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# Modeling the evolution of the US opioid crisis for national policy development

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**The opioid crisis is a major public health challenge in the United States, killing about 70,000 people in 2020 alone. Long delays and feedbacks between policy actions and their effects on drug-use behavior create dynamic complexity, complicating policy decision-making. In 2017, the National Academies of Sciences, Engineering, and Medicine called for a quantitative systems model to help understand and address this complexity and guide policy decisions. Here, we present SOURCE (Simulation of Opioid Use, Response, Consequences, and Effects), a dynamic simulation model developed in response to that charge. SOURCE tracks the US population aged ≥12 y through the stages of prescription and illicit opioid (e.g., heroin, illicit fentanyl) misuse and use disorder, addiction treatment, remission, and overdose death. Using data spanning from 1999 to 2020, we highlight how risks of drug use initiation and overdose have evolved in response to essential endogenous feedback mechanisms, including: 1) social influence on drug use initiation and escalation among people who use opioids; 2) risk perception and response based on overdose mortality, influencing potential new initiates; and 3) capacity limits on treatment engagement; as well as other drivers, such as 4) supply-side changes in prescription opioid and heroin availability; and 5) the competing influences of illicit fentanyl and overdose death prevention efforts. Our estimates yield a more nuanced understanding of the historical trajectory of the crisis, providing a basis for projecting future scenarios and informing policy planning.**

prescription opioids | heroin | fentanyl | overdose mortality | simulation modeling

## Significance

The opioid crisis remains one of the greatest public health challenges in the United States. The crisis is complex, with long delays and feedbacks between policy actions and their effects, which creates a risk of unintended consequences and complicates policy decision-making. We present SOURCE (Simulation of Opioid Use, Response, Consequences, and Effects), an operationally detailed national-level model of the opioid crisis, intended to enhance understanding of the crisis and guide policy decisions. Drawing on multiple data sources, SOURCE replicates how risks of opioid misuse initiation and overdose have evolved over time in response to behavioral and other changes and suggests how those risks may evolve in the future, providing a basis for projecting and analyzing potential policy impacts and solutions.

The opioid crisis is a major public health problem in the United States, with half a million opioid overdose deaths in the last 20 y (1). Deaths have risen rapidly since 2014, with nearly 70,000 in 2020 alone (1), driven in part by the continuing spread of illicit fentanyl and other deadly synthetic opioids (2, 3). Millions of people now suffer from opioid use disorder, with severe health, social, and economic consequences.

There are many potential policy levers government actors can use to address the opioid crisis, such as regulating approvals of prescription opioid analgesics or treatments for addiction and overdose, scheduling controlled substances, using law enforcement, and shaping medical and insurance practices around pain and addiction treatment. However, the net effects of these policy levers on the crisis and public health more broadly are often unclear. The opioid crisis acts as a complex adaptive system, with dynamic and nonlinear interactions between prescription opioid misuse, heroin/fentanyl use, overdose mortality, and more (4). As a result, policy decisions based on past patterns of behavior may lead to unintended consequences as those patterns evolve over time (5, 6). In addition, data on the crisis are limited and lagged, with large uncertainties even in basic quantities and parameters, such as the numbers of people using heroin/fentanyl and the hazard rate of developing opioid use disorder (7).

Better policy planning requires grappling with these complexities and uncertainties, as well as attaining a deeper understanding of the underlying dynamics of the crisis. The National Academies of Sciences, Engineering, and Medicine in 2017 therefore recommended that the US Food and Drug Administration (FDA) develop an integrated decision-making framework for policy decisions, based on a system-level quantitative model of the opioid crisis (4).

Here, we present SOURCE (Simulation of Opioid Use, Response, Consequences, and Effects), a data-driven simulation model developed in response to these recommendations. SOURCE is the first product of a multitiered systems modeling initiative (8, 9). SOURCE improves on existing models of the opioid crisis in several ways.

First, SOURCE highlights the role of feedback mechanisms, such as social influence and risk perceptions (10, 11), in shaping the evolution of the opioid crisis. It combines these feedbacks with policy-relevant operational details on the impacts of synthetic

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The authors declare no competing interest.

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opioids, overdose prevention measures, and addiction treatment, to elucidate how and why patterns of risk have changed over time.

These risks (e.g., hazard rates of initiation or overdose) are not static, but change endogenously as the crisis evolves. Most existing national-level models of the opioid crisis (12–15) do not account for these changing hazards, or do so only exogenously, impeding their ability to make realistic projections of future trends. The one published model that incorporates key feedbacks driving the crisis (16) lacks SOURCE's level of operational and input detail. A few models examine policy-relevant aspects of the crisis in more detail, like treatment (17) or fatal overdose prevention (18), but do not integrate these details into the complexities of the broader opioid crisis. By incorporating these feedbacks and details, SOURCE's estimates shed new light not only on the historical trajectory of the crisis, but also trends and developments still unfolding, to better inform policy decisions and anticipate unintended consequences.

