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Reducing Opioid use Disorder and Overdose Deaths in the United States: A Dynamic Modeling Analysis

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HEALTH AND MEDICINE

Reducing opioid use disorder and overdose deaths in the United States: A dynamic modeling analysis

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Opioid overdose deaths remain a major public health crisis. We used a system dynamics simulation model of the U.S. opioid-using population age 12 and older to explore the impacts of 11 strategies on the prevalence of opioid use disorder (OUD) and fatal opioid overdoses from 2022 to 2032. These strategies spanned opioid misuse and OUD prevention, buprenorphine capacity, recovery support, and overdose harm reduction. By 2032, three strategies saved the most lives: (i) reducing the risk of opioid overdose involving fentanyl use, which may be achieved through fentanyl-focused harm reduction services; (ii) increasing naloxone distribution to people who use opioids; and (iii) recovery support for people in remission, which reduced deaths by reducing OUD. Increasing buprenorphine providers' capacity to treat more people decreased fatal overdose, but only in the short term. Our analysis provides insight into the kinds of multifaceted approaches needed to save lives.

INTRODUCTION

Since 1999, nearly 650,000 Americans have died of an opioid overdose. More than half of these deaths have occurred since 2016 (*1*, *2*), reflecting a series of sequential and overlapping waves, each deadlier than the last. These waves have been driven by increasing misuse of prescription opioids, followed by heroin, and now synthetic opioids such as illicitly manufactured fentanyl, which dominates illicit opioid markets in many eastern parts of the United States and is quickly spreading west (*3*).

Billions of federal dollars have been spent to increase access to lifesaving naloxone and medications for opioid use disorder (OUD) (*4*), and opioid prescribing has dropped considerably (*5*). Yet, nationally, fatal opioid overdoses reached an all-time high in 2021 (*6*). At the same time, national household surveys indicate that initiation of both prescription opioids and heroin has steadily fallen over the last several years, and OUD has declined from its peak in 2015 (*7*). From a complex adaptive systems perspective, these ostensibly divergent population-level trends result from an interacting web of feedback loops. People who use drugs (PWUD) and national policies that target PWUD change the nature of the overdose crisis and thus the behavioral and policy responses that follow. Hence, many aspects of the crisis are endogenous, meaning they arise as a function of the current and historical state of the system rather than independently of it. Often, policies do not explicitly account for these endogenous responses, which can be difficult to anticipate and take years to manifest. Policies that worked in the past or that work now could become less effective in the future. Policies that until now have been less effective or infeasible could become more impactful as trends shift. Consequently, policies can lead to unintended consequences, including worse-before-better (i.e., worsening effects in the short term with net beneficial effects in the longer term) or better-before-worse dynamics. When these endogenous responses are identified and accounted for, there is greater potential to develop strategies that will likely lead to qualitative, meaningful shifts in outcomes and avoid strategies that yield little benefit.

Models that simulate future scenarios under different conditions are helpful because they account for population health and policy temporal dynamics and thus can identify potential consequences of policy interventions. Simulation models provide policymakers with an interactive approach to testing the effects of different strategies before implementation, including synergistic outcomes and unintended consequences (*8*). Feedback-based simulations use endogenous dynamics to replicate and explain historical trends and carry these dynamics forward in model projections (*9*, *10*), thus supporting the analysis of how policy interventions might interact with these dynamics (*11*).

Here, we present a model-based analysis of 11 strategies related to opioid misuse and OUD prevention, buprenorphine capacity, recovery support, and overdose harm reduction and their impacts on OUD prevalence and fatal opioid overdoses. We use a national-level simulation model of the opioid crisis, SOURCE (Simulation of Opioid Use, Response, Consequences, and Effects), developed in collaboration with the U.S. Food and Drug Administration (FDA) (*12*). SOURCE is a compartmental feedback model that simulates the movement of the U.S. opioid-using population through opioid misuse, OUD, and remission; treatment with medications for OUD (MOUD); and nonfatal and fatal opioid overdose. SOURCE builds on other opioid-focused models (*13*–*17*). It endogenously reproduces historical trends from 1999 to 2020 and, where the data support it, includes the operational detail necessary to compare specific mechanisms.

SOURCE was developed to guide strategic direction by identifying the approaches most likely to lead to qualitative, positive shifts in trends, and those most likely to yield little return. Thus, SOURCE is most useful for testing high-level targets for national policies rather than specific interventions. The most impactful strategies revealed by model testing do not always correspond to any existing evidence-based interventions. Thus, SOURCE is well suited for testing hypothetical "what if" questions that encourage thinking beyond the existing intervention toolset, ideally providing the impetus needed

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to develop such interventions. Model-based findings regarding high-impact strategies, even if they do not correspond to existing interventions, provide valuable insight when there are limited resources and it is not feasible to direct energies equally toward all strategies. We report the impacts of the 11 strategies analyzed and combinations thereof on the projected annual and cumulative prevalence of OUD and fatal opioid overdose from 2022 to 2032.

RESULTS

Strategy selection and testing

The "Glossary" section in the Supplementary Materials provides definitions for terms used throughout this paper. We assessed the effects of 11 high-level strategies on annual fatal opioid overdoses and OUD prevalence, cumulative fatal opioid overdoses, and cumulative person-years of OUD from 2022 to 2032. These strategies fall into four categories: (i) opioid misuse and OUD prevention, (ii) buprenorphine treatment capacity, (iii) recovery support, and (iv) overdose harm reduction. Table 1 presents the 11 strategies, their operationalization in the model (indicated in the numbered rows), and corresponding intervention or policy examples to guide interpretation. More detail on each of the strategies tested is available in the "Rationale for and implementation of strategy testing" section in Materials and Methods.

We chose strategies to compare the relative impacts across a breadth of potential intervention points; the assessment of specific policies and interventions is outside the scope of this paper. Thus,

Table 1. Strategies simulated in SOURCE (each changed by 20% in desired direction).

Category (#) Strategy defined in terms of operational implementation in SOURCE (↓↑ labels show the direction of change and are used in Fig. 1 as well)	Intervention or policy example
(A) Opioid misuse and OUD prevention	
(1) Reduce initiation of diverted prescription (Rx) opioids (↓Diverted Rx Init)	Programs that target children and adolescents at risk of substance use, including prescription opioids or heroin, with the most robust evidence for prescription opioids (*42*, *43*)
(2) Reduce heroin initiation with or without prior Rx use (↓Heroin Init)	
(3) Reduce misuse initiation of own Rx opioids (↓Own Rx Init)	Patient education on the risks of misuse (*68*); disposal programs for excess pills (*69*)
(4) Reduce the number of people who receive an opioid Rx (↓People with Rx)	Prescriber education and guidelines (*70*); policies to support non-opioid pain management therapies (*47*)
(5) Reduce OUD development rate (↓Developing OUD)	Effective treatment for mental health disorders that are associated with risk of OUD development (*49*, *71*); multifaceted support during economic crises (*51*)
(B) Buprenorphine treatment capacity*	
(6) Increase providers who can legally prescribe buprenorphine (↑Bup Providers)	Increased waiver training or modifying/removing DATA 2000 waiver requirements (*72*, *73*)
(7) Increase buprenorphine providers' capacity to treat more patients (↑Bup Prov Capacity)†	Remove barriers to and enhance facilitators of buprenorphine prescribing (*37*); policies that target clinicians directly or enact changes to health care structure, delivery, and payment (*40*)
(C) Recovery support	
(8) Reduce return to OUD rate from remission (↓Return to OUD)‡	Remove barriers to and enhance facilitators of improved functioning for people in remission (*74*, *75*)
(9) Add a reinforcing loop that reduces return to OUD rate as more people enter remission (↑Peer Recovery)	Peer recovery support services, mutual aid (*64*, *65*)
(D) Overdose harm reduction	
(10) Reduce excess overdose risk associated with fentanyl use (↓Fent OD Risk)§	Fentanyl test strips and other drug-checking services (*25*, *76*); harm reduction education on how to adjust drug use behavior, such as titrating or decreasing dose (*26*–*28*)
(11) Increase distribution of naloxone (Nx) kits to people who use opioids (↑Nx Kits)	Increased naloxone kit distribution (*77*, *78*)

