23730942]

Coffin PO, Tracy M, Bucciarelli A, Ompad D, Vlahov D, Galea S, 2007. Identifying injection drug users at risk of nonfatal overdose. Acad Emerg Med 14(7), 616–623. [PubMed: 17554010]

Darke S, Mills KL, Ross J, Teesson M, 2011. Rates and correlates of mortality amongst heroin users: findings from the Australian Treatment Outcome Study (ATOS), 2001-2009. Drug Alcohol Depend 115(3), 190–195. [PubMed: 21130585]

Darke S, Ross J, Hall W, 1996a. Overdose among heroin users in Sydney, Australia: I. Prevalence and correlates of non-fatal overdose. Addiction 91(3), 405–411. [PubMed: 8867202]

Darke S, Ross J, Hall W, 1996b. Overdose among heroin users in Sydney, Australia: II. responses to overdose. Addiction 91(3), 413–417. [PubMed: 8867203]

Darke S, Williamson A, Ross J, Mills KL, Havard A, Teesson M, 2007. Patterns of nonfatal heroin overdose over a 3-year period: findings from the Australian treatment outcome study. J Urban Health 84(2), 283–291. [PubMed: 17265131]

Davidson PJ, McLean RL, Kral AH, Gleghorn AA, Edlin BR, Moss AR, 2003. Fatal heroin-related overdose in San Francisco, 1997-2000: a case for targeted intervention. J Urban Health 80(2), 261–273. [PubMed: 12791802]

Davidson PJ, Ochoa KC, Hahn JA, Evans JL, Moss AR, 2002. Witnessing heroin-related overdoses: the experiences of young injectors in San Francisco. Addiction 97(12), 1511–1516. [PubMed: 12472634]

Doe-Simkins M, Walley AY, Epstein A, Moyer P, 2009. Saved by the nose: bystander-administered intranasal naloxone hydrochloride for opioid overdose. Am J Public Health 99(5), 788–791. [PubMed: 19363214]

Enteen L, Bauer J, McLean R, Wheeler E, Huriaux E, Kral AH, Bamberger JD, 2010. Overdose prevention and naloxone prescription for opioid users in San Francisco. J Urban Health 87(6), 931–941. [PubMed: 20967505]

Evans JL, Hahn JA, Lum PJ, Stein ES, Page K, 2009. Predictors of injection drug use cessation and relapse in a prospective cohort of young injection drug users in San Francisco, CA (UFO Study). Drug Alcohol Depend 101(3), 152–157. [PubMed: 19181458]

Evans JL, Tsui JI, Hahn JA, Davidson PJ, Lum PJ, Page K, 2012. Mortality Among Young Injection Drug Users in San Francisco: A 10-Year Follow-up of the UFO Study. Am J Epidemiol 175(4), 302–308. [PubMed: 22227793]

Fox LM, Hoffman RS, Vlahov D, Manini AF, 2018. Risk factors for severe respiratory depression from prescription opioid overdose. Addiction 113(1), 59–66. [PubMed: 28646524]

Galea S, Worthington N, Piper TM, Nandi VV, Curtis M, Rosenthal DM, 2006. Provision of naloxone to injection drug users as an overdose prevention strategy: Early evidence from a pilot study in New York City. Addict Behav 31(5), 907–912. [PubMed: 16139434]

Geiger C, Smart R, Stein BD, 2020. Who receives naloxone from emergency medical services? Characteristics of calls and recent trends. Subst Abus 41(3), 400–407. [PubMed: 31361589]

Gossop M, Griffiths P, Powis B, Williamson S, Strang J, 1996. Frequency of non-fatal heroin overdose: survey of heroin users recruited in non-clinical settings. BMJ 313(7054), 402. [PubMed: 8761230]

Green TC, Heimer R, Grau LE, 2008. Distinguishing signs of opioid overdose and indication for naloxone: an evaluation of six overdose training and naloxone distribution programs in the United States. Addiction 103(6), 979–989. [PubMed: 18422830]