Finally, SOURCE is explicitly intended for use within a broader decision support process to inform FDA policy decisions. It thus provides a concrete example of how simulation models can introduce an integrative, systemic perspective to complement more traditional sources of evidence. In addition, SOURCE's systemic scope enables exploration of a range of potential policies, individually and in combination, that fall outside of any one agency's purview. As such, SOURCE could potentially be useful for identifying synergies—or unintended interference—and therefore could help better coordinate interagency efforts to address the opioid crisis.

**Model Specification.** SOURCE is a dynamic, continuous-time differential equation model that tracks the US noninstitutionalized opioid-using population aged 12+ y through several use states or compartments. These include: misuse of prescription opioids; use of heroin, possibly including illicitly manufactured fentanyl (IMF); opioid use disorder (OUD) associated with prescription opioids or heroin; treatment with medications for OUD (MOUD); and remission from OUD (see *SI Appendix*, section S1 for definitions and *SI Appendix*, section S2 for full model structure). People transition between states at time-varying rates, including initiation of prescription opioid or heroin misuse, development of OUD, engagement in treatment, remitting from or returning to OUD, and opioid overdose death.

SOURCE explicitly represents several dynamic factors that influence these transition rates (Fig. 1 and *SI Appendix*, section S2). Two key endogenous processes in the model are social influence, whereby existing users of a substance can increase initiation rates or accelerate use disorder development, and risk perception, whereby overdoses, especially overdose deaths, increase the perceived risk associated with prescription opioid or heroin use and discourage initiation (10, 11). The model also endogenously represents the dynamics of demand for and availability of prescription opioids for misuse, which influence initiation and use disorder development. We also represent several other influences exogenously, including supply-side changes (e.g., opioid prescribing practices, heroin prices, and IMF prevalence in heroin supply), naloxone availability, and MOUD capacity.

SOURCE tracks several public health outcomes, such as overdose mortality and OUD prevalence. It also allows for calculation and tracking of a range of other outcomes (*SI Appendix*, section S5), to better anticipate potential indirect effects of policies on the broader public health. While SOURCE contains substantial operational detail, important complexities—such as polysubstance use, mental health comorbidities, and undertreated pain—go beyond its present scope, as discussed in detail in *Limitations and Areas for Expansion*. It is critical to consider these limitations when using the model to inform potential policies.

## Results and Discussion

SOURCE closely replicates the historical trajectory of the opioid crisis from 1999 to 2020 (Fig. 2 and *SI Appendix*, section S5). Across all 15 time series used in model estimation, average $R^2$ for simulated values against data are 0.756, while mean absolute errors normalized by mean (MAEN) are 12.7%. For total overdose deaths, $R^2 = 0.969$ and MAEN = 8.3%. The model's ability to simultaneously replicate several different historical trajectories as a result of its endogenous structure gives confidence that this structure is a robust representation of the real system (19) (see also *Model Validation*, below).

**Shifting Risks Over Time.** SOURCE replicates the fluctuations over time of several key transitions between states (e.g., drug use initiation, overdose death) (Fig. 3). These fluctuations result from changes in the sizes of populations at risk for each transition as the overall scale of the crisis has grown, and changes in the per person-year hazard rates of transitions (i.e., transition probabilities/risks). Crucially, these risks or hazard rates are not static. But most existing models either represent them as constant over time, or vary them exogenously, without constraint, to fit historical data (12–14). SOURCE's feedback and operational structure constrains how hazard rates evolve

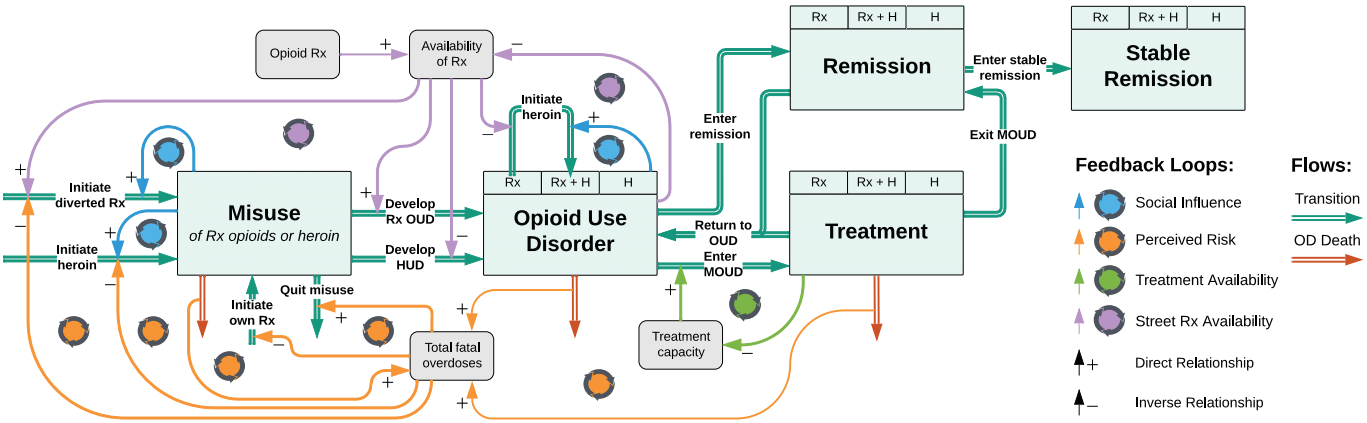


**Fig. 1.** Overview of key transitions and feedback effects in the model. See *SI Appendix*, section S2 for full structure.