*We increase buprenorphine capacity but not methadone or extended-release injectable naltrexone capacities because buprenorphine is the only MOUD with reliable national capacity estimates. †We modified a model-estimated parameter that abstractly accounts for provider and system constraints and, in SOURCE, affects how many people providers can treat, on average (see section S6A). We assume that these capacity constraints are a primary cause of accessibility barriers faced by patients. ‡"Return to OUD" occurs after remission, where "remission" reflects the DSM-5 definition of not meeting OUD criteria for at least 1 year. Return to OUD is sometimes referred to as relapse, but we prefer a less pejorative term. §This excess overdose risk was estimated during model calibration. It does not represent a change in the drug supply or a reduction in the lethality of a fentanyl overdose. We also refer to this in the text as "fentanyl harm reduction." Harm reduction strategies such as not using alone, which works by reducing the likelihood of fatality once an overdose has occurred, are not examples of this strategy.

while the examples in the table reflect many of the more commonly discussed ways that OUD and opioid overdose could be reduced, they are not exhaustive. Moreover, not all examples directly correspond to their implementation in the model, and their level of evidence varies. Because identifying high-impact targets sometimes means thinking beyond the existing toolset, we did not limit ourselves to strategies corresponding to existing evidence-based policies or interventions. For instance, we could not find evidence-based policies or interventions for #5 and #8, so the corresponding hypothetical examples in Table 1 are potential interventions that target associated risk factors such as socioeconomic status and mental illness. We operationalized these strategies in SOURCE to directly reduce the calibrated base transition rates, which implicitly include the influence of factors that drive opioid use and OUD, such as social determinants of health, trauma exposure, mental illness, genetics, and so on. These factors' implicit inclusion in the base rates means that we assume that they are not part of population-level feedback loops and have remained consistent over the model's time horizon (1999 to 2020) rather than varying dynamically.

Even existing interventions or policies rarely have reliably documented effect sizes, let alone effect sizes readily translated to a national level. Prescription opioid misuse prevention interventions were the only ones that we identified with reliable effect sizes, but these have not been tested at a national level. Because of the lack of documented effect sizes and varying levels of evidence across the 11 strategies, we facilitate comparison by testing an across-the-board 20% effect size. Twenty percent is large enough to identify effects but not so large as to be unrealistic. We also tested the strategies at 10 and 50% effect sizes to identify potential nonlinearities in impacts. To identify synergies, in which the combination of strategies is greater than the sum of its parts, we tested three packages of multiple strategies enacted simultaneously, as well as all 55 pairwise combinations of strategies.

The simulation starts in 2022, and all strategies are assumed to come gradually into full effect over 3 years, reflecting time to implementation; they are thereafter permanent. Thus, these changes represent sustained interventions or policies, not short-term bursts of additional resources.

Strategy analysis

We describe the effects of the 11 strategies on annual OUD prevalence and opioid overdose deaths and their effects on cumulative person-years of OUD and cumulative opioid overdose deaths from

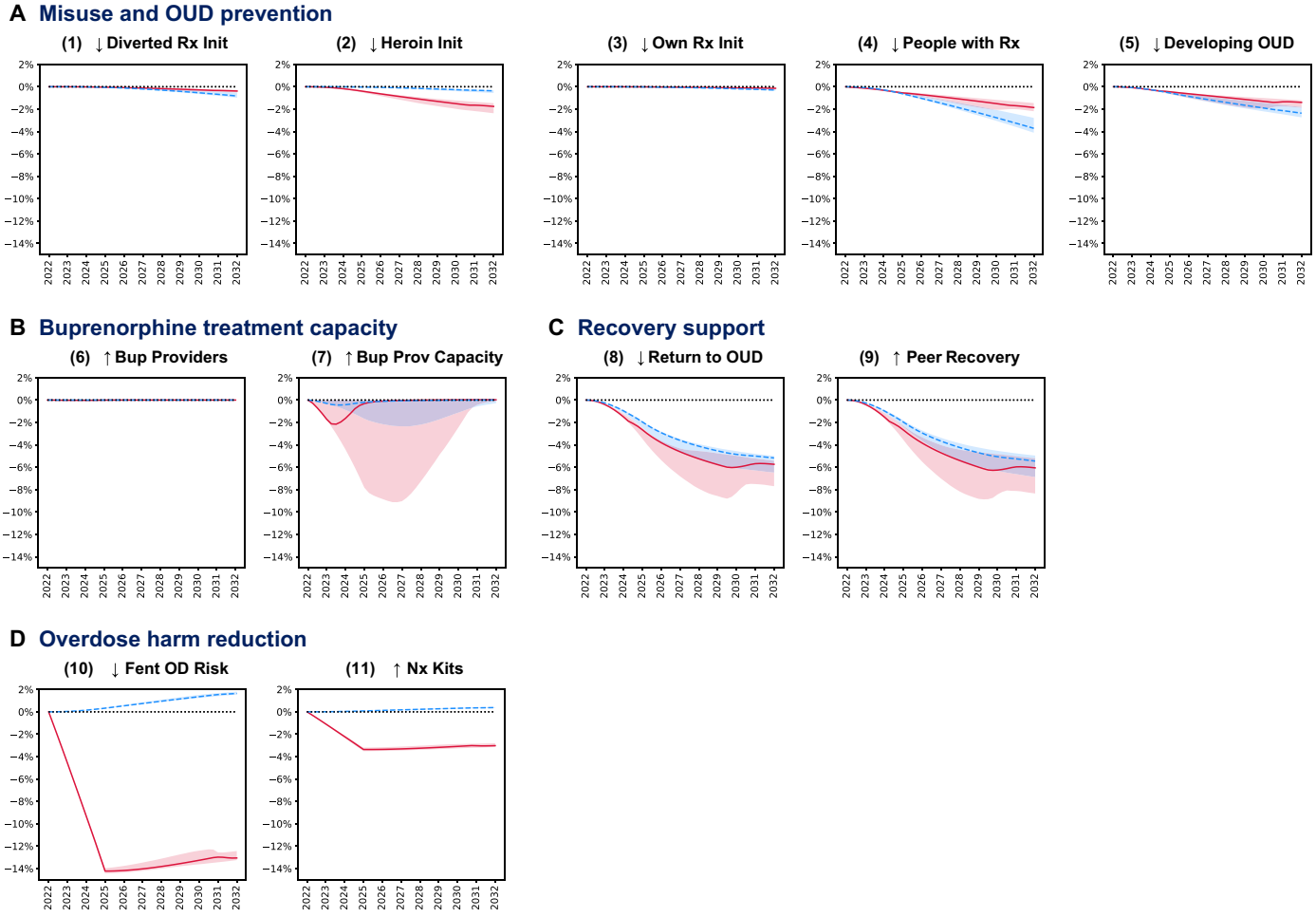

Fig. 1. Annual effects of strategies. Annual fractional change and 95% credible intervals across 11 strategies evaluated within the categories of (**A**) misuse and OUD prevention (five strategies), (**B**) buprenorphine treatment capacity (two strategies), (**C**) recovery support (two strategies), and (**D**) overdose harm reduction (two strategies). The outcomes are the prevalence of OUD (dashed blue line with blue shading for intervals) and opioid overdose deaths (solid red line with red shading for intervals) relative to baseline (dotted horizontal line at 0%), 2022–2032.

2022 to 2032. We end by analyzing combinations of strategies and the impacts of strategies at 10 and 50% compared to the main results tested at 20%. Figure 1 shows the effects of the 11 strategies on annual opioid overdose deaths and OUD from 2022 to 2032 with 95% credible intervals (also see S2) relative to the baseline scenario.

Effects of strategies on annual OUD prevalence

The annual effects of reducing opioid initiation on OUD prevalence (Fig. 1A, 1 to and 3) are minor, regardless of strategy (with a maximum reduction of 0.8% for diverted misuse, 0.4% for heroin, and 0.3% for own prescription misuse by 2032). However, their effects grow over time because the impact of misuse prevention interventions on OUD takes years to manifest.

Decreasing the number of people who receive an opioid prescription (Fig. 1A, 4) has a larger effect on OUD prevalence (−3.7%) than does a reduction in OUD development rates (−2.4%) as of 2032 (Fig. 1A, 5). This is because reducing the prescribing rate has multiple channels of effect in SOURCE by limiting the volume of prescription opioids in circulation. Specifically, in SOURCE, reducing prescribing reduces misuse initiation by reducing patients receiving opioids and among those who would use diverted opioids. It also reduces OUD development and increases the rate at which people quit misusing prescription opioids (because they are harder to obtain).

