The Opioid Crisis: A Contextual Framework and Call for Systems Science Research

Mohammad S. Jalali, PhD[a,b,*]; Michael Botticelli, MEd[c]; Rachael C. Hwang[d]; Howard K. Koh, MD, MPH [e,f]; R. Kathryn McHugh, PhD[a,g]

[a] Harvard Medical School, Harvard University, Boston, MA
[b] Institute for Technology Assessment, Massachusetts General Hospital, Boston, MA
[c] Grayken Center for Addiction, Boston Medical Center, Boston, MA
[d] MIT Sloan School of Management, Boston, MA
[e] T.H. Chan School of Public Health, Harvard University, Boston, MA
[f] Harvard Kennedy School, Harvard University, Cambridge, MA
[g] Division of Alcohol and Drug Abuse, McLean Hospital, Belmont, MA

*** Corresponding author:**
Mohammad S. Jalali, PhD
101 Merrimac St, Suite 1010, Room 1032, Boston, MA 02114
msjalali@mgh.harvard.edu | (617) 724-3738

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Policy Points:

- Opioid misuse has gained the attention of health researchers, professionals, and politicians, and many call for a broad public health approach; however, the full breadth of such a strategy has not yet been articulated.
- We present a social-ecological framework as the first step to represent the complexity of the opioid epidemic at a broad level, conceptualizing several domains of risk factors associated with opioid misuse.
- Similar to how a stream of systems science research helped policy development in infectious diseases (e.g., HIV/AIDS) and obesity, more systems science research is needed in opioids.

Context: The prevalence of opioid use and misuse has provoked a staggering number of deaths over the past two and a half decades. Much attention has focused on individual risks according to various characteristics and experiences. However, broader social and contextual domains are also essential contributors to the opioid crisis, as interpersonal relationships and the conditions of the community and society people live in. Despite efforts to tackle the issue, the rates of opioid misuse, non-fatal overdose, and overdose death remain high. Many call for a broad public health approach, but articulation of what such a strategy could entail has not been fully realized. Broader systems policies, especially those that emphasize prevention, could more effectively intervene in this crisis.

Methods: In order to improve the awareness surrounding opioid misuse, we developed a social-ecological framework that helps conceptualize the multivariable risk factors of opioid misuse and facilitates reviewing them in individual, interpersonal, communal, and societal levels.

Findings: Our framework illustrates the multi-layer complexity of the opioid crisis that more completely captures the crisis as a multidimensional issue requiring a broader and integrated approach to prevention and treatment.

Conclusions: Future research can elucidate the interconnections among the risk factors as well as leverage systems science tools (e.g., simulation modeling) to uncover the complexities of the crisis, and help evaluate, analyze, and forecast the effectiveness of ongoing and new policy interventions. We explain and call for the need for more systems science approaches in opioid research.

Keywords: opioids, opioid use disorder, systems science

Introduction

The alarming rise in opioid misuse over the past two and a half decades has resulted in a public health crisis, characterized most prominently by a dramatic increase in drug overdose deaths. In 2017, about 12 million Americans misused opioids,[1] and more than 47,000 people died of opioid overdose.[2] This fatal overdose rate reflects an increase of 345% between 2001 and 2016,[3] with particularly steep annual increases in overdose fatalities since 2015. The growing opioid misuse issue was recognized as a national public health emergency by the U.S. Department of Health and Human Services (HHS) in 2017.

Over the last several years, opioid misuse gained the attention of scholars, researchers, health professionals, and politicians.[4] Many call for a broad public health approach but the full breadth of such a strategy has not yet been articulated or realized. While various interventions have been implemented over time, they have generally been insufficient to slow the growth of non-fatal and fatal overdoses at a national level.[5] Interventions that only target a single aspect of the issue, such as restricting opioid supply, will not be sufficient to ameliorate the opioid epidemic. This is further complicated by the rapidly evolving nature of the epidemic. For example, the widespread availability of fentanyl and fentanyl analogues beginning around 2013 has resulted in steep escalation of overdose death rates, even as other public health indicators (e.g., prescription opioid misuse) have begun to improve. The complexity of the crisis is represented by the multiple spheres of influence derived from individual factors, interpersonal relationships, community, and societal influences indicating the necessity of a broader, and a more integrated approach that includes prevention, treatment, and overdose rescue interventions in addition to supply reduction strategies.