Hakansson A, Schlyter F, Berglund M, 2008. Factors associated with history of non-fatal overdose among opioid users in the Swedish criminal justice system. Drug Alcohol Depend 94(1–3), 48–55. [PubMed: 18082338]

Havens JR, Oser CB, Knudsen HK, Lofwall M, Stoops WW, Walsh SL, Leukefeld CG, Kral AH, 2011. Individual and network factors associated with non-fatal overdose among rural Appalachian drug users. Drug Alcohol Depend 115(1-2), 107–112. [PubMed: 21126831]

Hser YI, 2002. Drug use careers: Recovery and mortality., in Substance Abuse and Mental Health Services Administration, Office of Applied Studies. Substance Use by Older Adults: Estimates of Future Impact on the Treatment System. OAS Analytic Series #A-21, DHHS Publication No. (SMA) 03-3763 Rockville, MD.

Hser YI, Hoffman V, Grella CE, Anglin MD, 2001. A 33-year follow-up of narcotics addicts. Archives of general psychiatry 58(5), 503–508. [PubMed: 11343531]

Huo D, Bailey SL, Ouellet LJ, 2006. Cessation of injection drug use and change in injection frequency: the Chicago Needle Exchange Evaluation Study. Addiction 101(11), 1606–1613. [PubMed: 17034440]

Jenkins LM, Banta-Green CJ, Maynard C, Kingston S, Hanrahan M, Merrill JO, Coffin PO, 2011. Risk factors for nonfatal overdose at Seattle-area syringe exchanges. J Urban Health 88(1), 118–128. [PubMed: 21246299]

Krotulski AJ, Chapman BP, Marks SJ, Ontiveros ST, Devin-Holcombe K, Fogarty MF, Trieu H, Logan BK, Merchant RC, Babu KM, 2021. Sentanyl: a comparison of blood fentanyl concentrations and naloxone dosing after non-fatal overdose. Clin Toxicol (Phila), 1–8.

Langham S, Wright A, Kenworthy J, Grieve R, Dunlop WCN, 2018. Cost-Effectiveness of Take-Home Naloxone for the Prevention of Overdose Fatalities among Heroin Users in the United Kingdom. Value Health 21(4), 407–415. [PubMed: 29680097]

Latimer J, Ling S, Flaherty I, Jauncey M, Salmon AM, 2016. Risk of fentanyl overdose among clients of the Sydney Medically Supervised Injecting Centre. The International journal on drug policy 37, 111–114. [PubMed: 27750104]

Maxwell S, Bigg D, Stanczykiewicz K, Carlberg-Racich S, 2006. Prescribing naloxone to actively injecting heroin users: a program to reduce heroin overdose deaths. J Addict Dis 25(3), 89–96.

Milloy MJ, Kerr T, Mathias R, Zhang R, Montaner JS, Tyndall M, Wood E, 2008. Non-fatal overdose among a cohort of active injection drug users recruited from a supervised injection facility. Am J Drug Alcohol Abuse 34(4), 499–509. [PubMed: 18584579]

Ochoa KC, Davidson PJ, Evans JL, Hahn JA, Page-Shafer K, Moss AR, 2005. Heroin overdose among young injection drug users in San Francisco. Drug Alcohol Depend 80(3), 297–302. [PubMed: 15961257]

Paone D, Heller D, Olson C, Kerker B, 2010. Illicit drug use in New York City. NYC Vital Signs. Department of Mental Health and Hygeine, New York NY, pp. 1–4.

Paone D, Nolan ML, Tuazon E, Blachman-Forsay J, 2017. NYC Epi Data Brief: Unintentional Drug Poisoning (Overdose) Deaths in New York City, 2000 to 2016. https://www1.nyc.gov/assets/doh/downloads/pdf/epi/databrief89.pdf. (Accessed 22 April 2022).