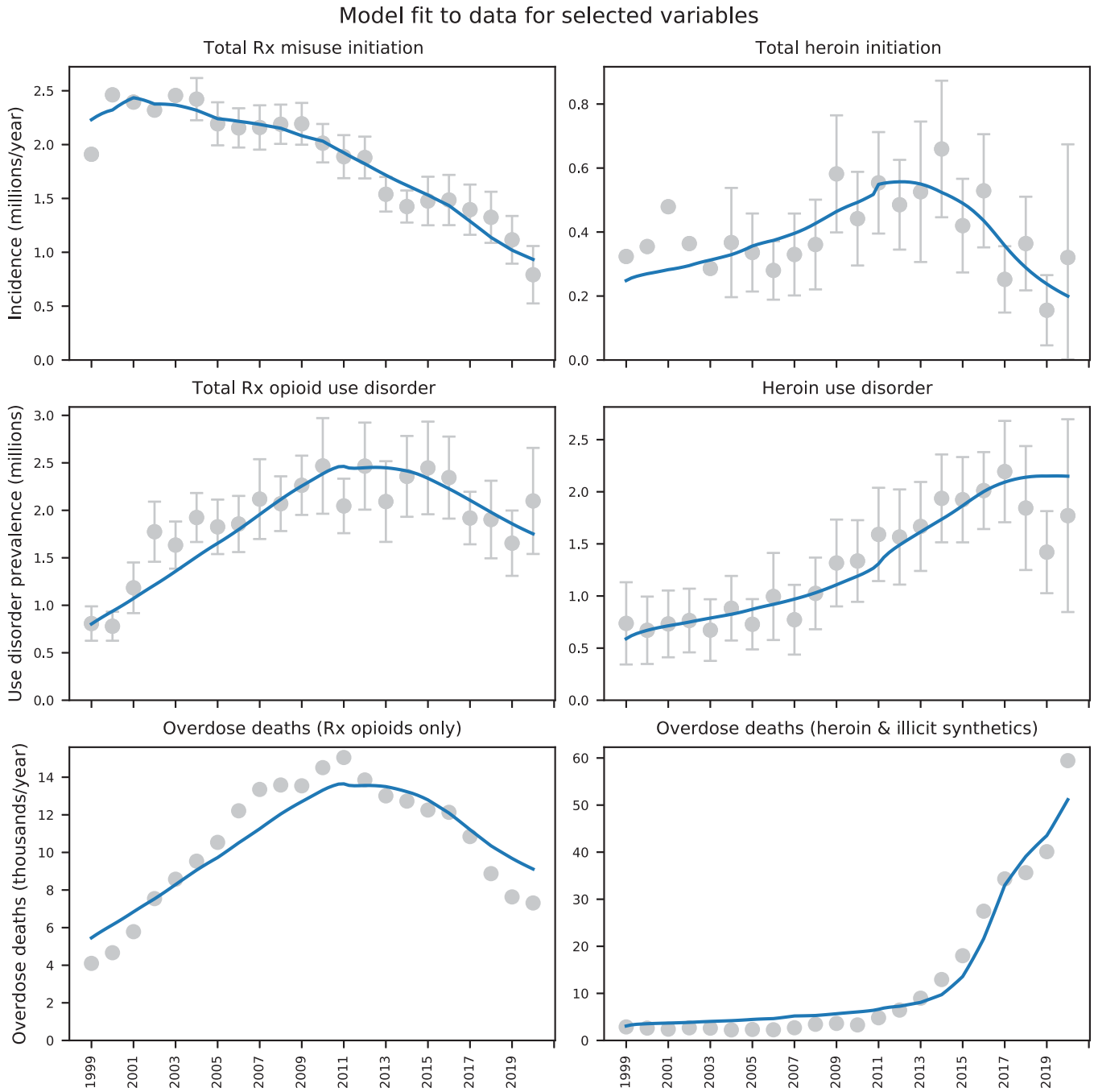


**Fig. 2.** Comparison of simulated model output (blue) to historical data (gray, 95% CIs where available) for selected time-series variables. Note that "heroin" implicitly includes IMF (*SI Appendix*, section S2). Rx overdose deaths exclude heroin and IMF. Note the different *y* axis scales in the *Left* and *Right* panels. CIs for 2020 are disproportionately wide due to smaller NSDUH sample sizes during the COVID-19 pandemic. Historical data sources: NSDUH (initiation, use disorder prevalence), NVSS (overdose deaths). Full results are in *SI Appendix*, section S5.

over time in relation to the state of the crisis, yielding an internally consistent understanding of shifting risk patterns.