The reduction in OUD achieved through opioid prescribing reductions is almost entirely in OUD involving prescription opioids. The effect of reducing opioid prescribing on OUD involving heroin exhibits a worse-before-better dynamic. At first, it increases slightly compared to baseline because reducing prescription opioid availability leads some people to switch to heroin, who then subsequently develop an OUD involving heroin. However, starting around 2028, OUD involving heroin falls compared to baseline because the lower prevalence of OUD involving prescription opioids reduces the population at risk of switching to heroin.

Increasing the number of buprenorphine providers does not affect OUD prevalence (Fig. 1B, 6). However, growing buprenorphine providers' capacity by increasing the average number of patients they can treat does reduce OUD prevalence in the short term (Fig. 1B, 7), although the effects are small (achieving no more than a 0.44% reduction, in 2023, before falling to 0%). The effects are short term because increasing buprenorphine providers' capacity is helpful only when capacity would otherwise not be able to meet demand. We project that, by 2024, buprenorphine capacity will be able to meet demand in the baseline scenario due to the projected declining prevalence of OUD, especially that involving heroin. We estimate that a 20% increase in capacity would translate to providers treating, on average, nearly seven patients at a time compared to five in the baseline by 2025.

The recovery support strategies (Fig. 1C, 8 and 9) are the most impactful in reducing OUD prevalence by 2032 (−5.2% for return to OUD and −5.4% for peer recovery). We project that people returning to OUD after at least a year of remission (i.e., "relapse") will be an increasingly larger source of OUD prevalence compared to incident OUD. Thus, reducing the return to OUD rate has greater effects on OUD than reducing misuse initiation and OUD development have. The peer recovery loop has an even larger impact than the direct reduction in the return to OUD rate because of the loop's reinforcing nature. Over time, as more people are in remission, the reduction in the return to OUD rates grows, keeping even more people in remission. (Conversely, as fewer people are in remission, the magnitude of the rate reduction diminishes.) As OUD declines in the baseline model, remission rates also fall, reducing the impact of the recovery support strategies in later years relative to baseline. Last, the overdose harm reduction strategies (Fig. 1D, 10 and 11) lead to a slight increase in OUD prevalence (+1.6% and +0.3%, respectively) because of lives saved. For more discussion about the interaction between changes in OUD and the prescription opioid availability balancing loop, and how this interaction changes the annual effects of the strategies, see section S9B.

Effects of strategies on annual opioid overdose deaths

Prescription opioid misuse prevention strategies have small annual effects on opioid overdose deaths through 2032, whether targeting people at risk of misusing with diverted prescriptions (−0.4%; Fig. 1A, 1) or with their own prescription (−0.1%; Fig. 1A, 3).

Reducing heroin initiation (Fig. 1A, 2), the number of people receiving a prescription (Fig. 1A, 4), and the rate of development of OUD Fig. 1A, 5) have roughly equivalent effects on overdose deaths. None of these strategies achieves more than 2% reductions by 2032; however, as with OUD, their preventative nature means that their impacts grow over time.

In contrast to the other prevention strategies, reducing heroin initiation has a greater impact on overdose deaths than on OUD prevalence. Even new initiates to heroin use are at risk of fentanyl exposure and hence immediately experience higher overdose risk, whereas there is a delay before they develop OUD. Therefore, reducing heroin initiation has a more immediate and disproportionate impact on overdose deaths than reducing prescription opioid initiation has.

Increasing the number of buprenorphine providers does not reduce overdose deaths in the near or long term (Fig. 1B, 6). Growing buprenorphine providers' capacity to treat more people (Fig. 1B, 7), on the other hand, has among the largest effects on opioid overdose deaths in the near term, reaching a peak annual reduction of approximately 2% by mid-2023 before falling quickly to having no impact relative to baseline. After mid-2023, we project that capacity limitations will ease due to less demand for treatment arising from continued decreases in OUD involving heroin. The large uncertainty around the effect of buprenorphine capacity on opioid overdose deaths, as reflected in the shading in Fig. 1B, 7, is due to uncertainty about how quickly OUD involving heroin will fall.

By 2032, the two recovery support strategies have among the largest effects on lives saved: 5.7% for the reduction in the return to OUD rate (Fig. 1C, 8) and 6.1% for the peer recovery loop (Fig. 1C, 9). The recovery support strategies have such a large effect because they keep people in remission who otherwise would have returned to OUD, reducing the number of people at risk of overdose relative to baseline. Similar to the effects on OUD prevalence, the peer recovery loop is slightly stronger than reducing the rate of return to OUD. The impact of both strategies relative to baseline wanes over time.

The fentanyl harm reduction strategy (Fig. 1D, 10) and increasing naloxone distribution to people who use opioids (Fig. 1D, 11) have the largest and most immediate annual effects on opioid overdose deaths, peaking at reductions of 14.2% for fentanyl harm reduction and 3.4% for naloxone kits, both in 2025. The harm reduction strategies' impacts do not grow after the 3-year implementation ends because they do not affect the underlying structure of the system, i.e., they do not affect developing or remitting from OUD.

The fentanyl harm reduction strategy and the two recovery support strategies appear to surpass the effects of naloxone kit distribution by 2032. However, the implementation of these strategies in SOURCE is not directly comparable. The availability of relevant data (see table S2) and decades of research on naloxone, including

inefficiencies in distribution, supported a more realistic test of the effects of increasing its distribution (see section S6D). Thus, a 20% increase in naloxone distribution in SOURCE equates to an approximately 10% increase in naloxone actually being administered in the event of an overdose. Similar data and background research are not available for the fentanyl harm reduction and recovery support strategies, which correspond to many potential interventions with various levels of (not necessarily known or well-documented) efficiency and efficacy.

Effects of strategies on cumulative person-years of OUD and opioid overdose deaths

Figure 2 shows the cumulative effects, from 2022 to 2032, of implementing the 11 strategies on OUD person-years and fatal opioid overdoses. Compared to the baseline scenario (point [0, 0]), strategies toward the bottom left achieve larger reductions in cumulative person-years of OUD and opioid overdose deaths. See table S7 for the cumulative opioid overdoses and person-years of OUD for baseline and each strategy tested.

All 11 strategies have rather small effects on cumulative person-years of OUD—no more than a 3% reduction. The greatest effect, from peer recovery (−2.9%), translates to about 850,000 fewer person-years of OUD (of more than 28.9 million cumulative person-years) compared to baseline. The fentanyl harm reduction strategy ("Fent OD Risk") reduces cumulative overdose deaths by 11.3% (more than 61,000 lives saved), whereas every other strategy reduces cumulative deaths by less than 4%.

An unintended consequence of overdose harm reduction strategies is a small (<0.7% total) increase in person-years of OUD due to fewer people dying, which is offset when combined with other strategies. Moreover, even with the increased person-years of OUD, the overdose harm reduction strategies still lead to fewer people dying of overdose compared to baseline.

Effects of combinations of strategies on cumulative person-years of OUD and opioid overdose deaths

We tested three examples of combinations of strategies ("packages"), including a combination of the seven strategies that produced at least a 0.5% reduction in either cumulative person-years of OUD or opioid overdose deaths from 2022 to 2032 (i.e., strategies #2, 4, 5, 8, 9, 10, and 11 in Table 1). We show the annual effects of these packages in Fig. 3, while the cumulative effects are shown in fig. S4.

Package 1 (Fig. 3A and fig. S4, "package 1") was the most effective package identified annually and cumulatively. It achieved a maximum annual reduction of 29.9% in opioid overdose deaths and 15.1% in OUD prevalence in 2032, while, cumulatively, the reduction was 21.7% in overdose deaths and 7.3% in person-years of OUD. However, these effects are additive, meaning there were no synergistic impacts (i.e., multiplicative effects). The large initial reduction in opioid overdose deaths in package 1 is due to the inclusion of the fentanyl harm reduction strategy.

Package 2 (Fig. 3B and fig. S4) included the same strategies as package 1, except that we removed the fentanyl harm reduction strategy (#10 in Table 1). Removing the fentanyl harm reduction strategy means that package 2 achieves much smaller annual and cumulative reductions in opioid overdose deaths by 2032 (a maximum of 19.1% annually in 2032 and 11.8% cumulatively) than package 1. These reductions are only slightly larger than the reductions from the fentanyl harm reduction strategy alone (14.2% peak annual reduction in 2025 and a cumulative reduction of 11.3%). The OUD annual reduction as of 2032 is slightly larger relative to baseline (16.3% compared to 15.1%) due to more people with OUD dying absent the fentanyl harm reduction strategy. This package is also additive.

