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Research Report

Enumerating contributions of fentanyls and other factors to the unprecedented 2020 rise in opioid overdose deaths: model-based analysis

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Abstract

In 2020, the ongoing US opioid overdose crisis collided with the emerging COVID-19 pandemic. Opioid overdose deaths (OODs) rose an unprecedented 38%, due to a combination of COVID-19 disrupting services essential to people who use drugs, continued increases in fentanyls in the illicit drug supply, and other factors. How much did these factors contribute to increased OODs? We used a validated simulation model of the opioid overdose crisis, SOURCE, to estimate excess OODs in 2020 and the distribution of that excess attributable to various factors. Factors affecting OODs that could have been disrupted by COVID-19, and for which data were available, included opioid prescribing, naloxone distribution, and receipt of medications for opioid use disorder. We also accounted for fentanyls' presence in the heroin supply. We estimated a total of 18,276 potential excess OODs, including 1,792 lives saved due to increases in buprenorphine receipt and naloxone distribution and decreases in opioid prescribing. Critically, growth in fentanyls drove 43% (7,879) of the excess OODs. A further 8% is attributable to first-ever declines in methadone maintenance treatment and extended-released injectable naltrexone treatment, most likely due to COVID-19-related disruptions. In all, 49% of potential excess OODs remain unexplained, at least some of which are likely due to additional COVID-19-related disruptions. While the confluence of various COVID-19-related factors could have been responsible for more than half of excess OODs, fentanyls continued to play a singular role in excess OODs, highlighting the urgency of mitigating their effects on overdoses.

Keywords: opioid overdose, fentanyl, COVID-19

Significance Statement

The continued rise of illicit fentanyls in the heroin supply and COVID-19-related disruptions both contributed to the unprecedented 38% rise in opioid overdose deaths (OODs) in 2020. We used a validated simulation model, SOURCE, to enumerate their relative contributions. We estimate that there were 18,276 potential excess OODs in 2020, after accounting for increases in buprenorphine prescribing and naloxone distribution and decreases in opioid prescribing that saved lives. Forty-three percent of the excess OODs were due to a continued increase in fentanyls; 8% were attributable to declines in methadone and extended-release injectable naltrexone treatment, likely due to COVID-19-related disruptions. The remainder (49%) of the excess OODs are unexplained, at least some of which could also be attributed to such disruptions.

Introduction

In 2020, the United States witnessed an unprecedented 38% increase in opioid overdose deaths (OODs), from 50,000 in 2019 to nearly 70,000 (1). The most rapid increase started during the first wave of the COVID-19 pandemic (2), implicating COVID-19-related disruptions. Before the rapid rise in OODs was apparent, researchers hypothesized that they would increase due to the unique circumstances of the pandemic (3). However, since 2016, the increasing presence of illicitly manufactured fentanyls (fentanyl and its analogs) in the unregulated drug supply, particularly the heroin supply (3), has been the dominant factor driving increased OODs (4), suggesting a likely important role for them as well.

One recent analysis reported larger quarterly increases in all overdose deaths across many states relative to the same quarters in 2019, but did not examine the potential role of fentanyls (5). Intriguingly, a separate analysis of 11 states found that 2020 OOD increases in several of them were consistent with trends from 2018 to 2019, and only some states were experiencing new

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increases—notably, in OODs involving synthetic opioids (i.e. fentanyls) (6). These papers suggest that the 2020 rise in OODs must be understood in the context of ongoing trends, in particular the westward spread of illicit fentanyls (7, 8).