For example, prescription opioid misuse initiation from medical use has declined over time (Fig. 3 *A*, *Top*). SOURCE attributes this decline primarily to a rapid fall in the per person-year hazard of initiation in the 2000s (Fig. 3 *A*, *Middle*), driven by a combination of growing perceived risk associated with opioid analgesic use and declining popularity (i.e., social influence). As a result, misuse initiation from medical use fell even as prescribing rates and the patient population receiving opioids (Fig. 3 *A*, *Bottom*) continued to increase until around 2011. After 2011, falling prescribing rates played a role in the continued decline of misuse initiation as well.

In contrast, SOURCE estimates that hazard rates of heroin initiation from prior prescription opioid use (Fig. 3 *B* and *C*) rose through 2013, driven primarily by processes of social influence, before eventually falling as growing overdose deaths increased the perceived risk of heroin use. As a result, heroin initiation continued to rise, even after the prevalence of prescription opioid misuse (Fig. 3*B*) and prescription OUD* (Fig. 3*C*) peaked and fell earlier, around 2009 to 2011.

*Specifically, *Diagnostic and Statistical Manual of Mental Disorders 5* substance use disorder associated with use of prescription opioid analgesics but not heroin (*SI Appendix*, section S3).

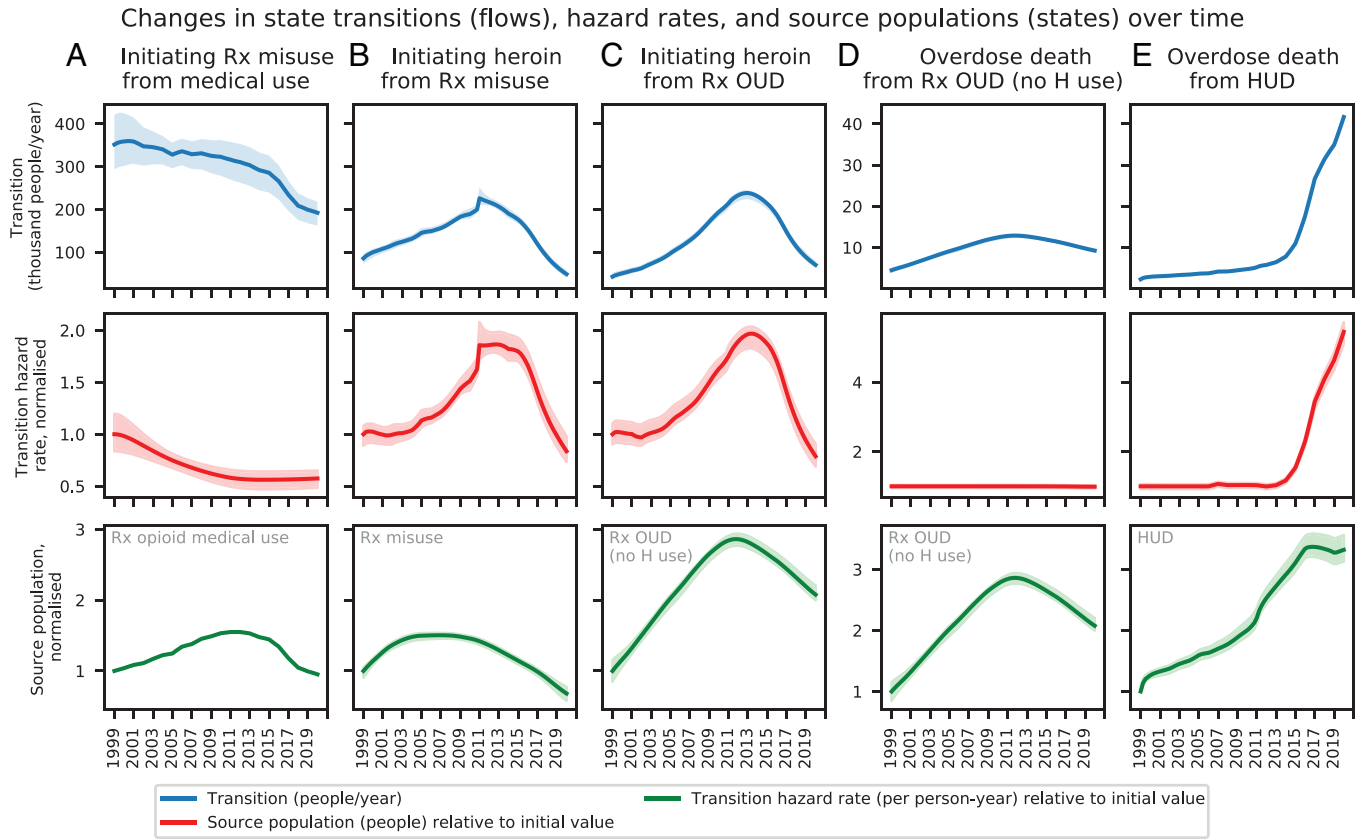


**Fig. 3.** (*A–E*) Changes in key transitions (flows) over time (*Top*, blue), distinguishing effects of changes in transition hazard rates (*Middle*, red), and source populations (*Bottom*, green). Bands are 95% CrIs. Source populations and hazard rates are normalized to their initial values. HUD, heroin use disorder; Rx, prescription opioid; Rx OUD, prescription opioid use disorder.