Piper TM, Stancliff S, Rudenstine S, Sherman S, Nandi V, Clear A, Galea S, 2008. Evaluation of a naloxone distribution and administration program in New York City. Subst Use Misuse 43(7), 858–870. [PubMed: 18570021]

Pollini RA, McCall L, Mehta SH, Vlahov D, Strathdee SA, 2006. Non-fatal overdose and subsequent drug treatment among injection drug users. Drug Alcohol Depend 83(2), 104–110. [PubMed: 16310322]

Somerville NJ, O'Donnell J, Gladden RM, Zibbell JE, Green TC, Younkin M, Ruiz S, Babakhanlou-Chase H, Chan M, Callis BP, 2017. Characteristics of Fentanyl Overdose-Massachusetts, 2014-2016. MMWR. Morbidity and mortality weekly report 66(14), 382–386. [PubMed: 28406883]

Sporer KA, 1999. Acute heroin overdose. Ann Intern Med 130(7), 584–590. [PubMed: 10189329]

Sporer KA, Firestone J, Isaacs SM, 1996. Out-of-hospital treatment of opioid overdoses in an urban setting. Academic emergency medicine : official journal of the Society for Academic Emergency Medicine 3(7), 660–667. [PubMed: 8816181]

Sporer KA, Kral AH, 2007. Prescription naloxone: a novel approach to heroin overdose prevention. Ann Emerg Med 49(2), 172–177. [PubMed: 17141138]

Stoove MA, Dietze PM, Jolley D, 2009. Overdose deaths following previous non-fatal heroin overdose: record linkage of ambulance attendance and death registry data. Drug Alcohol Rev 28(4), 347–352. [PubMed: 19594787]

Stout NK, Knudsen AB, Kong CY, McMahon PM, Gazelle GS, 2009. Calibration methods used in cancer simulation models and suggested reporting guidelines. PharmacoEconomics 27(7), 533–545. [PubMed: 19663525]

Strang J, Manning V, Mayet S, Best D, Titherington E, Santana L, Offor E, Semmler C, 2008. Overdose training and take-home naloxone for opiate users: prospective cohort study of impact on knowledge and attitudes and subsequent management of overdoses. Addiction 103(10), 1648–1657. [PubMed: 18821875]

Teesson M, Mills K, Ross J, Darke S, Williamson A, Havard A, 2008. The impact of treatment on 3 years' outcome for heroin dependence: findings from the Australian Treatment Outcome Study (ATOS). Addiction 103(1), 80–88. [PubMed: 17995994]

Tobin KE, Sherman SG, Beilenson P, Welsh C, Latkin CA, 2009. Evaluation of the Staying Alive programme: training injection drug users to properly administer naloxone and save lives. The International journal on drug policy 20(2), 131–136. [PubMed: 18434126]

Tracy M, Piper TM, Ompad D, Bucciarelli A, Coffin PO, Vlahov D, Galea S, 2005. Circumstances of witnessed drug overdose in New York City: implications for intervention. Drug Alcohol Depend 79(2), 181–190. [PubMed: 16002027]

Uyei J, Fiellin DA, Buchelli M, Rodriguez-Santana R, Braithwaite RS, 2017. Effects of naloxone distribution alone or in combination with addiction treatment with or without pre-exposure prophylaxis for HIV prevention in people who inject drugs: a cost-effectiveness modelling study. Lancet Public Health 2(3), e133–e140. [PubMed: 29253386]

Vlahov D, Anthony JC, Munoz A, Margolick J, Nelson KE, Celentano DD, Solomon L, Polk FB, 1991. The ALIVE Study, A Longitudinal Study Of HIV-1 Infection in Intravenous Drug Users: Description of Methods and Characteristics of Participants, Longitudinal Studies of HIV Infection in Intravenous Drug Users: Methodological Issues in Natural History Research. National Institute on Drug Abuse, Rockville MD, pp. 75–100.