The understanding that the opioid crisis is not solely a behavioral and/or a biological problem, but is also a problem influenced by many moving parts in the broader social-ecological system indicates the importance of systems science tools to help assess the interconnections of the risk factors. Despite the increased attention to opioids, there are still two major shortcomings in the literature: 1) a lack of understanding of the complexity of the system—e.g., the interconnections of the risk factors at different levels; and 2) a tremendous lack of evidence to inform policy-making. Moreover, data sources are often not integrated across agencies or across federal, state, and local levels.

In this paper, we present a social-ecological framework as the first step to conceptualize the complexity of the opioid epidemic. This framework can help inform the design of impactful interventions to curb the opioid crisis. We present our framework and provide a brief overview of the literature informing its components. We discuss how systems science tools can help fill these gaps and integrate those data sources to better understand the big picture and enhance policy analysis. Building upon other recent systems-based models that have been presented,[6-9] we take a wide-ranging view of the multi-level complex factors that may play a role in the opioid crisis. We explain and call for the need for more systems science approaches in opioid research.

Social-ecological Framework

Our social-ecological framework, illustrated in Figure 1, depicts the major risk factors for opioid misuse on four main levels: the individual, interpersonal, communal, and societal—see the supplementary document for our use of the term “framework”. Each of these levels must be acknowledged to develop multifaceted and effective interventions to mitigate the opioid crisis.

In the following sections, we provide a brief overview of how these levels of factors contribute to the opioid epidemic.