**Competing Influences of Naloxone and Fentanyl.** Risks and drivers of overdose mortality have evolved over time as well. Comparing fentanyl prevalence, naloxone distribution, and overdose mortality data, SOURCE estimates that overdose death hazard has remained relatively stable over time for people with prescription OUD who do not also use heroin/IMF (Fig. 3*D*), although this could change as fentanyl-contaminated counterfeit pills spread (20, 21). Among people who use heroin/IMF, however, overdose death hazard has shifted noticeably (Fig. 3*E*), due to two growing and competing influences starting around 2013 to 2015: increasing IMF presence in the heroin supply (2, 22), followed by numerous efforts to increase access to the lifesaving overdose reversal drug naloxone (23).

On balance, overdose death hazard has increased substantially since 2014, as naloxone distribution to laypersons is not keeping pace with the growing mortality risk from IMF. Among people with heroin use disorder, who are both more exposed to illicit synthetics and more likely to receive naloxone (24), SOURCE estimates the overdose death hazard in 2020 would be 18.0% (90% credible interval [CrI]: 11.8 to 23.1%) higher absent naloxone distribution efforts. In the absence of IMF, however, it would be 84.5% (90%CrI: 83.7 to 85.5%) lower.

Across all people who use opioids, we estimate 19,800 (90%CrI: 19,000 to 20,900) deaths averted due to layperson naloxone over the entire period from 1999 to 2020 (Fig. 4), mostly in the last few years when naloxone distribution has increased rapidly. This estimate of layperson naloxone's impact on overdose death hazard is broadly consistent with other existing estimates (25, 26).

We also estimate that in a counterfactual situation where IMF were completely absent, there would have been 59,000 (90%CrI: 55,000 to 65,000) fewer overdose deaths from 1999 to 2020 (Fig. 4). This estimate of the net impact of IMF on mortality is lower than the raw total of ∼228,000 synthetic opioid-involved overdose deaths reported in the National Vital Statistics System (NVSS) from 1999 to 2020 (27). There are

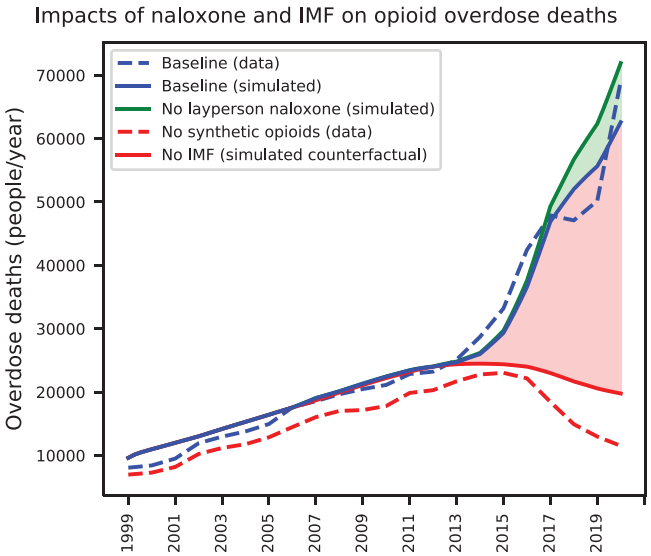


**Fig. 4.** Comparison of impact of naloxone distribution and IMF on opioid overdose mortality, showing total deaths averted due to layperson naloxone (green shading), and excess deaths due to IMF (red shading). Dashed lines are observed data. Simulated deaths absent IMF (red, solid) are higher than reported deaths not involving synthetic opioids (red, dashed): in earlier years, due to prescription fentanyl, and in later years, due to attenuated risk response in the counterfactual absence of IMF.

two reasons for this difference. First, the raw total includes deaths from prescription as well as illicit fentanyl; second, the raw data overestimate the true net mortality effect of IMF. SOURCE suggests that in reality, the fentanyl surge caused a rapid increase in the perceived risk associated with heroin use, which led to less heroin use by 2020 than there would have been otherwise. Absent the surge in mortality from IMF, an attenuated risk response would have meant higher ongoing initiation of heroin use in recent years, with attendant higher mortality. SOURCE's estimate of net IMF impact reflects this attenuation.

**Policy Analysis Process and Baseline Projections.** Based on its historical estimates, SOURCE can project potential future trajectories of the opioid crisis for use in policy analysis. Any such projections require some baseline assumptions about future trends in exogenous model inputs. SOURCE is designed to allow flexible testing of alternative baseline assumptions. For example, here we present three scenarios: an "exogenous trends continue" (ETC) scenario, where SOURCE's exogenous inputs are assumed to continue their present trends at decelerating rates, stabilizing at plausible levels by 2032, as well as two variants of this scenario with more "optimistic" and "pessimistic" outcomes (Table 1). The optimistic case assumes lower IMF prevalence, higher naloxone and MOUD availability, and greater reductions in opioid prescribing than the ETC case, while the pessimistic case is the reverse. These scenarios should not be considered precise forecasts nor analyses of any particular policy interventions, but instead plausible future trajectories for the evolving crisis.