The relative impact comparison between packages 1 and 2 is sensitive to assumptions about the future growth of fentanyl (see section S9D and fig. S7). If fentanyl penetration does not grow beyond its estimated 2020 level of 56% of the heroin supply, the cumulative effect of fentanyl harm reduction is only 9%. If we assume that fentanyl penetration reaches 100% by 2032, the fentanyl risk reduction strategy reduces cumulative overdose deaths by 12.8%, surpassing the effects of the six other strategies combined (package 2) (see fig. S8).

Last, given the ongoing interest in expanding buprenorphine capacity, we tested a slightly different package of seven strategies

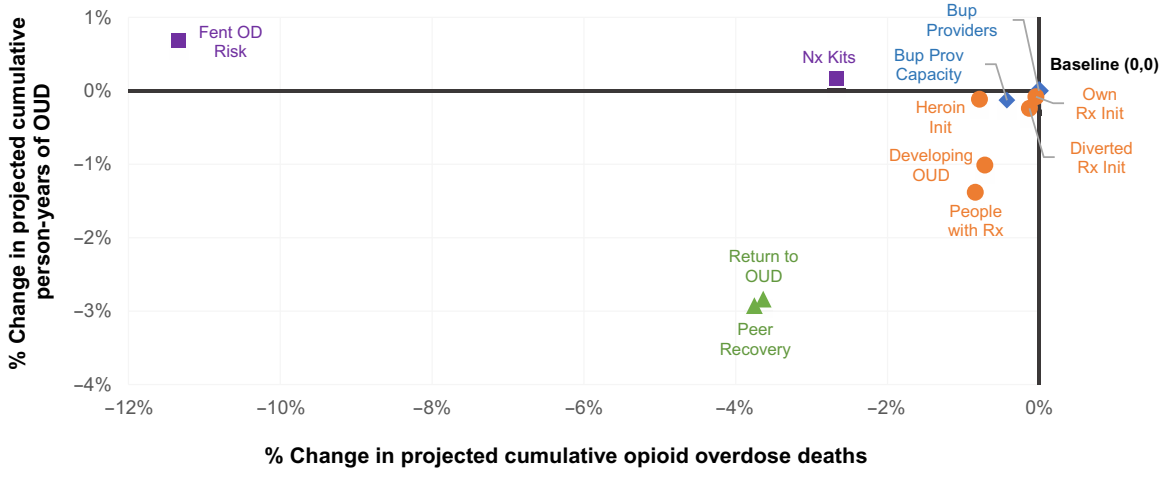

Fig. 2. Cumulative effects of strategies. This figure shows effects on cumulative percentage reduction of opioid overdose deaths and person-years of OUD relative to baseline projections in 2032. The results for 11 strategies span four categories: prevention of misuse and OUD (orange circles), buprenorphine capacity (blue diamonds), recovery supports (green triangles), and harm reduction (purple squares). The *x* axis shows the fractional change in cumulative overdose deaths, while the *y* axis shows the fractional change in cumulative person-years of OUD relative to the baseline scenario.

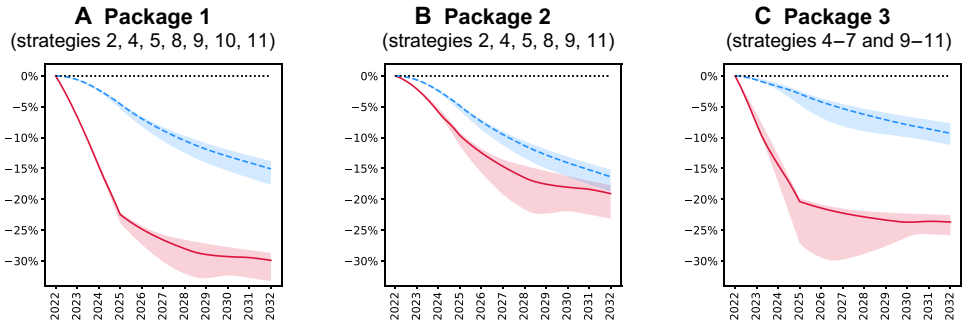

Fig. 3. Annual change from combined strategies, or "packages." This figure plots annual fractional change and 95% credible intervals across three packages of combined strategies in people with OUD (dashed blue line with blue shading for intervals) and opioid overdose deaths (solid red line with red shading for intervals) relative to baseline (dotted horizontal line at 0%), 2022–2032.

("package 3," strategies 4 to 7 and 9 to 11 in Table 1 and Fig. 3C) that included buprenorphine capacity strategies, although their cumulative impacts were smaller. In addition, we removed the strategies that reduced the rate of heroin initiation (because it had among the smaller effects of the original seven included strategies) and the rate of return to OUD (because its mechanistic impact was redundant with and slightly weaker than the peer recovery loop). All other strategies remained, including the fentanyl harm reduction strategy. Package 3 achieved a maximum annual reduction in 2032 of 23.7% in opioid overdose deaths and 9.3% in OUD, and cumulative reductions of 18.5% in overdose deaths and 4.5% in OUD person-years (package 3; fig. S4). Fentanyl harm reduction again contributed to a large initial reduction in opioid overdose deaths, and this package was also additive.

We conducted an additional pairwise analysis (55 paired strategies), still finding no synergies. Note that a combination of all 11 strategies did not perform much better than our package 1, achieving a maximum annual reduction in opioid overdose deaths of 30.2%, and a 15.8% reduction in OUD prevalence, in 2032. Cumulative reductions were 22.1% for overdose deaths and 7.7% for person-years of OUD.

The packages presented above are only examples of the more than 2000 possible combinations of strategies that could be tested. However, in our exploratory testing of other combinations of strategies, we have yet to identify any synergies. Thus, to approximate the combined impact of any of the strategies presented here, their individual effects can simply be added.

Effects of strategies tested at 10 and 50% on cumulative person-years of OUD and opioid overdose deaths

To identify potential nonlinear effects on outcomes of effect sizes other than 20%, we also tested effect sizes of 10 and 50%, examining the impact on cumulative opioid overdose deaths and person-years of OUD by 2032 (see figs. S5 and S6). For most strategies, the effects of 10 and 50% reductions in the initiation rates were proportionate for both outcomes, i.e., approximately 0.5× and 2.5× the effect of a 20% change, respectively. Some strategies had nonlinear effects, although none was large.

Increasing buprenorphine provider capacity failed to reach proportional reductions in overdose deaths at a 10% effect size. Both recovery support strategies show greater proportional reductions at 10% for both outcomes.

We only report those strategies with disproportionate outcomes at 10% effect sizes because it is a more realistic effect size than 50%. Results for 50% effect sizes are described in section S9C.

DISCUSSION

This simulation analysis sought to identify which strategies targeting opioid use and opioid overdose could save lives and reduce OUD. We found that fentanyl harm reduction, increased naloxone distribution, recovery support, and—if implemented quickly—increasing buprenorphine providers' capacity had the largest impacts on reducing opioid overdose deaths, with modest effects on reducing OUD.

Our analysis, coupled with syntheses of the available literature and expert opinions [e.g., (*18*)], can inform what may be needed to achieve our projected reductions in opioid overdose deaths and OUD. The feasibility, time scale, and cost of achieving a 10, 20, or 50% change vary widely across the strategies tested. In addition, strategies differ in the strength of evidence for their benefit and the externalities and potential unintended consequences. With those nuances in mind, we offer some illustrative examples of the types of interventions that correspond to the higher-impact strategies identified in SOURCE. Our intent is also to provoke readers to think more expansively, beyond existing interventions and policies, about how to reduce overdoses, overdose deaths, and OUD.

Fentanyl and other synthetic opioids are playing an unprecedented role in overdose deaths, implicated in at least 67,000 fatal overdoses during the 12 months ending November 2021, a 21% increase compared to the previous 12-month period (*6*). In our analysis, increased naloxone distribution (which SOURCE assumes goes primarily to people who use opioids) reduced fatal opioid overdoses. This finding is consistent with other models (*13*–*17*) and empirical evidence that naloxone saves lives when made widely and freely available to people who use opioids (*19*). Our analysis points additionally to the importance of addressing naloxone distribution inefficiencies. In SOURCE, increasing naloxone distribution by 20% led to only a 10% increase in the probability of naloxone administration in the event of an overdose. Lowering the practical and logistical barriers to carrying naloxone (*20*) could save additional lives. Regions with low saturation would benefit the most (*21*). The source of naloxone matters, too: Recent modeling analysis suggests that pharmacy standing order- and community-based naloxone distributions are more efficient channels than provider-based distribution (*22*).