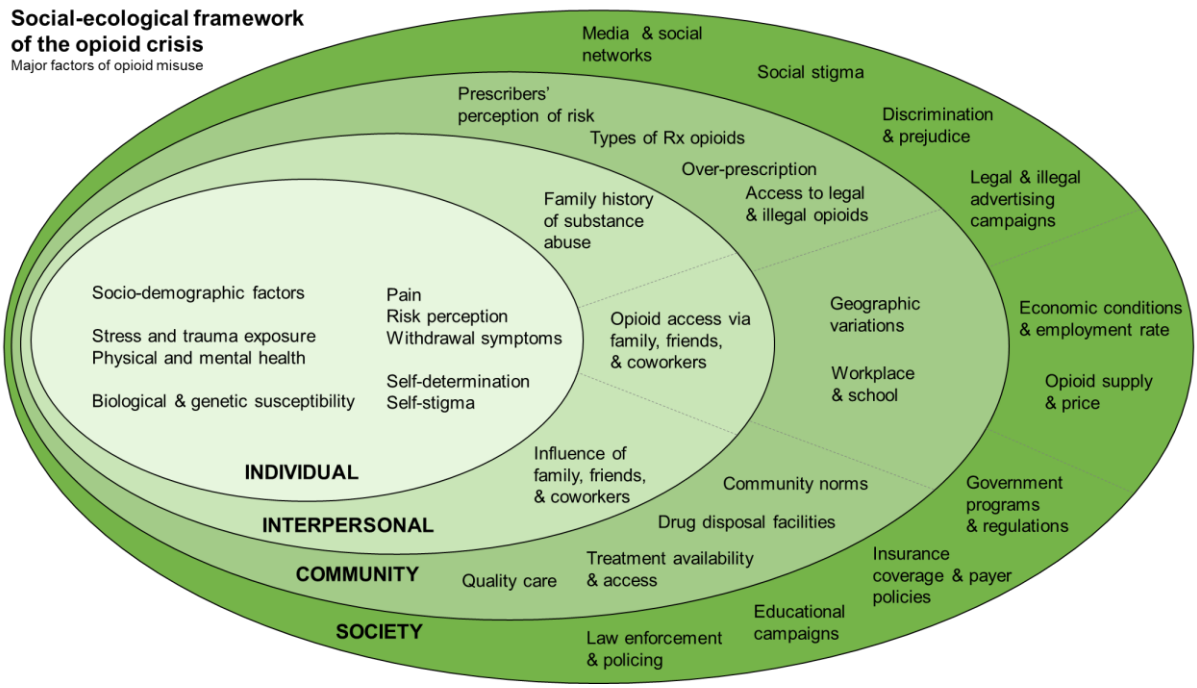

Figure 1: Social-ecological framework of the opioid crisis

Socio-demographic status consists of age, race, gender, ethnicity, education, income, and unemployment factors.

Individual Level

Individual-level factors in opioid misuse and opioid use disorder (OUD) span sociodemographic, health and mental health, biological, and psychosocial domains. Individual factors can influence every aspect of the spectrum of opioid use and misuse, including the likelihood of exposure to opioids, initiation of opioid misuse, the development and maintenance of OUD, entry to and engagement in treatment, and relapse following an attempt to quit. These factors are complex, often interact, and in some instances, can be both a cause and consequence of opioid misuse (e.g., financial strain).

Many sociodemographic factors interact with opioid misuse, with implications for identifying at-risk populations. Opioid misuse peaks in early adulthood (approximately 18-25 years).[10] Early initiation of opioid misuse is a significant risk factor for the development of an OUD,[11] and thus adolescence and young adulthood are key risk periods for opioid misuse. Gender also can play a role in risk for opioid misuse. For example, women are more likely than men to receive an opioid prescription,[12,13] and sex differences in the pharmacological effects of opioids have been demonstrated.[14] Critically, opioids are known teratogens and untreated OUD presents risks to both neonatal and maternal outcomes.[15]

Race also plays a complex role in the opioid epidemic. People identified as non-Hispanic white are more likely to receive an opioid prescription, increasing the risk of exposure via this route.[16] Disparities in health care for pain often leave pain untreated or undertreated in racial and ethnic minorities.[17] Although the opioid epidemic initially predominantly affected non-Hispanic whites,[18] opioid overdose is rapidly increasing among racial minorities.[19] Race also impacts access to treatment; access to effective medication for OUD is lower in communities with higher African American and Hispanic populations.[20,21]

A wide array of health and mental health factors may increase the likelihood of risk for misuse, some of which overlap with those that increase the likelihood of a prescription

(e.g., pain). Pain is a core element of the opioid crisis, and the majority of people seeking treatment for prescription OUD report first using opioids for pain with a legitimate prescription.[22] Similarly, mental health factors are a significant contributor to opioid misuse. The majority of people with OUD also suffer from a mood or anxiety disorder,[23] and psychiatric symptoms are associated with incident risk for prescription opioid misuse.[24] Similarly, history of other substance misuse and other substance use disorders is a significant risk factor for opioid misuse; it is the most robust predictor of opioid misuse in people with chronic pain.[25]

A number of biological factors and genetic susceptibility can also predispose individuals to develop OUD. In addition to biological vulnerability to substance use disorders in general,[26,27] factors that influence the effects of opioids include genetic factors that alter the opioid receptors in the brain.[28,29] Once physiological tolerance is developed to an opioid, decreases in dose or removal of the medication will result in withdrawal symptoms.[30] Although these symptoms are not fatal, they are extremely unpleasant and a significant reason for continued opioid use and relapse in people with OUD.[31] Indeed, over time, the primary reason for use tends to shift to avoiding/relieving withdrawal more than managing pain or feeling good.[22]