In all three scenarios, we project continued declines in the initiation and prevalence of heroin/IMF use and use disorder (Fig. 5). These declines are driven primarily by the continued influences of risk response feedbacks (*SI Appendix*, section S6), which are already apparent in falling initiation rates, as outlined above.

Overdose deaths involving heroin/IMF continue to rise for a few years (slightly under ETC assumptions, or sharply under pessimistic assumptions), due primarily to the continued spread of IMF in the heroin supply. In all three scenarios, the trend eventually reverses and deaths start to decline as the prevalence of heroin/IMF use falls. Projections from other models, formal or implicit, which do not account for the dynamic changes in initiation may miss the impending peak and decline, instead projecting continued growth in opioid overdose mortality (e.g., refs. 12–14). Total projected deaths for 2020 to 2032 remain high across scenarios, however, ranging from 543,000 to 842,000 in the optimistic vs. pessimistic scenarios.

In addition, while ETC and optimistic scenarios show continued declines in prescription opioid misuse, OUD, and overdose, the pessimistic scenario shows a potential rebound by 2032. The rebound arises primarily from assumptions in the pessimistic scenario that the trend of reduced prescribing over the last decade weakens substantially, highlighting the importance of continued prudence in prescribing and patient management for maintaining the falling trends in prescription opioid misuse and associated outcomes.

These projections require several caveats. First, as with any model's forecasts, the validity of SOURCE's projections is vulnerable to unforeseeable exogenous shocks, which could disrupt short- or long-term patterns of opioid use in unexpected ways.

Second, projected trends in overdose mortality are sensitive to input assumptions about further IMF penetration in the illicit drug supply. IMF's presence in the supply of both illicit opioids and other drugs is expected to increase, but there is great uncertainty around just how much, how quickly, and where (28). Greater IMF penetration could result in a substantially larger and longer-lasting rise in overdose mortality before it peaks (*SI Appendix*, section S6), though the overall pattern of an eventual peak and decline persists regardless of IMF penetration assumptions.

Third, SOURCE does not account for the possibility of increasing contamination of stimulant supplies (e.g., cocaine, methamphetamine) with IMF (29) and consequent impacts on synthetic opioid-involved overdoses (30, 31). Growing IMF contamination of stimulants could expose large additional groups of people who use stimulants (but not opioids) to the threat of fentanyl, driving continued growth in opioid overdose mortality and potentially neutralizing or even reversing the projected declines. Given fentanyl's outsize role in determining the future of the crisis, understanding the dynamics underlying the

**Table 1. Exogenous input time series showing 2020 data values and assumptions for ETC, optimistic, and pessimistic cases**

| | | | 2032 Assumed value[†] | | |
|---|---|---|---|---|---|
| Exogenous input* | Source | 2020 value | ETC | Optimistic | Pessimistic |
| Fentanyl penetration | NFLIS | 56.2% | 80.7% | 69.8% | 99.5% |
| Naloxone kits distributed | IQVIA, various* | 2.30 million | 3.60 million | 4.22 million | 2.94 million |
| Heroin price index (1999 = 1) | UNODC, STRIDE | 0.49 | 0.49 | 0.58 | 0.40 |
| Buprenorphine-waivered treatment providers | Various* | 94,200 | 178,300 | 224,900 | 134,500 |
| Methadone maintenance treatment capacity[‡] | N-SSATS | 360,000 | 646,000 | 765,000 | 528,000 |
| Vivitrol treatment capacity[‡] | IQVIA | 32,900 | 45,800 | 52,700 | 39,900 |
| Patients receiving opioid analgesic prescription | IQVIA | 41.3 million | 28.4 million | 22.3 million | 35.1 million |
| Prescriptions per person | IQVIA | 3.49 | 3.31 | 3.01 | 3.50 |
| Average days per prescription | IQVIA | 24.4 | 26.8 | 24.0 | 28.0 |
| Average opioid MME per day | IQVIA | 31.3 | 23.6 | 20.2 | 28.0 |
| ADF fraction of prescribed opioids (percent of MME) | IQVIA | 4.9% | 3.1% | 3.1% | 3.1% |

MME, morphine milligram equivalent; NFLIS, National Forensic Laboratory Information System; N-SSATS, National Survey of Substance Abuse Treatment Services; STRIDE, System to Retrieve Information on Drug Evidence; UNODC, United Nations Office on Drugs and Crime.

*See *SI Appendix*, section S3 for details on input data derivations.

†Broadly, the optimistic scenario assumes stronger trends (1.5× ETC) in naloxone distribution, MOUD treatment capacity, and downward-trending aspects of prescribing, and weaker trends (0.5× ETC) in fentanyl penetration and upward-trending aspects of prescribing; vice-versa for the pessimistic scenario.

‡MMT/Vivitrol capacity are calculated based on treatment utilization data from listed sources (*SI Appendix*, section S3).