Vlahov D, Wang C, Ompad D, Fuller CM, Caceres W, Ouellet L, Kerndt P, Jarlais DC, Garfein RS, 2008. Mortality risk among recent-onset injection drug users in five U.S. cities. Subst Use Misuse 43(3-4), 413–428. [PubMed: 18365941]

Wagner KD, Valente TW, Casanova M, Partovi SM, Mendenhall BM, Hundley JH, Gonzalez M, Unger JB, 2010. Evaluation of an overdose prevention and response training programme for injection drug users in the Skid Row area of Los Angeles, CA. The International journal on drug policy 21(3), 186–193. [PubMed: 19268564]

Walley AY, 2012. Bystander overdose education and naloxone distribution in Massachusetts, Role of Naloxone in Opioid Overdose Fatality Prevention. Food and Drug Administration, Silver Spring MD.

Wampler DA, Molina DK, McManus J, Laws P, Manifold CA, 2011. No deaths associated with patient refusal of transport after naloxone-reversed opioid overdose. Prehosp Emerg Care 15(3), 320–324. [PubMed: 21612385]

Wu LT, Woody GE, Yang C, Mannelli P, Blazer DG, 2011. Differences in onset and abuse/dependence episodes between prescription opioids and heroin: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Subst Abuse Rehabil 2011(2), 77–88. [PubMed: 21686045]

Zador D, Sunjic S, Darke S, 1996. Heroin-related deaths in New South Wales, 1992: toxicological findings and circumstances. Med J Aust 164(4), 204–207. [PubMed: 8604187]