On the other hand, recent qualitative research has identified several potential factors associated with increased OODs during the pandemic, including (i) disruption in harm reduction services via capacity restrictions (9, 10), changes in operations (10, 11), and resource shortages (9, 12); (ii) disruption in treatment and recovery services due to reduced access (9, 12–15), reduced service capacity (10, 11), loss of social support (10, 13, 14), and decreased interest in treatment (16, 17); (iii) increased risk-taking behaviors such as increased substance use (9, 10, 14, 16, 18), polysubstance use (11, 14), sharing among users (11, 12), using alone (9, 12, 13), changing drugs (12, 19), and stocking drugs (16); (iv) changes in the drug market such as reduced supply (9, 12, 13, 19, 20), increased prices (9, 12, 19, 20), stronger drugs (12, 19), and decreased quality (10, 19); and (v) increased stressors such as financial stress (9, 12, 19), social isolation and loneliness (10, 14, 16, 18), mental health disorders (10–12, 16, 18, 19), and homelessness (10, 12).

If some combination of these pandemic effects were indeed largely responsible for the OOD rise—which continued into 2021 (1)—then interventions that target COVID-19's lingering disruptive impacts are key to curtailing OODs. Moreover, to the extent excess OODs in 2020 were due to pandemic effects, there are implications for public health planning for any future similar shocks to the system. Conversely, if fentanyls played a significant role in 2020, then knowing the magnitude of that role is important for understanding 2020 in the context of ongoing trends and necessary responses. There is no doubt that public health officials recognize the dangers of fentanyls continuing to spread across the country, but it is critical for them to understand to what extent the 2020 increase was consistent with prior trends and to what extent it was an aberration.

An enumeration of distinct contributors to the unprecedented rise in OODs in 2020 can inform the public health response to the overdose crisis, even as COVID-19's effects on overdoses wane. To quantify the effects of different factors, we used SOURCE (Simulation of Opioid Use, Response, Consequences, and Effects), a validated and calibrated national-level simulation model originally built to examine the effects of policy strategies on OODs and opioid use disorder (OUD) (21, 22). SOURCE uses data from as early as 1999 to incorporate the effects of secular trends on OODs and OUD, thus making it ideal for examining the extent to which the OOD rise in 2020 was consistent with prior trends. Specifically, in this study, we used SOURCE to estimate potential excess OODs—those that occurred beyond what would have been expected had driving factors in OODs remained at 2019 levels. Using 2020 data, we estimated the fraction of those OODs attributable to the rise in fentanyls in the heroin supply, as well as various other factors that both affect OODs and were likely affected by COVID-19, including changes in opioid prescribing (23), receipt of medications for OUD (MOUD) (24), and naloxone distribution (25). For this analysis, we included factors for which national-level data were available and that were already part of SOURCE's validated structure.

Results

Our estimate of potential excess OODs in 2020 consisted of two parts: first, the difference between the number of 2020 OODs reported by the Centers for Disease Control and Prevention (CDC) and SOURCE's baseline projection for 2020, and second, the estimated number of lives saved due to changes observed in 2020 data that would be expected to reduce OODs.

SOURCE's baseline projection estimates a median of 52,577 OODs (95% credible interval: 51,577–53,592) in 2020. This is 16,484 (15,469–17,484) fewer deaths, or 24% less (22–25%), than the CDC's report of 69,061 deaths (26); (16,484 = 69,061 reported − 52,577 estimated) (Fig. 1A).

There were several changes observed in the 2020 data that SOURCE estimates saved lives (i.e. reduced OODs) relative to our baseline projection: continued increases in buprenorphine receipt (6%) and buprenorphine providers (14%); a continued increase in