Interpersonal Level

Family, friends, and coworkers significantly shape the beliefs, attitudes, and behaviors of individuals to influence the likelihood of individuals' initiation and misuse of substances.[32-34] Family history of substance use disorder can influence opioid misuse through both genetic and environmental factors. People who have a family member with OUD are 10 times more vulnerable to misuse and overdose on the drug themselves, and youth witnesses of family member overdose are more prone to overdose themselves.[35,36] Individuals with a family history of opioid use are at a higher risk of suffering from symptoms of opioid dependence and becoming severely dependent.[37] This may be particularly important for women, for whom the risk of opioid misuse is higher when a spouse or partner misuses opioids.[38] Opioid misuse is also influenced by the accessibility to opioids from family, friends, and/or coworkers. Approximately, 70% of people who report nonmedical opioid use reportedly obtained opioids from family members or close friends.[39,40] Coworkers can also supply drugs since about 69% of people who misuse opioids are employed and 10% to 12% report drug use during work hours.[41,42]

Interpersonal relationships influence the actions of individuals to use opioids and seek treatment. Parental disapproval of drugs discourages substance use, and families are often the first to detect drug misuse because of their awareness of substance history.[34,43] Family support of recovery can increase the likelihood of receiving treatment by threefold.[39,44] The emotional support from social supports can increase medication adherence and motivate patients during their treatment sessions.[43,45]

Communal Level

The third level of our framework considers the communal settings and their contributions to opioid-related risks.[46] The community and the immediate context in which individuals live affect their daily behaviors in significant ways. Variables such as geographic conditions, treatment accessibility, medication disposal services, workplace environment, prescribers' perception of risk, over-prescription or under-treatment of pain, types of prescription opioid

formulations available, community norms, and access to legal and illegal opioids are major risk factors that can perpetuate opioid misuse.

Between 2006 and 2017, approximately 224 million opioid prescriptions were filled annually in the US, which is almost enough to distribute across the entire US population.[47] Over-prescription of opioids has been influenced by several interacting factors. Oftentimes, physicians' insufficient pain management training and knowledge on opioid misuse risk contribute to their inability to safely prescribe opioids, implement and interpret risk assessments, detect addiction, and facilitate discussions with patients.[48-50] Furthermore, prescribers who overestimate the benefits and underestimate the danger of opioids are likely to contribute to over-prescription by providing months' worth of medication, when only a few days may be needed for pain management.[51,52] The institution of guidelines (e.g., the Centers for Disease Control and Prevention *Guideline for Prescribing Opioids for Chronic Pain)* and other interventions to improving prescribing practices has resulted in decreases in opioid prescribing,[53] with reductions occurring since 2010.[47]

Over-prescription was also influenced by pharmaceutical marketing campaigns that falsely marketed opioids as non-addictive and "create[d] value" for doctors by offering monetary compensations.[54] Doctors who refused to prescribe opioids to patients were labeled as 'opiophobic'.[55] These incentives include sponsored meals, speaking fees, travel expenses, and education.[56] Although only 7% of opioid prescribing physicians received gifts from drug companies, they were more likely to prescribe opioids to their patients than doctors who did not benefit from the incentive.[56] Increases in prescriptions reflected unintended consequences of advocacy for the improved treatment of acute and chronic pain in the 1990s, which resulted in regulatory changes requiring assessment of pain as the "fifth vital sign."