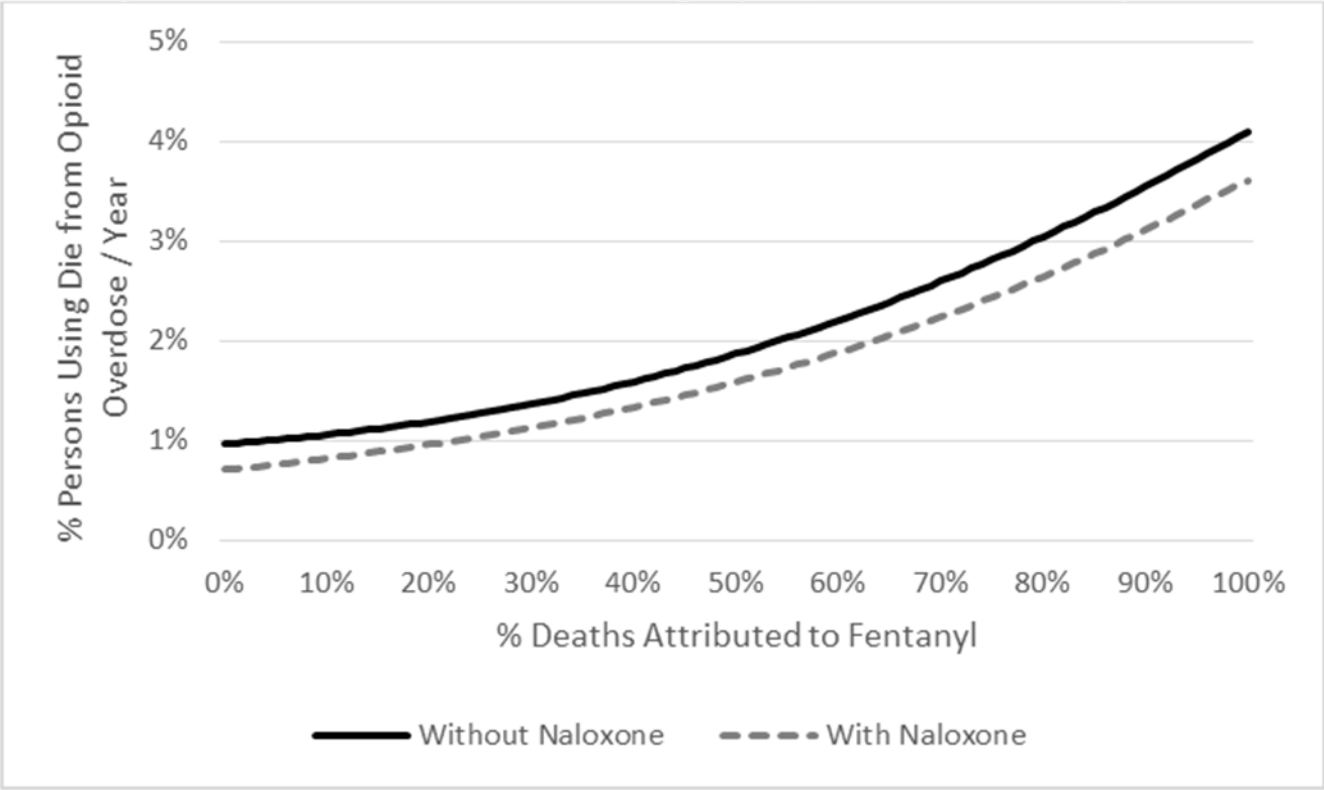

Figure 1:
Predicted Opioid Overdose Death Rate Among Persons Actively Using, by Presence of Fentanyl and 80% Naloxone Coverage (deterministic model)

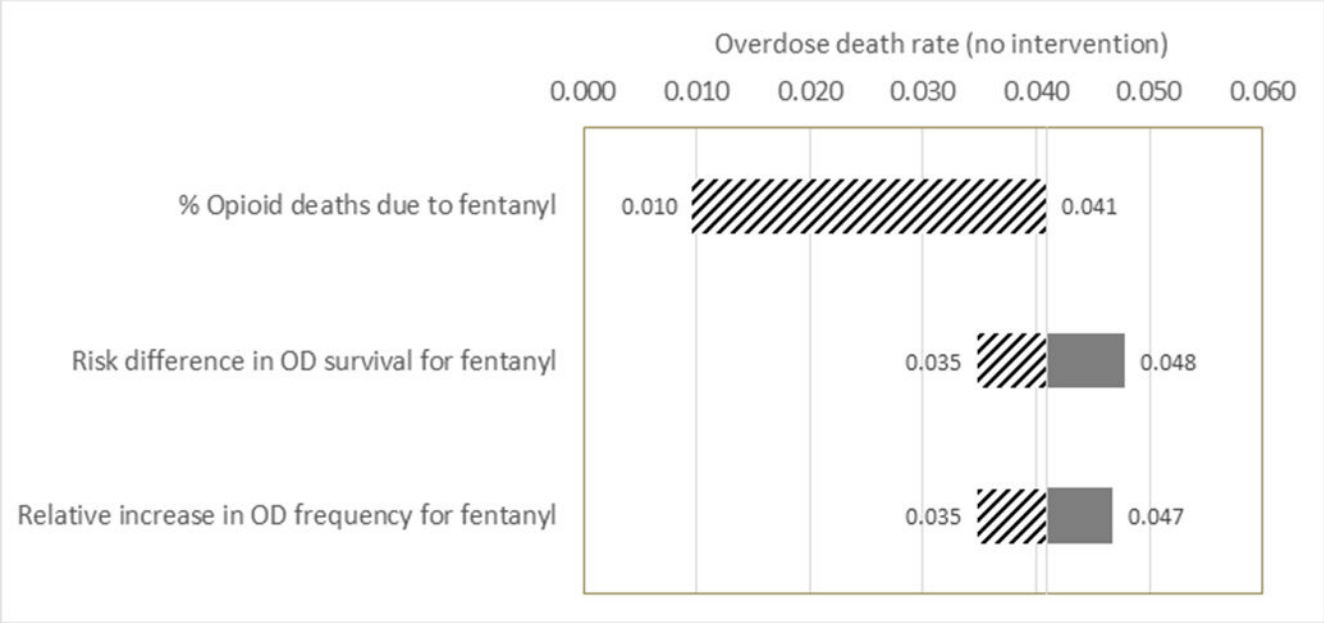

Figure 2: Impact of Fentanyl Parameter Adjustments on Annual Opioid Overdose Mortality Without Intervention

Baseline estimate is for 100% of opioid deaths due to fentanyl, corresponding to an annual opioid overdose death rate of 4.1% among persons actively using opioids in the absence of interventions. Solid bars represent upper range of parameters; hashed bars represent lower range of parameters (e.g., risk difference in OD survival for fentanyl ranges from an upper limit of 0.164, corresponding to a mortality of 4.8%, to a lower limit of 0.041, corresponding to 3.5% mortality).