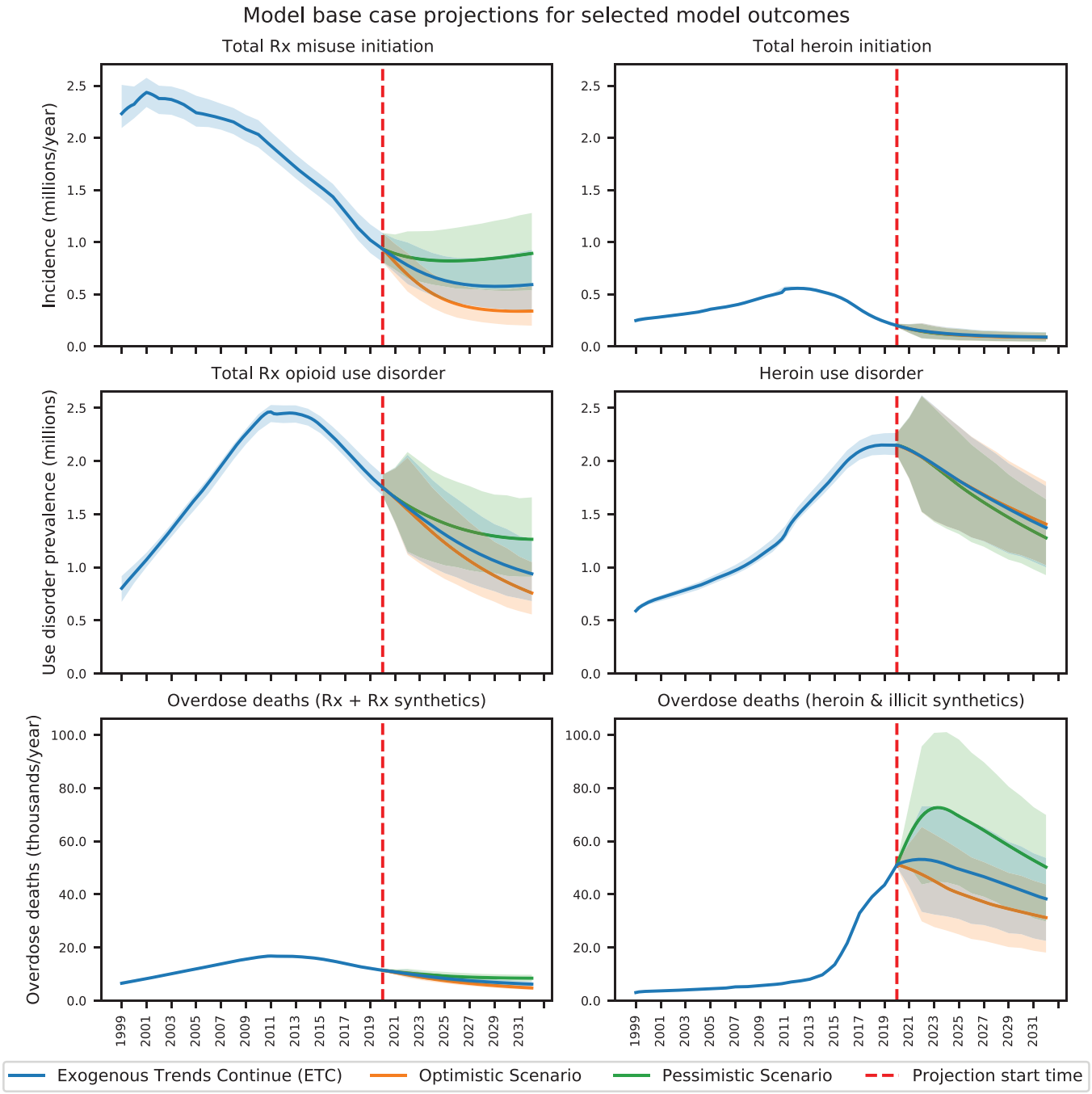


**Fig. 5.** Simulated historical and projected trajectories for selected variables, under three sets of assumptions: ETC (blue), optimistic (orange), and pessimistic (green). Bands are 95% CrIs for estimated underlying values (historical portion, before 2020) and for projected reported data (after 2020); CrIs for projected reported values account for measurement noise, and hence are wider. Full results are in *SI Appendix*, section S5.

spread of IMF and identifying measures to curb it (or at least better monitor its presence, especially as regards the supply of nonopioid illicit drugs) should be policy priorities.

SOURCE is currently undergoing beta-testing at the FDA, using its projections to help inform the analysis of potential policy impacts and identify key uncertainties. The model can also provide a focal point for problem-structuring discussions with subject-matter experts and policymakers. Additional work is also under way to use SOURCE to analyze the outcomes of various intervention strategies. In addition, we have made SOURCE publicly available for use or adaptation by other stakeholders, such as nonprofits, researchers, and other federal, state, or local agencies.

**Limitations and Areas for Expansion.** SOURCE has several limitations. First, SOURCE does not address the growing and intertwined challenges of co-occurring stimulant use (32, 33), counterfeit pharmaceuticals (20, 21), and their interaction with IMF, which could drive a significant fraction of drug overdose mortality in coming years (30). It also does not address in detail the interaction of mental health comorbidities and other social determinants of health with substance use, nor does it account for untreated or undertreated pain. These topics are all major targets for potential further research.