Our modeling analysis is the first to show that lives could be saved if people who use fentanyl (knowingly and willingly or not) had evidence-based strategies to reduce their overdose risk. That is, we shifted the intervention point from reducing the risk of death via

naloxone to reducing the risk of overdose. Drug-checking interventions that detect fentanyl have received greater attention recently. These could be useful insofar as they inform people of what they do not already know, thus allowing them to make more informed decisions about their drug use. Drug checking includes point-of-use fentanyl test strips (*23*) and higher-tech tools, such as spectrometry and spectroscopy, that community programs can use to detect the presence, and sometimes quantity, of fentanyl and its analogs (*24*). Which tool is most useful depends partly on how recently fentanyl has entered the local drug supply. In areas where fentanyl is already ubiquitous, and its presence assumed, alerting people who use opioids to the presence of potent fentanyl analogs in the local supply could be more useful than fentanyl test strips at point of use.

For drug-checking interventions to have the greatest impact, people must have the tools to change their drug use behavior, and those altered behaviors should reliably reduce the risk of overdose. Using less of the drug, using more slowly, and using a less risky mode of administration are common harm reduction behaviors when fentanyl's presence in drugs is known or suspected (*25*–*27*). However, there is room for improvement; more than half of PWUD do not engage in these fentanyl harm reduction practices (*25*, *28*). Moreover, some harm reduction behaviors are likely more effective than others at reducing overdose risk. Thus, whether drug-checking services and associated harm reduction behaviors can achieve the effect size modeled in SOURCE is not yet clear. Rather, our results should be interpreted as the number of lives that could be saved if people who use fentanyl could reduce their risk of overdose reliably. Further resource investment in learning how to achieve such risk reduction is a strategy worth pursuing.

Our simulations showed that two recovery support strategies had the largest and most sustained effects on reduced OUD and thus also on reduced opioid overdose deaths. Furthermore, these were the only strategies that showed disproportionately positive returns at 10% effect sizes compared to 20%, suggesting that even small improvements in recovery support represent potential leverage points. We project that return to OUD after remission will increasingly become the primary source of OUD prevalence rather than incident OUD. Thus, to reduce overdose deaths, it is critical to keep people in remission, including those who have not received MOUD treatment or any treatment.

Policies and interventions that could keep people in remission (i.e., reduce the return to OUD rate) include removing obstacles to full reintegration into society, such as employment supports (*29*). Other policies would support people to maintain improvements in social role functioning, which is a predictor of sustained abstinence (*30*). Existing interventions such as mutual aid, peer recovery support services, and recovery homes correspond most closely to the peer recovery loop. However, to achieve the effect sizes we tested, more research is needed to identify the most effective among these interventions—or identify new ones. Moreover, our strategy test drew on the 3+ million people in recovery from OUD (*31*), suggesting that many more will need to be engaged. Further research is needed on the potential of community or national peer recovery strategies. We also encourage further testing of recovery support in opioid modeling analyses; ours is the first to do so, despite recovery support being a component of the national overdose prevention strategy (*29*).

Buprenorphine treatment saves lives (*32*, *33*) and is a critical tool for reducing opioid overdoses and fatalities. Other models have tested the effect of more people receiving treatment, including buprenorphine, estimating large fatal overdose reductions (*13*–*17*). However, these models did not include capacity limitations, which are important to account for because buprenorphine providers would currently be unlikely to meet the level of increased demand tested in many models. Providers' inability to treat more patients is a primary reason treatment is inaccessible (*34*–*36*). Our analysis, therefore, focused on whether increasing buprenorphine capacity would allow more people to receive treatment, thereby reducing fatal opioid overdose and OUD prevalence. Our capacity strategy is therefore distinct from assessing whether increased treatment receipt would save lives; as noted above, empirical evidence and prior modeling suggest that it would.

We found that increasing the number of providers who can prescribe buprenorphine, which might be accomplished either through increased waiver training or by doing away with the waiver requirements altogether, has almost no effect on OUD or overdoses. This result is consistent with empirical research, which reports several barriers that are more prohibitive than the waiver requirement (*37*). As a result, a full one-half of providers who have obtained waivers to prescribe buprenorphine do not prescribe at all (*38*), and only a small minority (~5%) write half of the buprenorphine prescriptions (*39*). In contrast, increasing how many patients, on average, existing buprenorphine providers treat has one of the largest immediate effects on reducing mortality. However, this strategy only saved lives (relative to baseline) if implemented near term because of projected declines in OUD, which led to easing demand on capacity. Some policies that could achieve effects sooner rather than later include enforcing existing parity laws and increasing reimbursement (*40*), which could lead more providers to accept Medicaid insurance (*18*), thereby reducing a considerable affordability barrier faced by patients (*36*). Moreover, this strategy showed diminishing returns at a 10% effect size. Any efforts undertaken will need to increase capacity closer to the 20% effect size, translating to about two more patients on average per provider (at any given time), from five to seven.

Our finding regarding the short-term benefit of capacity increases holds if average treatment duration, i.e., retention, does not increase. However, retention is a key predictor of sustained abstinence (*30*), and improving retention is a primary goal of the National Institutes of Health's Helping to End Addiction Long-term (HEAL) Initiative (*41*). If average duration were to increase, meaning providers are treating patients for longer periods, then this would reduce their ability to bring in new patients. Even if there is no legal limit on how many patients providers can treat, there are only so many patients that they are logistically capable of treating. Thus, in the event of improvements in retention, supporting providers to increase their capacity will remain important even if OUD continues to fall. Addressing any of the myriad barriers that providers face could support buprenorphine prescribers to reach more patients. These barriers include a lack of psychosocial support and services for people with complex health and mental health conditions; limited knowledge, education, and confidence in treating OUD; low patient demand; stigma; and insufficient time and reimbursement (*37*).

We tested five misuse and OUD prevention strategies that proved to have negligible effects on both OUD prevalence and fatal opioid overdose, partly due to the time horizon of SOURCE's projections. Strategies that might have had larger impacts earlier, such as preventing initiation of opioid misuse, are now projected to have little impact in the near term because these major population shifts have already occurred. However, we project an increase in opioid

misuse initiation beginning in the late 2020s, suggesting that discussions of how to scale misuse prevention effectively will soon be relevant again.

Prescription opioid misuse interventions—which would correspond to our tests of diverted opioid misuse initiation, not misuse of one's own prescription—are among the more effective interventions available. Reductions of 4% (*42*) to 65% (*43*) have been reported, so the effect sizes that we tested—10, 20, and 50%—provide some insight into the effects of these interventions if scaled nationally. Prevention of heroin use, on the other hand, is understudied. We identified one study that reported the effects of an intervention on heroin initiation, but the follow-up was only through eighth grade (*44*)—too young to gauge the impact on behavior that usually begins much later.

Among the prevention strategies, reducing prescribing rates and the development of OUD had the largest effects on OUD prevalence and opioid overdose deaths. Our approach to testing prescribing reductions was less detailed than other opioid modeling analyses. These other analyses have found more lives saved via policy changes such as reducing diversion or disposing of excess pills, prescription monitoring programs, and drug rescheduling, rather than targeting individual prescribing practices directly (*14*, *15*, *17*). In SOURCE, the beneficial effects of reduced opioid prescribing occur primarily via a reduction in prescription opioids available for diversion rather than people initiating misuse with their own prescriptions. This finding points to the need to reduce excess and unnecessary opioid prescribing and identify strategies that can effectively address the root causes of diversion, for example, the desire to build social capital or supplement income (*45*).

Two distinct ways of reducing the number of people who receive prescription opioids include reductions in initiating opioid prescriptions for new patients versus tapering the dosage of existing patients (i.e., deprescribing), which we do not distinguish in SOURCE. Numerous potential harms are associated with tapering individuals on chronic opioids, including increased risk of opioid overdose, inadequately treated pain, and mental distress or suicidality; more rigorous studies of these effects are limited and only just starting to emerge (*46*). Reducing incident prescriptions and using alternatives to opioids for pain management in their place (*47*) could reduce patients with opioid prescriptions with fewer potential harms. The risks and benefits of opioid prescribing for chronic and incident pain management are understudied, and long-term tracking of patient outcomes is needed to inform prescribing practices (*18*).