Formulations of opioids also play a role in opioid misuse. Standard opioid pills can be crushed to attain a more rapid effect via routes of administration such as intranasal or intravenous.[58] Despite the lack of sufficient supporting evidence for the efficacy of abuse-deterrent drugs in preventing misuse, the Food and Drug Administration (FDA) has supported the development of such types of prescription opioids to address the growth in opioid-related abuse and deaths.[59,60] The misconception of the abuse-deterrent opioids as a panacea dangerously marks the issue as a pharmaceutical problem, rather than a complex one integrated by biological, psychological, and social challenges.[58]

The illicit market is another significant source of misused opioids. Heroin is cheap and widely available in most regions in the US. Furthermore, there is a large online opioid market, which enables customers to purchase unregulated opioids from the web.[61,62] The increased availability of highly potent synthetic opioids, such as fentanyl and carfentanil has contributed to the dramatic increase in rates of overdose deaths since 2015.[19]

There has been substantial geographical variation in opioids misuse and overdose, which may be attributable to a range of factors.[63] Nonmetropolitan areas are known to have higher rates of opioid prescribing,[64] perhaps because the rural population disproportionately consists of older adults and people employed in physically demanding jobs who may be particularly susceptible to pain-related conditions;[65-68] overdose deaths are more prevalent in nonmetropolitan areas relative to urban areas.[69]

Workplaces and schools are also important settings where individuals spend significant time. Some careers have particularly high rates of opioid misuse, and are typically those characterized by demanding physical labor and/or easy access to opioids; individuals involved with construction occupations suffer from the highest rate of opioid overdose.[70]

Schools are also an important setting, given that adolescence is a significant risk period and diversion of medication is common in this group.[71]

Community norms with respect to alcohol, tobacco, and drug use also can impact the likelihood of initiation of substance misuse.[63,72] Finally, drug disposal and collection sites can potentially deter misuse and discourage opioid diversion amongst patients' friends and family by restricting the available supply in households and communities.[34]

Similarly, the availability and access to treatment are crucial for both the adequate management of health and mental health conditions that increase risks for opioid misuse (e.g., pain, psychiatric disorders) and for the effective treatment of OUD.[73] Access to care, and to evidence-based care, varies across regions. The availability of high-quality care is also impacted by society factors (see below). OUD is associated with high rates of relapse, and the type of care received has substantial implications for outcomes.[74,75]

Societal Level

The major risk factors of opioid misuse are shaped by the larger social context, which encompass opioid supply and demand, government regulations, economic conditions and unemployment rates, elements of the media, social stigma, discrimination and prejudice, advertising campaigns, educational campaigns, and law enforcement.

The market economy of opioids is altered by the fluctuations in the drug's supply and demand. A tremendous increase in the supply and availability of opioids arose from the over-prescription, diversion, and redistribution of the pills to family, friends, and/or coworkers. This was exacerbated by pharmaceutical companies' extensive legal advertising tactics, which can lower consumers' perception of the risks of opioids and increase their knowledge on prescription drug availability.[76,77] Over time, the epidemic intensified as illicit opioids flooded the market and heroin became inexpensive[73,78]—heroin is only a third of its price in the 1990s and remains cheaper than opioid prescriptions.[79] Indeed, over 80% of people who initiate heroin use first started opioid use with prescription opioids;[80] cost is one of the most commonly reported reasons for this transition.[81] Opioid supply can be managed through reduced prescribing or increased use of misuse-deterrent formulations, but these efforts can be challenged by unintended, short-term negative consequences. In particular, decreased availability of prescription opioid analgesics can lead to increases in the use of illicitly produced opioids, such as heroin.[58]

Government programs and regulations related to opioids may take many forms, such as drug scheduling through the Drug Enforcement Agency, regulation of opioid prescribing practices (e.g., use of Prescription Drug Monitoring Programs),[82] and Medicare/Medicaid regulations. Government regulations also have implications for treatment availability, as federal and state governments regulate accreditation and licensing requirements as well as elements of training and service provision. For example, the Drug Addiction Treatment Act of 2000 requires that prescribers complete additional training to prescribe or dispense buprenorphine. Likewise, government regulations require that methadone is only dispensed in licensed opioid treatment programs and cannot be used for the treatment of OUD in primary care, unlike in other countries.