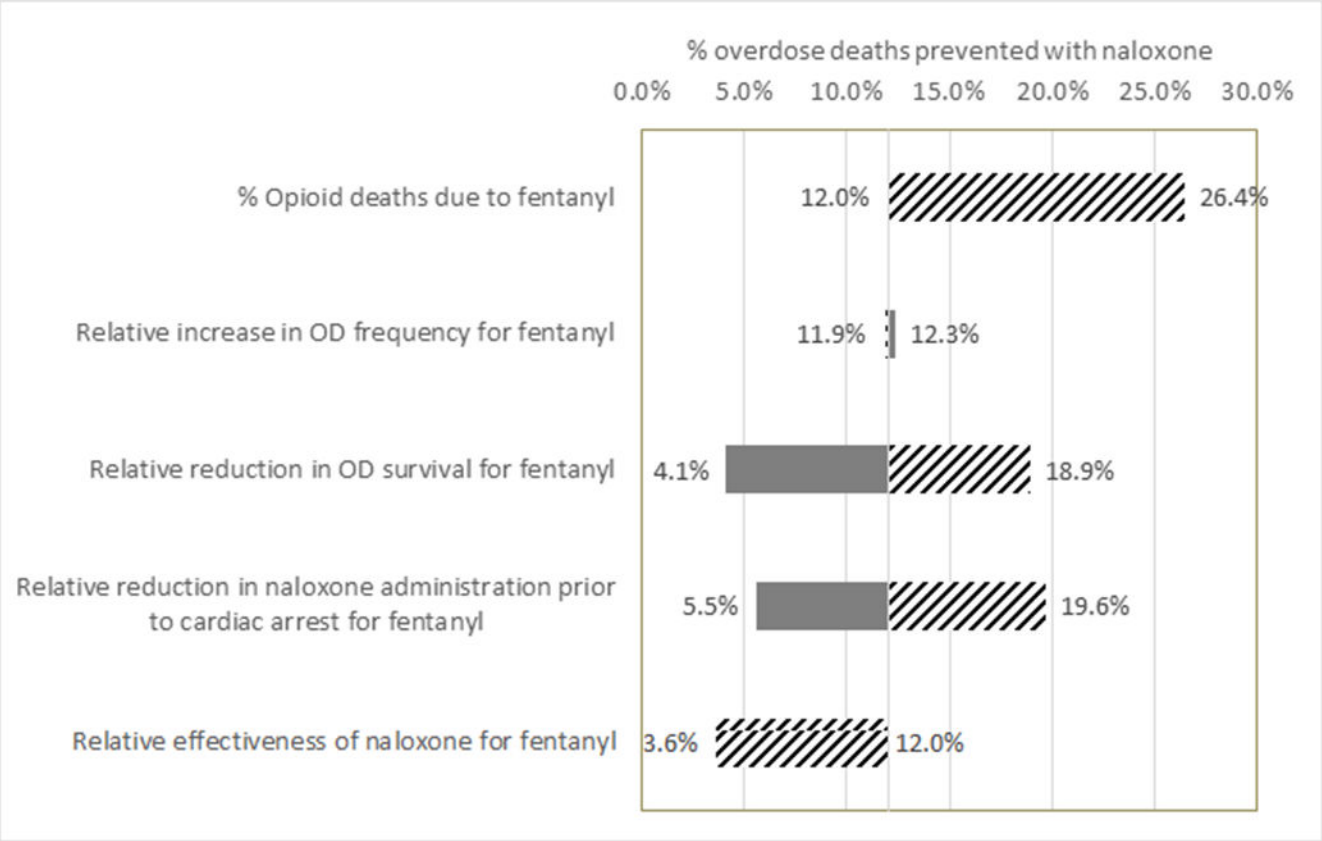

Figure 3: Impact of Fentanyl Parameter Adjustments on the Proportion of Opioid Overdose Deaths Prevented by Naloxone Distribution with 80% Coverage