Ours was the first model to examine the effect of preventing the transition from misuse to OUD, not just diverted opioid misuse prevention as tested previously (*48*). We tested both, finding larger impacts from reducing OUD development than reducing misuse initiation on cumulative person-years of OUD and cumulative fatal opioid overdoses. There are no formalized evidence-based interventions for reducing this transition from misuse to OUD. Clues for where to start can be found in the literature. For instance, psychiatric disorders are prospectively associated with risk for opioid misuse and OUD (*49*), and problematic opioid use is also often associated with economic deprivation (*50*). Thus, strategies for reducing OUD development might include increasing access to mental health treatment and multifaceted support during economic crises (*51*). Establishing a causal relationship between mental illness or poverty and OUD development (and not just the broader category of "misuse") is critical to more effectively intervene and a more detailed representation of OUD prevention in SOURCE.

Our modeling analysis has several limitations. First, while SOURCE includes all overdose deaths involving opioids, including those that also had methamphetamine or cocaine present or were due to counterfeit pills, it does not explicitly track those or the broader category of polysubstance use. Strategies may affect polysubstance use or overdose differently, and our analysis may miss those interaction effects. Second, although we included 2020 data, which we assume reflected some of the effects of the coronavirus disease 2019 (COVID-19) pandemic, we underestimated the number of deaths that occurred in 2020, suggesting that there are additional effects not yet included. Third, many data gaps in the OUD literature make building any opioid model challenging (e.g., comprehensive national data on naloxone do not exist) (*52*). Longitudinal natural history studies that follow a nationally representative group of people with OUD in and out of treatment and remission lasting at least 1 year would be especially useful for improving transition rate estimates once people have developed OUD.

Fourth, the opioid crisis is driven by many factors that we have not explicitly included in SOURCE, including socioeconomic status and other social determinants of health, trauma exposure and mental illness, and involvement in the criminal legal system (*53*). Their effects on transitions are poorly measured in the literature, so they are implicitly reflected in the estimated baseline transition rates rather than being separately estimated. These factors' implicit inclusion limits our ability to test the effects of intervening on these factors. Absent this mechanistic detail, we allude to these factors as potential intervention points where evidence suggests that they are particularly relevant. Our future research will engage PWUD and their communities more directly in model development. We anticipate that this will lead to models focusing on the root causes of addiction and will likely be more qualitative than SOURCE. These new efforts will complement the insight gained from SOURCE.

Fifth and last, SOURCE is a national model that, like many such models (whether addressing opioids or almost any other nationwide phenomenon), does not attempt to capture or project regional heterogeneity. Nonetheless, questions might arise about whether the implications of our findings could differ in some regions, states, or locales. We offer some guidance on thinking about and using our findings here.

Our findings hold across regions insofar as the basic structure of SOURCE, in terms of how drug use behavior and overdose risk evolve (e.g., social influence, risk perception, and the role of fentanyl in driving overdoses), is consistent across the country. We know of no evidence to suggest otherwise. Such structural similarity could be undermined if basic population trends such as misuse initiation and OUD prevalence were moving in different directions across the country. However, they are moving downward across all regions (*54*). Given these assumptions of structural similarity and evidence of similar cross-regional trends, the relative impact of strategies would remain. However, the strategic timing might shift depending on local conditions, e.g., fentanyl penetration or buprenorphine capacity. For example, there is substantial geographic heterogeneity in buprenorphine access. Increasing providers in underserved areas, which would follow the national trend over the past several years, could have a disproportionate impact even if this approach is ineffective at the national population level. Alternatively, areas already implementing some of the more impactful strategies might see a

reduced impact relative to our results. Thus, our results could offer insight into preventive planning in regions that are not as far along in the overdose crisis while highlighting for others the importance of maintaining effective strategies.

Despite these limitations, SOURCE is the most detailed national-level model to date that aims to address the opioid overdose crisis. We build on other opioid-related models by combining features from all of them, including the inclusion of 2020 data (*17*), the incorporation of feedback loops (*15*), an analysis of misuse prevention (*48*), opioid prescribing reductions (*13*–*17*), and naloxone distribution (*13*–*17*). However, we tested a broader range of strategies than reported in other modeling papers. This broad range allowed us to identify potential leverage points for intervention that others have not explored, including fentanyl harm reduction, recovery support, and increases in buprenorphine capacity (as opposed to testing the effects of treatment receipt). As a result, we provide new insights based on a model that endogenously replicates historical trends, using the best available data and the combined input of more than two dozen academic, clinical, and public health experts.

MATERIALS AND METHODS

Model development

Complete information on model development is detailed elsewhere (*12*). Institutional Review Board approval was not required for this study. All data are publicly available.

Overview of SOURCE

SOURCE is a continuous-time differential equations model (*12*) developed using a system dynamics approach in which endogenous feedbacks drive change over time (*9*, *10*). Endogeneity refers to system behavior arising as a function of the current and historical dynamics of the system itself rather than arising independently of those dynamics (*55*). In system dynamics, these processes are referred to as feedback loops, either reinforcing—leading to exponential growth or decay—or balancing, which limits that growth or decay. An endogenous perspective assumes that observed behavior arises for reasons found in the state of the system, e.g., opioid initiation is influenced by how many people already use opioids and the consequences people are experiencing due to opioid use. Figure 4 provides an overview of the model population groups, their transitions, and the key factors affecting those transitions, including feedback loops and (diverted) prescription opioid and heroin availability. Transitions affected by feedback loops are not static over time, but instead vary with changing population-level dynamics.

Dynamic hypothesis

SOURCE is the mathematical representation of our team's dynamic, feedback-based hypothesis about how the so-called opioid crisis has evolved on a national level since 1999, when the model simulation starts, through 2020, which is the last year to which the model is currently calibrated (due to data delays). SOURCE is a national-level model, so we use national-level data to capture relevant trends. These trends include misuse and OUD as reported