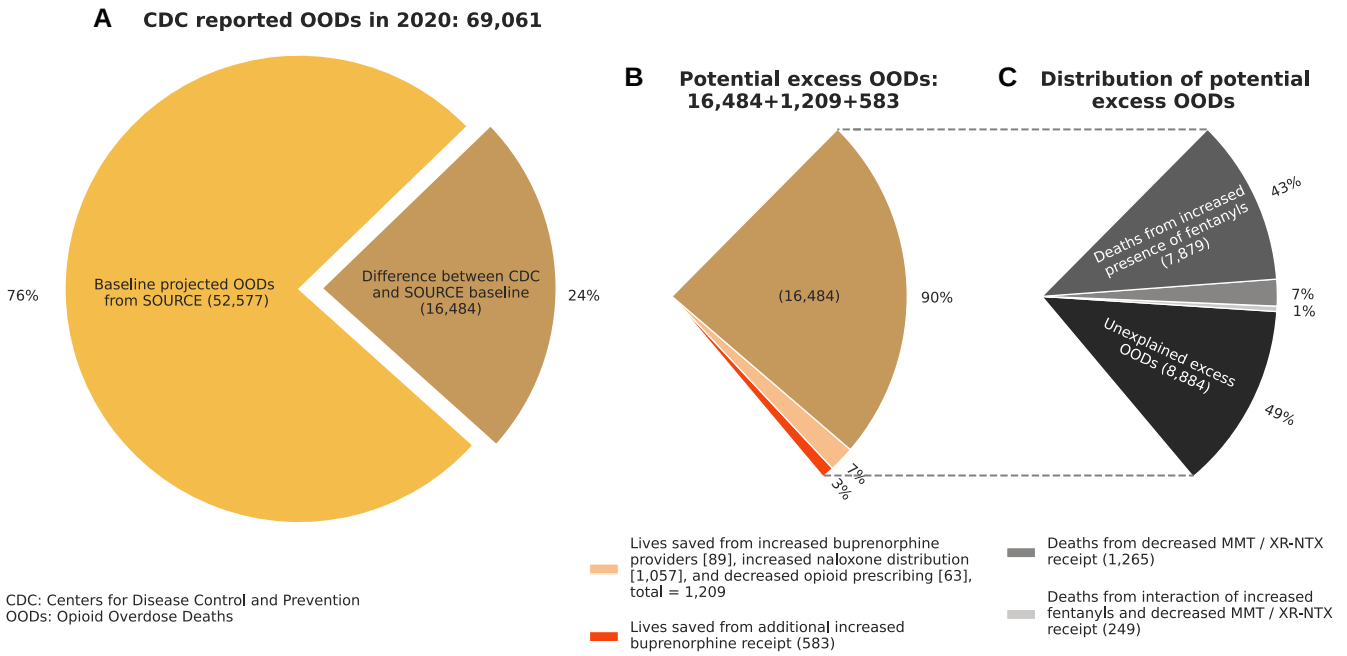

Fig. 1. A) SOURCE's baseline projection compared to CDC's reported opioid overdose deaths; B) Potential excess opioid overdose deaths after accounting for lives saved; C) Distribution of potential excess opioid overdose deaths.

naloxone distribution (19%), and a continued drop in opioid prescribing (−7% in opioid prescriptions, −8% in morphine milligram equivalents [MMEs] prescribed, and −10% in patients with prescription opioids). SOURCE estimates that, in total, the increases in buprenorphine providers and naloxone distribution, combined with the decreases in opioid prescribing, saved 1,209 (1,150–1,266) lives. The rise in buprenorphine providers accounted for only part of the rise in buprenorphine receipt. Accounting for the remainder of the rise in buprenorphine receipt saved an additional 583 (548–610) lives, for a total of 1,792 saved lives. (The breakdown for each contributing factor is shown in the legend of Fig. 1B).

Because these saved lives reduce OODs relative to our projection for 2020, the effect is to *increase* potential excess OODs to 18,276 (17,345–19,183) in 2020 (18,276 = 16,484 + 1,209 + 583; 16,484 excess OODs due to the difference between our baseline projection and CDC's report, plus the 1,792 lives saved, as shown in Fig. 1B).

To attribute the potential excess OODs to changes reflected in 2020 data, we first accounted for factors likely due to COVID-19-related disruptions. These included the first-ever declines in methadone maintenance treatment (MMT) (−24%) and extended-release injectable naltrexone (XR-NTX) receipt (−10%). These changes account for 1,264 deaths (1,188–1,229), or 6.9% (6.4–7.5%) of all potential excess deaths; 98% of these were due to the decrease in MMT. Separately, the continued rise (19%) in fentanyls' presence in the heroin supply contributed 7,879 deaths (7,609–8,167), or 42.6% (39.7–47.1%) of the potential excess OODs. Finally, combining the observed decreases in MMT and XR-NTX with the increase in fentanyls accounted for an additional 249 deaths (230–264), or 1.4% (1.2–1.5%) of potential excess OODs; we consider these due to COVID-19-related disruptions as well. (Figure 1 shows these numbers rounded.)