Baseline estimate is for 100% of opioid deaths due to fentanyl, corresponding to 12.0% of deaths reduced by naloxone provision. Solid bars represent upper range of parameters; hashed bars represent lower range of parameters (e.g., relative reduction in naloxone administration prior to cardiac arrest for fentanyl ranges from an upper limit of 60%, corresponding to 5.5% of opioid overdose deaths prevented by naloxone, to a lower limit of 20%, corresponding to 19.6% of deaths prevented by naloxone).

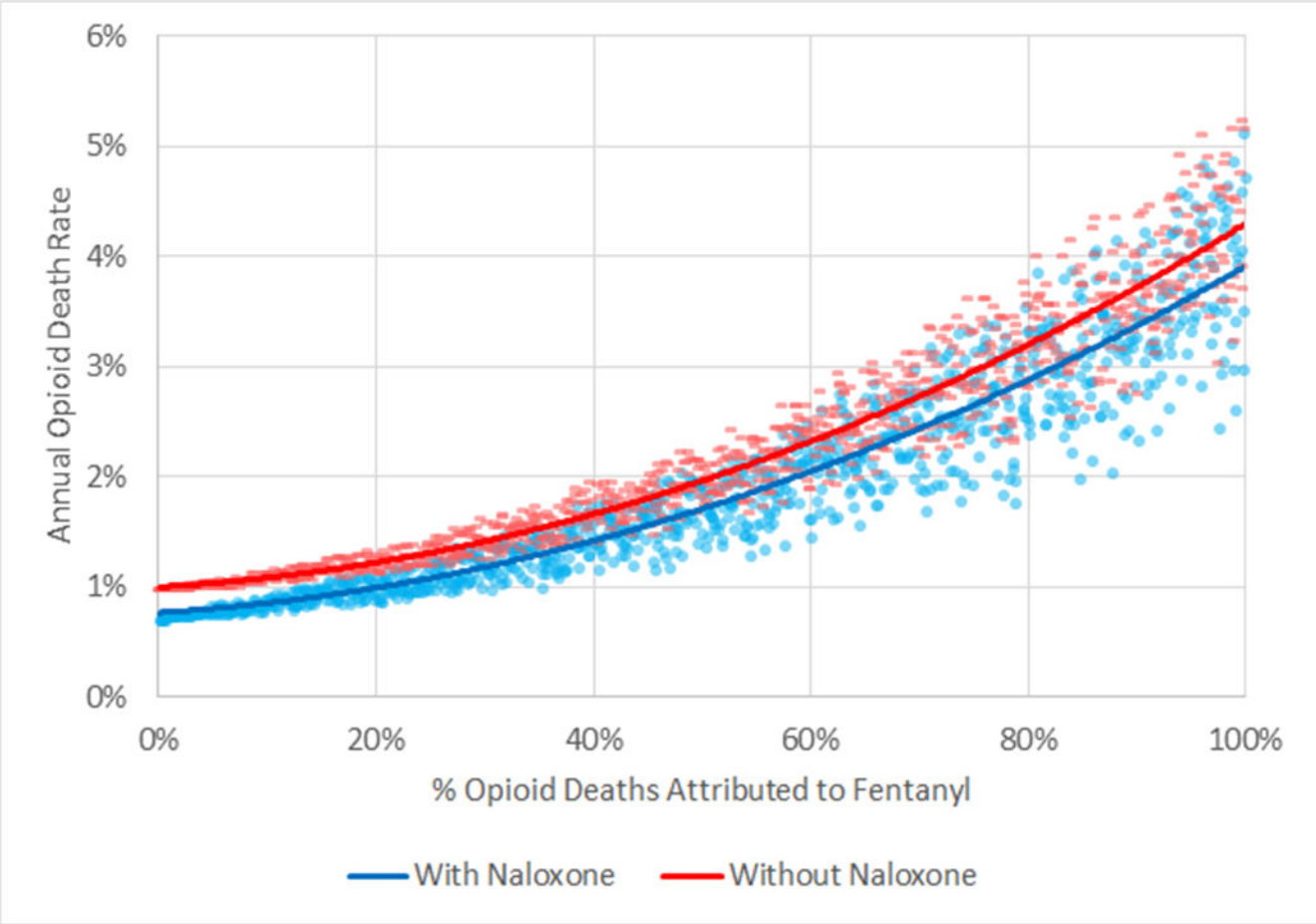

Figure 4: Predicted Opioid Overdose Death Rate Among Persons Actively Using, by Presence of Fentanyl and 80% Naloxone Coverage (probabilistic model)

Proportion of opioid deaths due to fentanyl, relative increase in overdose frequency with fentanyl, relative reduction in overdose survival without intervention for fentanyl, reduction in naloxone use prior to cardiac arrest for fentanyl, and relative increase in survival with naloxone were varied at once in a Monte Carlo simulation with 1,000 iterations.

Table 1:
Naloxone distribution model parameters

Parameters related to cost-effectiveness excluded and only base-case presented for the original model parameters

Parameter	Base-case (Range)	Sources
Proportions		
Proportion of heroin users prescribed naloxone	0.80	(Bassett and Walensky, 2010), **
Proportion of overdoses witnessed	0.85	(Darke et al., 1996a; Davidson et al., 2003; Davidson et al., 2002)
Proportion in possession of naloxone at an overdose who use it to attempt reversal prior to cardiac arrest	0.8	(Wagner et al., 2010)
Adjustment for fentanyl due to rapidity of overdose (subtracted)	**0.4 (0.2-0.6)**	(Somerville et al., 2017; Sporer et al., 1996)