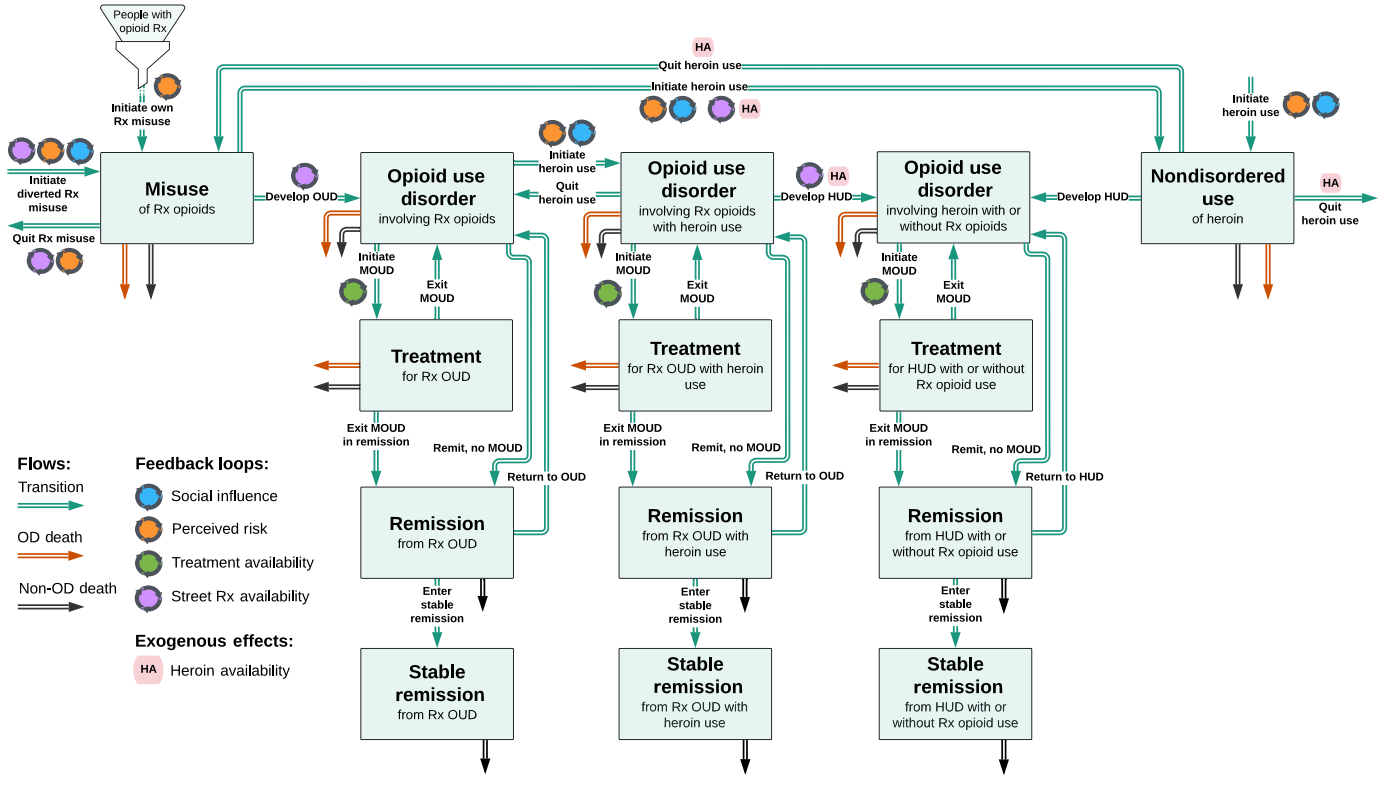

Fig. 4. SOURCE model overview. This figure maps the model states and transitions, with feedback loops denoted. "Rx" denotes prescription opioids. Treatment states are further separated by MOUD type: methadone maintenance treatment, buprenorphine, and extended-release injectable naltrexone. An earlier version of this figure also appeared in (*12*).

in the National Survey on Drug Use and Health (NSDUH) (*7*) and opioid overdose deaths as reported by U.S. Centers for Disease Control and Prevention (CDC) (*1*). See fig. S1, which compares these historical data against our calibrated output (*12*). We correct for NSDUH's likely underestimation in people who use heroin (see section S4A, iv).

We offer a brief qualitative summary of the overall trends depicted in fig, S1. In the early 2000s, there was a steady fall in prescription opioid misuse initiation and prevalence of misuse. At the same time, OUD involving prescription opioids ("Rx OUD") continued to rise until a peak around 2011, simultaneous with a continued rise in opioid prescribing. During this same time (the 2000s), there was an exponential rise in prescription opioid overdose deaths. From 2008 to 2015, heroin initiation rose rapidly, fueling a rapid rise in people with OUD involving heroin ("HUD") and heroin overdose deaths. However, since 2015, there has been a marked drop in heroin initiation, and HUD appears to have peaked in 2017. Fentanyl-involved overdoses began to rise in 2014 and have not decreased since. Total opioid overdose deaths appeared to be plateauing in 2017, but 2020 (as well as provisional 2021) data show a reversal of that trend, with the largest rise yet (*6*).

SOURCE is a high-level, data-driven, national epidemiological model. Thus, it relies on a parsimonious dynamic hypothesis to explain and then replicate through formal model estimation the above-described trends. The model includes two competing feedback processes, identified based on interviews and close collaboration with subject matter experts over 2 years (see S1). These processes drive the observed national trends in opioid initiation and therefore also affect the national prevalence of use and use disorder: (i) social influence, which leads more people to use opioids as others around them increasingly use (*56*, *57*)—or, conversely, to less initiation as fewer people use, and (ii) risk perception, which slows initiation and increases quitting as the perceived risk associated with opioids use rises (but can also have the opposite effect) (*58*). The risk perception feedback is informed by literature, suggesting a generational effect that drives the cyclical nature of drug "epidemics" in the United States, i.e., the historical population-level switching between opioids and stimulants (*59*, *60*). This view posits that falls in the initiation of popular drugs are, in part, due to a growing perceived risk of those drugs, thus making other drug classes more attractive to potential initiates. In SOURCE, once opioid overdose deaths begin to drop, risk perception declines after a long delay, leading to greater initiation. The rapid drop in heroin initiation cannot be reproduced without including perceived risk balancing effects (*12*).

The availability of prescription opioids and heroin to potential and existing misusers also affects initiation, OUD development, and quitting in the model (although we assume that drug availability does not influence remission rates). Prescription opioid availability is part of a balancing feedback loop; as more people use prescription opioids obtained on the street, there are fewer available for others with which to initiate or develop an OUD. Heroin price (and its inverse, availability) is exogenous, meaning we do not attempt to replicate these dynamics endogenously.

The relative availability of prescription opioids compared to heroin affects heroin initiation and development of OUD involving heroin; as prescription opioids become less available relative to heroin, heroin initiation and OUD development rise. The strength of this effect is also determined by how much heroin availability has already changed. Our data sources (table S2) suggest that heroin (not to mention illicitly manufactured fentanyl) has been more available than diverted/street-level prescription opioids for the past several years. Thus, further reductions in prescription opioid street availability would not be expected to have the same effect on heroin use as would occur if heroin were less available. The feedback loops and availability effects interact with base rates of initiation and quitting to create dynamic transition rates that vary over time—in reality, and SOURCE (*12*).

Last, varying levels of treatment availability affect MOUD treatment entry, as part of a balancing loop. Increasing numbers of people in MOUD treatment leads to reduced capacity available for new patients.

Figure 5 shows the feedback loops in a simplified visual diagram. There are four social influence reinforcing loops (blue): as more people misuse prescription opioids, more people initiate misuse with diverted prescription opioids (#1); as more people have non-disordered heroin use, more people initiate heroin, either with or

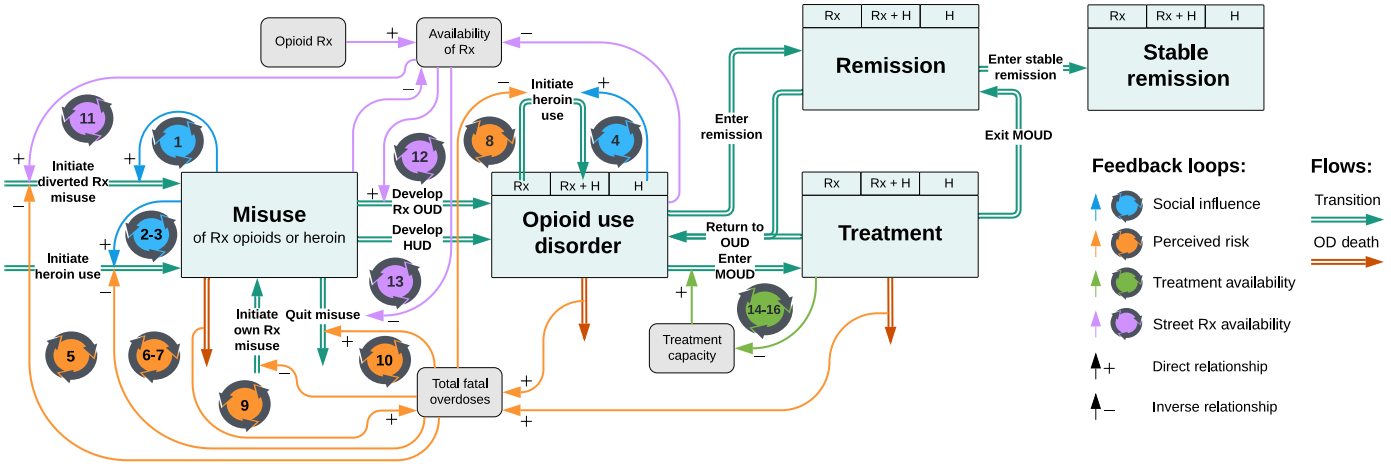

Fig. 5. SOURCE feedback loops in a simplified model structure. The loop numbers shown here are referred to and discussed in the text. "Rx" denotes prescription opioids, and "H" denotes heroin. Treatment includes methadone maintenance therapy, buprenorphine, and extended-release injectable naltrexone. An earlier version of this figure also appeared in (*12*).

without prior prescription opioid misuse (#2-3, shown together for simplicity). Finally, the more people who have Rx OUD with non-disordered heroin use (Rx + H in the 'opioid use disorder' stock) or OUD involving heroin, the more people who initiate heroin from Rx OUD (#4). In SOURCE, all people who use prescription opioids, including those with an OUD or who also use heroin, exert a social influence on diverted prescription opioid misuse initiation (but not misuse initiation with one's own prescription, which we assume is not socially influenced). Similarly, all people who use heroin, including those with an OUD, influence heroin initiation. For simplicity, these extra inputs are not shown in the figure.