In all, these observed changes from 2019 to 2020 account for 9,392 (9,090–9,708) excess OODs, or 50.9% (47.4–55.9%) of the estimated 18,276 potential excess OODs (Fig. 1C). This leaves 8,884 (7,627–10,104) OODs unexplained, or 49.1% (44.1–52.6%) of all excess OODs. Thus, after accounting for 2020 data, SOURCE's projected OODs (60,180: 58,957–61,434) are still 13.1% under (11–14.6%) the CDC's reported figure (69,061).

Sensitivity analysis

To account for the potential impact of under-reporting or mischaracterization of overdose deaths (27), we repeated the entire analysis using corrected mortality data (for 1999–2020). Specifically, for overdoses recorded with no specific substance involved (ICD code T50.9), we imputed opioid involvement each year based on the proportion of overdoses with known substance involvement that involve opioids. When including all likely opioid overdose deaths, including those not officially counted as such, the growth in fentanyls explains even more of the OOD rise in 2020. There were fewer excess OODs (17,113), which included 1,937 lives saved due to increases in buprenorphine and naloxone receipt and decreases in opioid prescribing. Of the excess OODs, 55% were accounted for by fentanyls' continued increase in the heroin supply (45.8%), the declines in MMT (7.7%), and XR-NTX treatment (0.2%), and the interaction among them (1.4%), leaving 45% unexplained.

Discussion

Our analysis suggests that the rise in OODs in 2020 was not only unprecedented, but an aberration within ongoing trends; the full rise cannot be explained even after accounting for increasing fentanyls in the heroin supply, which alone accounted for 43% of the estimated 18,276 potential excess OODs that year. Though we were able to attribute 8% of the excess OODs to likely COVID-19-related disruptions (the decline in methadone and XR-NTX treatment), there were many other disruptions we were unable to directly account for due to lack of precise estimates of their prevalence in the OUD population and their lack of explicit inclusion in SOURCE. These include social isolation and distancing (12), economic distress (12), and reduced access to harm reduction (28) and recovery groups (29), among others. Together, these changes could account for at least some of the 49% of excess OODs that remain unexplained. However, it is unlikely that any *one* of these COVID-19-related factors was responsible for as many excess OODs as fentanyls alone were (43%). Thus, we conclude that fentanyls were the *single* largest factor driving the rise in OODs in 2020, while the COVID-19 pandemic, as a collection of multiple factors, could have been responsible for the majority of the rise (up to 57%)—notwithstanding model error, which we discuss more below.

Fentanyls' singular role in excess OODs in 2020 represents a systemic failure to address the ongoing poisoning of an unregulated drug supply. However, our analysis also points to systemic successes, in particular the lives saved due to continued increases in buprenorphine receipt, at least partially due to exemplary efforts early in the pandemic to expand telehealth services (30), which might have helped sustain buprenorphine access (31, 32). Nonetheless, we estimate these improvements did not save nearly as many lives as fentanyls took. Moreover, while buprenorphine receipt and naloxone distribution increased, we cannot know how much more they might have increased had the pandemic not occurred.