Proportion call EMS		
First-time overdose	0.6	(Bohnert et al., 2012; Darke et al., 1996b; Tracy et al., 2005)
Subsequent overdoses	0.4	
Proportion survive overdose		
First overdose	0.918	
Adjustment for fentanyl (subtracted)	**0.082 (0.041-0.164)**	(Fox et al., 2018; Sporer, 1999; Sporer and Kral, 2007)
Absolute reduction for second overdose	0.015	
Additional reduction for subsequent overdoses	0.015	
Relative increase in survival with emergency medical services	1.089	(Wampler et al., 2011)
Relative increase in survival with naloxone (heroin)	1.089	(Doe-Simkins et al., 2009; Piper et al., 2008; Stoove et al., 2009; Strang et al., 2008; Tobin et al., 2009; Wagner et al., 2010)
Relative increase in survival with naloxone (fentanyl)	**1.196 (1.089-1.196)**	Assumption
Annual transition rates		
Heroin use to non-overdose death (in excess of background mortality)	0.0075	(Sporer and Kral, 2007)
Heroin use to overdose		
First overdose	0.09	(Coffin et al., 2007; Darke et al., 2011; Darke et al., 2007; Stoove et al., 2009)
Second overdose	0.22	
Subsequent overdoses	0.34	
Adjustment for fentanyl (multiplied)	**2.316 (1.987-2.645)**	(Darke et al., 2011; Latimer et al., 2016; Teesson et al., 2008)
Annual relative reduction in risk of first overdose *	0.933	
Heroin use to discontinuation of heroin use	0.05646	(Bruneau et al., 2004; Huo et al., 2006)
Discontinuation of heroin use to heroin use	0.070	(Hser, 2002)
Annual relative reduction in risk of relapse *	0.933	(Evans et al., 2009)
Overdose to discontinuation of heroin use	0.062	(Pollini et al., 2006)

* Parameter is exponentiated to the preceding number of model cycles and multiplied by its reference parameter to reduce likelihood of the event over time.