The perceived risk loops (Fig. 5, orange) show that as opioid overdoses increase, especially fatal overdoses, risk perception does as well. There are six perceived risk loops in SOURCE. Increasing perceived risk leads to decreased initiation of prescription opioid misuse with diverted prescriptions (#5), decreased initiation of heroin with or without prior prescription opioid misuse (#6-7) or with prior prescription opioid use disorder (#8), and decreased prescription opioid misuse initiation with own prescriptions (#9). Increasing risk perception also increases prescription opioid misuse quitting (#10).

There are five balancing feedback loops involving street availability of prescription opioids (Fig. 5, purple). Two of these operate in tandem with an exogenous heroin availability effect; these are only shown in Fig. 4, but not Fig. 5. The three that do not involve heroin are the following: as the number of people with Rx OUD or prescription opioid misuse increases, so does prescription opioid demand and thus consumption, limiting street prescription opioid availability for others, which then reduces misuse initiation (#11) and OUD development (#12) and increases quitting of prescription opioid misuse (#13). Finally, treatment availability balancing loops (Fig. 5, green) limit treatment entry as available capacity is utilized (#14-16, one for each OUD).

Feedback loops' impacts vary over time and are determined by a combination of the strength of their effect, i.e., how sensitive the population is to them and the relative magnitude of the factors driving them. For instance, if social influence on initiation is strong, indicating great sensitivity within the at-risk population to how many other people are already using a given drug, then many people using that drug will powerfully influence others to initiate. Conversely, a small number of people using will also greatly suppress initiation if the feedback loop is strong. A weaker feedback loop exerts less influence, positively or negatively.

Model calibration

SOURCE is calibrated using 15 time-series data targets from 1999 to 2020. These data targets are incidence and prevalence data from NSDUH, opioid overdose deaths from the CDC National Vital Statistics System, and IQVIA data on prescriptions dispensed for buprenorphine OUD products (table S1) (*12*). Model parameters were estimated using a combination of four types of inputs: (i) exogenous historical data inputs (table S2); (ii) a set of priors to inform treatment-, remission-, and overdose-related estimates (table S3); (iii) literature, datasets, and expert judgment (table S4); and, where there were no reliable data, (iv) formal estimation (table S5). All feedback loop strengths and most base transition rates are formally estimated to achieve the best fit to history and were constrained to plausible ranges (see section S2 for more detail on estimation).

Historical replication is a primary form of validation in simulation modeling (*61*) but one too infrequently used in opioid modeling (*62*). The goal with SOURCE is to replicate trends endogenously, i.e., using the model structure itself, which is critical for making reliable projections. Such endogenous processes will continue to play out in the future and thus interact with policies and interventions in complex and often unanticipated ways. SOURCE successfully replicates historically observed patterns of opioid use and overdose mortality (*12*). The average R^2 against data is 0.76, while mean absolute errors normalized by mean are 12.7% (see table S6).

Baseline model and projections

In the baseline model, both OUD and fatal opioid overdoses are projected to decline through 2032 (see fig. S2) (*12*), although how soon and how quickly depends on assumptions about fentanyl's continued penetration of the heroin market (fig. S7). We assumed that fentanyl penetration would continue to rise, albeit at a decelerating rate. We assumed that naloxone distribution and buprenorphine providers would also rise and that opioid prescribing would continue to fall, all at decelerating rates. (These are all exogenous inputs, not the time-series data to which we calibrate.) See section S5 and table S2 for more details on data sources and section S8 for how we established plausible trends for these exogenous time series.

Rationale for and implementation of strategy testing

Opioid misuse and OUD prevention

Interventions to reduce misuse of prescription opioids or heroin and the rate of OUD development are operationalized in SOURCE by adjusting the base transition rates, which implicitly include important risk factors not captured in our feedback loops, including socioeconomic status and mental illness. We operationalized a reduction in the opioid prescribing rate by adjusting downward our base case projections, derived from IQVIA Total Patient Tracker® data, of how many people will receive prescription opioids annually.

Buprenorphine capacity

Increased treatment engagement could occur by increasing treatment capacity. We could only find national capacity data for buprenorphine. National capacity data are not available for methadone maintenance treatment or extended-release injectable naltrexone (i.e., Vivitrol), so we could not test increases in their capacity.

We assume that accessibility barriers experienced by patients are largely the result of provider capacity limitations and systemic barriers such as lack of public transportation and are therefore not problems to be solved by individual patients. Hence, we discuss capacity rather than accessibility, although these are two sides of the same coin. For instance, increasing buprenorphine capacity might decrease wait times, thereby increasing accessibility.

We test two ways to increase buprenorphine capacity. The first is to increase beyond base projections the number of providers who will legally be able to prescribe buprenorphine (see section S5C). The second is to increase the average number of patients buprenorphine providers can treat, which we call "effective capacity." Effective capacity is operationalized in SOURCE using a model-calibrated parameter that estimates the rate of observed diminishing returns on each additional waivered provider (see section S6A). Other patient barriers to treatment, such as lack of affordability, are accounted for in SOURCE but not part of our strategy testing (see section S1A, ii).

Recovery support

We test two ways of reducing the return to OUD (i.e., relapse) after remission. We use the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition) definition of remission: at least 1 year

without meeting OUD criteria, after having met OUD criteria before (*63*). The first strategy is a reduction in the return to OUD rate, which is best conceptualized as any policy or set of policies that target factors that increase the risk of relapse, such as declining social role functioning (*30*). This transition in SOURCE involves people who are no longer or never were in MOUD treatment, so it does not correspond to interventions targeting people currently enrolled in MOUD treatment.

The second recovery support strategy that we tested is a peer recovery loop, where we added a new reinforcing loop (see fig. S3). The theory of change is that people in remission can provide positive role modeling and hopeful examples for others to maintain their own positive changes. The peer recovery loop is operationalized such that an increase in the number of people in remission slows the rate of return to use disorder. We tested this loop to gauge the potential of a strategy that harnesses reinforcing social dynamics and observe whether it would yield different results than a simple reduction in the return to OUD rate. Although peer recovery could include social network effects naturally occurring without outside intervention, the evidence was not strong enough to include it in the base model. While self-help, mutual aid, and peer recovery support services are somewhat efficacious in supporting abstinence (*64*, *65*), the effect sizes that we tested were hypothetical. To facilitate comparison, we set the strength of this loop to achieve a 20% reduction in the return to OUD rate as of 2025.

Overdose harm reduction

SOURCE supports testing what might happen were the likelihood of experiencing overdose reduced, distinct from the likelihood of naloxone administration in the event of an overdose. Thus, we tested overdose harm reduction in two ways. The first was to reduce the risk of overdose, specifically involving illicitly manufactured fentanyl (Fent OD Risk in Table 1, which we also refer to as the fentanyl harm reduction strategy). The second was to reduce fatality in the event of an overdose by testing the effects of an increase in naloxone kit distribution beyond baseline assumed increases.

Our decision to test the risk of overdose involving illicitly manufactured fentanyl assumes that (i) fentanyl will continue to be present in the heroin supply, and increasingly so (*66*); (ii) people who use opioids, as well as other drugs, will be increasingly likely to use fentanyl, willingly or not (*67*); (iii) many people will decide to use the drugs they have purchased, even if they know or suspect fentanyl's presence (*28*); and (iv) fentanyl's presence in the drug supply and its inherent lethality are less amenable to sustainable intervention than changing the behavior of people who use fentanyl so that they are less likely to experience overdose in the first place (i.e., through drug-checking services and associated harm reduction behaviors).

We did not identify any national-level estimates of the availability of drug-checking services. We also did not identify the effect sizes of various other harm reduction strategies, such as titration, on reducing the likelihood of overdose. Therefore, the fentanyl harm reduction strategy is operationalized as a direct reduction in the excess overdose risk associated with fentanyl relative to heroin. In contrast, the naloxone kit distribution strategy is operationalized as an increase in the number of kits distributed, which was possible because we have historical estimates of naloxone distribution via harm reduction programs and prescription channels (table S2 and section S5D). In addition, prior research on the efficiency of distribution [e.g., (*22*)] supported estimating an efficiency parameter (section S6D).

SUPPLEMENTARY MATERIALS

Supplementary material for this article is available at https://science.org/doi/10.1126/sciadv.abm8147

View/request a protocol for this paper from *Bio-protocol*.

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