Our findings may induce a feeling of futility. A shock as disruptive as COVID-19 did little to slow the flood of fentanyls into the nation's heroin supply (and, increasingly, other drugs as well) (33). It is time to consider bold approaches beyond what is already being done (34), including safe supply initiatives that directly address the toxicity of the drug supply (35). Vancouver (in British Columbia, Canada) is supplying fentanyl directly to people who use it, providing a reliable supply of consistent potency, thereby hopefully reducing overdose risk (36). We anxiously await the results of this experiment. Prescribed heroin treatment for OUD, used in other countries (37), is currently illegal in the United States, but could be a more effective treatment for fentanyl-tolerant patients who have not done well on buprenorphine or methadone (38). Drug checking, such as the use of fentanyl test strips (FTS), is another approach. Results of these tests can help people who use drugs determine whether and how much, or how quickly, to use their drugs. While more states are decriminalizing FTS (39), they are still considered illegal paraphernalia in other states, forcing public health workers to create workarounds to speed their adoption (40). Moreover, high-tech, expensive spectrometry will increasingly be needed to go beyond dichotomous results to discern what types of fentanyls, and how much, are present (41). Programs that could make use of these will need significant financial support to ensure widespread accessibility. Other harm reduction approaches, such as supervised consumption sites, could also prevent more OODs, though they, too, are often disallowed in the United States. (42).

Expanding these strategies in the United States would contrast with the current criminalization-heavy approach, with significant criminal penalties for fentanyls trafficking (37). There are mandatory minimum sentences of 20 years if death or seriously bodily injury results, even if the seller did not know fentanyls were present, and regardless of the quantity; analogues are subject to higher penalties than fentanyl despite many of them being less potent

than fentanyl (37). There is no evidence yet that these policies have any positive benefits. These challenges around fentanyl will only grow more severe if contamination of unregulated drugs besides heroin, such as cocaine or methamphetamine, increases.

In our analysis, there are still over 8,800 additional excess OODs beyond what SOURCE projected after accounting for available 2020 data, representing nearly one-half of all potential excess OODs. This is a 13% underestimation, exceeding SOURCE's absolute average of 8.3% for all other years (see Materials and methods). COVID-19-related disruptions almost certainly played a significant role in these OODs, in addition to those we estimated from reductions in MMT and XR-NTX treatment.

The current understanding of specific COVID-19 contributors to increased OOD risk is limited. We attempted to find research that could support further enumeration of distinct pandemic contributors. For instance, social distancing led to an increased frequency of alcohol and cigarette use (43), but thus far, findings regarding its effects on opioid use are mixed. Among people who use opioids in the United States, one study found a greater fraction decreased their use than increased it (44), while a study of people with OUD in Canada found 47% were using more drugs than usual, 44% were using a wider variety of drugs (a finding echoed in another Canadian study showing destabilization in the local drug market (45)), and 39% were more often using alone (46). A small US study also found increases in use while alone (12), and a recent analysis of Reddit users found disruptions to supply, especially among pill users (47).

The findings regarding the increased frequency of use among Canadians with OUD present difficulties for translation into SOURCE, which does not track the frequency of use explicitly. Moreover, analyses of overdose deaths in the United States cast doubt on the import of increased use while alone. Fatal illicit fentanyl use was just as likely to be witnessed in 2020 (48) as all fatal opioid use was in 2019 (49), and the presence of a potential bystander was even more likely (48, 49).

Nonetheless, we suspect there was significant convergence of COVID-19-related disruptions and changes in drug use behavior that could account for additional deaths. This is in addition to all other potential COVID-19 effects that we could not account for (e.g. reduced access to harm reduction and recovery services). All of this suggests that the systemic improvements achieved via telehealth access are the minimum needed when the next inevitable shock occurs in these increasingly unstable times (50).

Limitations

Our analysis has several limitations. First, in 2018 and 2019, our model overestimated OODs by 7 and 8%, respectively, so our baseline projection in 2020 is more likely underestimating, rather than overestimating, excess deaths.

Second, we used data from the National Forensic Laboratory of Information Systems (NFLIS) to estimate the penetration of fentanyls into the heroin supply. However, NFLIS is not a random sample of the drug supply, and changing levels of detection of fentanyls could be due to changes in enforcement, which would affect our estimate of fentanyls' role in OODs in 2020 (e.g. while enforcement overall might have increased in recent years, it might have decreased in 2020 due to COVID-19 disruptions).

Third, many people who use fentanyls also use methamphetamine or cocaine, and deaths involving the combinations of these substances have been rising (48, 49). To the extent that polysubstance deaths rose in 2020 due to, e.g. riskier injection practices independent of pandemic-driven changes, SOURCE does not account for them.