Second, SOURCE is a national-level model that aggregates potentially important geographic and demographic heterogeneities, as well as specifics of prescribing practices. In part, this

aggregation is due to data limitations; given more detailed data, the model could be parametrized for specific geographies (e.g., states) or demographics. Aggregation also provides computational tractability, allowing more extensive analysis and testing at the cost of some precision (34). Nonetheless, care must be taken to consider potentially important but hidden heterogeneities (3, 35), particularly in the geography of fentanyl exposure (28). Additional work is presently under way to incorporate demographic attributes into the model and quantify disparities in outcomes.

Third, the model necessarily relies on imperfect data (7). Much data around drug use is incomplete or suffers sampling bias. True longitudinal national-level data are not available. National-level data sources also do not report data on the growing problem of fentanyl (e.g., use, use disorder, overdose, treatment), preventing us from representing its effects other than on overdose and mortality. We have attempted to address some of these limitations (*SI Appendix*, section S3), including correcting for established underreporting of heroin use (36), and sensitivity testing can clarify the implications of uncertainties. Nevertheless, these shortcomings limit any model's quantitative precision.

Fourth, SOURCE currently lacks a unified outcome measure, such as quality-adjusted life years or monetary cost, that would allow more direct comparison of tradeoffs. Adding measures to enable use of SOURCE for cost-effectiveness analysis is the subject of ongoing FDA-funded work, which will facilitate future use of SOURCE for additional policy analysis.

## Materials and Methods

This section summarizes model estimation, data sources, and testing; full details and documentation are in *SI Appendix*, and all relevant files are publicly available at https://github.com/FDA/SOURCE.

**Data Sources.** SOURCE includes 95 parameters, such as baseline hazard rates of state transitions (e.g., overdose, drug use initiation, relapse) and feedback effect sensitivities (see *SI Appendix*, section S5 for full list). Of these, 15 are derived from literature sources, 22 calculated from data, and 5 from expert input. Where possible, we synthesized multiple existing studies to derive parameter values, to address heterogeneity or nonrepresentativeness of study populations (*SI Appendix*, section S3). Tests of model sensitivity to parametric assumptions are presented in *SI Appendix*, section S6.

We formally estimated the remaining 53 parameters using a panel of national-level data from 1999 to 2020, drawn from both publicly available and proprietary nationally representative datasets, primarily the National Survey on Drug Use and Health (NSDUH), NVSS, and IQVIA (*SI Appendix*, Table S8). The panel includes annual initiation and prevalence of prescription opioid and heroin misuse and use disorder, patients receiving MOUD, and overdose mortality, as well as prescribing, treatment capacity, naloxone distribution, heroin prices, and fentanyl prevalence.

**Model Estimation.** The model uses 11 time series from the data panel as exogenous inputs, which correspond closely to real-world phenomena whose drivers are outside the model's scope (Table 1).

We used the remainder of the data panel for formal model estimation, detailed in *SI Appendix*, section S4. Estimation is by maximum likelihood (37), using a Gaussian likelihood function to identify the set of parameter values that maximizes the likelihood of observing historical data given historical inputs and those parameter values.

We quantified uncertainties in parameter estimates using a Markov chain Monte Carlo method intended for exploring high-dimensional parameter spaces (38). From the credible region of parameter space thus quantified, we generated a subsample of 5,000 plausible alternative model specifications for use in sensitivity analysis, and as the basis for credible intervals on model projections.

**Model Validation.** SOURCE's role in policy decision support demands high confidence in its structure, quantification, and projections. To establish confidence, we developed SOURCE's structure through an iterative process of expert consultation, detailed in *SI Appendix*, section S3. In addition, SOURCE has been subject to multiple reviews by third-party consultants contracted by the FDA (2019 to 2020) to evaluate the model. Reviewers assessed the model against sound modeling principles and best practices, checking model behavior and reviewing parametric and structural assumptions.

We also validated our estimation framework using a synthetic data analysis and an out-of-sample prediction test. For the synthetic data analysis, we generated 20 artificial datasets statistically similar to historical data and attempted to recover "true" parameter values using our estimation procedure. The absolute error between estimated and true parameter values was considerably smaller than the estimated uncertainty, and estimated credible intervals were close to their theoretically expected accuracies (*SI Appendix*, section S4). For the out-of-sample test, we estimated the model using data only up to 2012, and used those estimates to predict observed values in the holdout dataset from 2012 to 2020. Of holdout data points, 72% fell within the predicted 95% CrIs, and the model successfully projected trend changes in several variables (*SI Appendix*, section S4). Full results of these analyses, along with additional sensitivity analyses and robustness tests, are presented in *SI Appendix*, section S6.

Finally, we recognize that both the opioid crisis itself, and our knowledge of it, continue to evolve; we will continue to update and revise SOURCE and its scope as more data emerge.

**Data Availability.** All data, code, and materials are available in *SI Appendix* and the online repository (version associated with this article archived at https://zenodo.org/record/6544836 and most up-to-date version maintained at https://github.com/FDA/SOURCE). All other study data are included in the main text and *SI Appendix*.

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