Fourth, we did not attempt to account for the 25% of overdose deaths that occur without opioid involvement (51). These deaths would have been affected by COVID-19, but not by fentanyls' penetration of the heroin supply.

Fifth, fentanyls' presence in the unregulated drug supply extends beyond heroin; there are increasing anecdotal reports of fentanyls contaminating stimulants, such as cocaine and methamphetamine. SOURCE accounts for all OODs involving fentanyls, but assumes they occur among intentional "heroin" users (recognizing that in some areas of the country, heroin has been almost entirely displaced by fentanyls). To the extent OODs involving fentanyls occur among other users, these deaths are misattributed to intentional "heroin" users, which could affect SOURCE's OOD projections because of different baseline levels of risk between intentional heroin users versus others. While evidence shows limited presence of fentanyls in unregulated drugs besides heroin from 2014 to 2019 (52), if such fentanyl contamination in other drugs increased substantially in 2020 (the DEA did not release a report covering 2020), this could account for some of the unexplained increase in OODs.

Sixth, counterfeit pills are increasingly being made with illicit fentanyls (48), and there is some suggestion the pandemic accelerated this trend (47). However, we know of no national-level data that would allow us to estimate who the primary users of counterfeit pills are (i.e. people who would have previously used heroin, versus prescription opioids) and how that has changed over time. If changes in who uses these pills occurred between 2019 and 2020, then SOURCE's projections could be under- or overestimated.

Seventh, while the CDC's Multiple Cause of Death data and SAMHSA's National Survey on Drug Use and Health (NSDUH) for 2021 have both been released, significant changes in NSDUH 2021 represent the second trend break in as many years. Thus, for the time being, we have decided against updating SOURCE to account for the 2021 trend break.

Finally, SOURCE is calibrated to national-level data, and has not been calibrated to the state level as many of the necessary data streams (particularly around opioid use) are not available at the necessary resolution; this precludes any state-level analysis at present.

Despite these limitations, this analysis is the first known attempt to enumerate distinct contributors to the unprecedented rise in OODs in 2020. This is a critical contribution because fentanyls' role in 2020, independent of COVID-19's disruptions, represents part of a larger, ongoing trend that has not yet been adequately addressed. Before, during, and after 2020 (26), illicitly manufactured fentanyls have played a large, if not the largest, role in OODs. To reduce deaths in 2023 and beyond, fentanyls' poisoning of the unregulated drug supply must be curtailed, regardless of any future shocks like COVID-19. However, COVID-19-related disruptions could be responsible for more than half of all excess OODs, pointing just as urgently to the need to better prepare for future similar shocks. Part of this preparation should include a more robust measurement of disruptions to services and changes to drug use behavior, which would not only allow for more timely adjustments to services but also for a more precise enumeration of distinct contributors in the future.

Materials and methods

SOURCE model

SOURCE (21, 22) is a mechanistic compartmental model that tracks opioid-using populations through the following states: initiation and misuse of prescription opioids and heroin, OUD, and remission; treatment with medications for OUD (MOUD), which

includes buprenorphine, MMT, or XR-NTX; and fatal and nonfatal opioid overdose. Each of the misuse, OUD, treatment, and remission states has different overdose death hazards. SOURCE is parameterized using a combination of literature and data sources, expert input, and formal estimation. Most parameters (53/95) are formally estimated (i.e. calibrated) using 21 years (1999–2019) of data across 15 time series (Table 1); an additional 10 time series are used as historical inputs (Table 2). (The originally published version of SOURCE uses data from 1999 to 2020; for this analysis, we re-estimated the model using data only up to 2019.)

Data from NSDUH (53) represent 10 of the 15 time series to which SOURCE is calibrated (Table 1). We assume the absolute numbers of heroin users in NSDUH are inaccurate, but that the trends are relatively accurate. Thus, we adjust the initiation and use of heroin and OUD involving heroin by a multiplier of 3.11, which was calculated by comparing the prevalence estimates from NSDUH with the estimate of heroin users from 2006 to 2016 in the 2019 RAND report (54). Remission is estimated using priors from published studies of Wave 1 of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC-I) (55–57) and our primary data analysis of NESARC-III (representing a different cohort) (58).

SOURCE is calibrated to buprenorphine receipt (Table 1), while MMT and XR-NTX are used as inputs (Table 2). Calibration of receipt is impossible in SOURCE without capacity numbers, and there are no national capacity estimates for MMT and XR-NTX. Buprenorphine-waivered providers are estimated using a combination of peer-reviewed literature, governmental reports, and the Substance Abuse and Mental Health Services Administration's (SAMHSA) year-end website statistics (Table 2). See Stringfellow et al. (59) for buprenorphine treatment analysis in SOURCE.

The model is calibrated to four time series on OODs estimated from the CDC's National Vital Statistics System (NVSS) (26) (Table 1). Other non-opioid drugs could have been involved in these OODs, but those are not tracked in SOURCE. Naloxone distribution is estimated from a variety of sources (Table 2) and is used in the model to reduce the probability of death given an opioid overdose. In contrast, the probability of opioid overdoses and associated deaths is increased by our estimates of fentanyls' penetration into the heroin supply, based on data from NFLIS (60) (Table 2). Currently, this increased hazard only affects those using heroin.

Finally, five separate time series data from IQVIA are used to estimate prescription opioid availability, while the price of heroin is used as a proxy for its availability, estimated using data from UNODC (61–64). Prescription opioids and heroin prices are inputs to SOURCE (Table 2).

Table 1. Calibration targets for the SOURCE model.

Calibration targets (15 time series)	Sources
Annual initiation and prevalence of prescription (Rx) opioid misuse and nondisordered heroin use (NDHU), and prevalence of opioid use disorder (OUD) involving Rx opioids and/or heroin (10 time series)	NSDUH (53)
Initiation (2 series) and prevalence (1 series) of Rx opioid misuse	
Initiation (3 series) and prevalence of NDHU (1 series)	
OUD involving Rx opioids, with (1 series) and without NDHU (1 series)	
OUD involving heroin (with or without Rx misuse or OUD) (1 series)	
Annual opioid overdose fatalities (4 time series)	CDC NVSS (26)
Rx opioids without heroin or synthetic opioids	
Heroin without synthetic opioids; could also include Rx opioids	
Heroin and synthetic opioids; could also include Rx opioids	
Synthetic opioids without heroin or Rx opioids	
Buprenorphine receipt (1 time series)	IQVIA Total Patient Tracker (TPT) (21)

Table 2. Historical input data used in the SOURCE model.

Historical input data (10 time series)	Sources
Opioid prescription-related data	
Annual opioid prescriptions	IQVIA NPA
Patients with prescription opioids	IQVIA TPT
Annual morphine milligram equivalents (MMEs) prescribed	IQVIA NPA and (65–68)
Fraction of MMEs that are of an abuse-deterrent formulation (ADF)[a]	IQVIA NPA
Annual buprenorphine-waivered providers	SAMHSA (69)
Point-in-time methadone maintenance (MMT) utilization	N-SSATS (70)
Estimated monthly extended-release injectable naltrexone (XR-NTX) receipt	IQVIA NSP
Annual naloxone kit distribution	Naloxone buyer's club (71, 72), IQVIA NPA
Penetration of fentanyls into heroin market	NFLIS (60)
Average annual retail/street-level price of heroin[b]	UNODC (61, 62) and (63, 64)

[a]This time series is calibrated to have no effect in SOURCE on opioid overdoses (21), nor does it have an effect in this analysis.
[b]No 2020 data available, though some reports (33) indicate prices might have increased. 2019 data from UNODC include only two data points, showing a large decline in price; hence, we used 2018 data.
NPA, National Prescription Audit; TPT, Total Patient Tracker; NSP, National Sales Perspective; UNODC, United Nations Office on Drugs and Crime; NSSATS, National Survey on Substance Abuse Treatment Services.

Feedback loops

Transition rates in SOURCE are dynamic and feedback-driven (21). Specifically, as users of opioids increase, initiation of opioids increases, in a reinforcing loop. As opioid overdoses (fatal and nonfatal) increase, initiation of opioids decreases—a balancing loop necessary to reproduce the decline in heroin initiation since 2014 observed in NSDUH (53). Finally, as prescription opioids become less available, initiation and OUD involving them decline (a balancing loop), but this is offset by reduced availability relative to heroin, which then leads to an increase in heroin initiation and OUD involving heroin. See Lim et al. (21) for more details.

Model estimation

SOURCE's estimation is by maximum likelihood using a Gaussian likelihood function, with Markov chain Monte Carlo analysis to quantify uncertainties in parameter estimates. SOURCE's simulated OODs track well with historical data (26), with an R^2 of 0.97 and mean absolute error normalized by mean of 8.3%. To build confidence in SOURCE, we conducted a sensitivity analysis by varying each input parameter by 10% and recalibrating the model; this showed a median absolute percentage change in estimated parameters of 0.2–0.7% (21). SOURCE has also been validated with an out-of-sample prediction test, estimating the model using

data up to 2012 and comparing projections to holdout data from 2012 to 2020—see Section S4.f of the supplement in (21) for details. Lim et al. (21) and its supplement contain greater technical detail on the model's development, estimation, and validation.

2019–2020 analysis

Our analysis proceeded stepwise. We first used SOURCE to establish a baseline for 2020 OODs. For this baseline, we re-estimated the model using data from 1999 to 2019 (excluding 2020 data, which the published model utilizes), and assumed the following driving factors remained at 2019 levels: opioid prescribing, treatment receipt, buprenorphine providers, naloxone distribution, and fentanyls' penetration of the heroin supply. We excluded 2020 data from baseline model estimation, as we were using the estimated model to project 2020 OODs. Similarly, if we had extrapolated prior trends into 2020, it would be impossible to discern what excess deaths, or saved lives, were attributable to those extrapolations versus actual observed changes.

We then sought to quantify the impact of several empirically observed changes from 2019 to 2020, to account for the difference between our projected estimate and CDC's report, i.e. potential excess OODs. Next, we estimated the contribution of several observed changes whose direct impacts should increase OODs and thus account for at least some of the 18.276 potential excess deaths.

Underlying assumptions in SOURCE are critical to understanding our results. First, SOURCE assumes that receipt of buprenorphine, methadone maintenance (MMT), and extended-release injectable naltrexone (XR-NTX) all reduce OODs among patients receiving these medications. Moreover, it assumes buprenorphine receipt increases with more buprenorphine providers, thereby decreasing OODs. Second, in SOURCE, opioid prescribing contributes a small number of OODs among patients, as well as a greater number of OODs due to diversion (22). Thus, reductions in opioid prescribing translate into fewer OODs. Finally, in SOURCE, OODs are reduced with an increasing likelihood that naloxone is used, while increased penetration of fentanyls into the heroin market translates into more OODs. These assumptions do not change with exogenous shocks such as COVID-19.

To quantify uncertainty in our estimates, we used a subsample of 5,000 draws from the joint posterior distribution of estimated parameters to generate our projections of OODs for 2020, both baseline projections and the effects of data-driven changes. We report the median value and 95% credible intervals across these 5,000 runs. Our repository includes the full subsample of 5,000 parameter draws used. In addition, interested readers can find instructions to reproduce point estimates that reflect the posterior parameter distribution without using the full calibration process.

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Author contributions

E.J.S., T.Y.L., and M.S.J. designed the research. E.J.S., C.D., and Z.H. performed investigations. E.J.S. wrote the original draft of the article, while all authors reviewed and edited.

Data availability

All code needed to replicate SOURCE is at https://github.com/FDA/SOURCE, while files pertaining to the present analysis are at https://github.com/tseyanglim/overdoses2020.

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