The number of people who have health insurance coverage varies by state and has implications for access to OUD treatment. Medicaid expansion has played a significant role in access to medication for OUD; states that elected to expand Medicaid as part of the Affordable Care Act had a more than four-fold higher increase in prescribing of effective medications for OUD (specifically buprenorphine and naltrexone) relative to non-expansion

states.[83] In addition to their contributions of the opioid supply, payer policies also impact access to treatment for pain, psychiatric illness, and OUD. For example, prior authorization for buprenorphine prescribing has been presented as a strategy for reducing diversion or other adverse events; however, this can also present a significant barrier to care.[84]

Social stigma, the misconception of substance misuse as a byproduct of weak willpower and moral corruption, is a significant barrier to seeking help for opioid misuse.[3,39,85] Likewise, cultural and social beliefs communication via media and social media can be either harmful (e.g., influencing an increase in substance use)[86-88] or protective (e.g., increase public awareness about opioids and their potential harms).[89]

The rise in "deaths of despair" (typically referring to overdose and suicide fatalities) between 1999 and 2015 has been linked to poor economic conditions.[73,90] During macroeconomic slumps, every percentage point increase in unemployment saw a 3.6% rise in opioid death rates and emergency visits. The fall in the employment rate resulted in lower life satisfaction and higher drug use among the population.[91,92] However, the macroeconomic variables should be further scrutinized since a recent working paper from the National Bureau of Economic Research concluded with contradictory findings that only 10% of the rise in opioid-related deaths could be explained by recessions.[93]

Law enforcement and the criminal justice systems are other significant components of the response to the opioid crisis. Law enforcement (along with other emergency responder groups) has been increasingly involved in overdose-rescue efforts. Some departments have expanded these efforts to include linkage to treatment and other supports. Law enforcement also plays a role in policing of the illicit opioid supply.[94] Finally, opioids are controlled substances that carry significant criminal penalties for possession and distribution. Substance use disorders are common among incarcerated people, and release from prison is associated with a significantly heightened risk for fatal overdose.[95] Racial and ethnic minorities are disproportionately affected by the criminalization of substance use, rather than a public health approach. Also, those recently released from prison were more likely to die from overdose than those who did not face the law enforcement.[96,97]

Need for Systems Science Approaches to the Opioid Crisis

As the opioid crisis is a multi-faceted issue, analyzing the interconnections among the fragments of the systems can inform policy development and public health decisions. The most common approach to research is that the large system is broken down into its components and they are studied individually. Also critical, and often missing, is identifying the explanatory pathways and potential interactions among the components of the system.

Furthermore, the complexity of this crisis requires consideration of unintended consequences of any policy actions. However, in complex systems, even experts fail to fully understand unintended consequences of their decisions particularly over the long-term;[98-102] consequently, proposed solutions may introduce new problems or fail to produce lasting results. For example, efforts to reduce access to prescription opioids will likely not substantively help people who have already developed an OUD and may have unintended consequences for people suffered from pain conditions. Such efforts may—at least in the short-term—have an impact on the prevalence of illicit opioid use. This issue is often attributable to observing and analyzing a fragment of the system (only seeing the top of the iceberg) or lack of understanding the interconnections among system components. The complexity of these trade-offs, which may result in different consequences for the short- and long-term, requires tools that can simultaneously consider these interrelationships over time.

Systems science is a broad and interdisciplinary class of analytical and simulation modeling approaches to uncover the complexities and dynamic behavior of a system. Using systems science allows us to understand the complex connections between the behavior of the system (i.e., the number of overdose death that we can see and measure) and its structure (i.e., the invisible web of interconnections among fragments of Figure 1). It also provides a way to conduct trade-off analysis, especially when many policy decisions require balancing competing values (e.g., decreasing opioid supply and adequately managing pain). System science provides methods to distinguish and understand the multiple interactions embedded in the crisis. Also, systems approach encourages the adoption of collaborative partnerships and the desertion of the traditionalist top-down and command-centric management methods to fill the knowledge gaps of the opioid crisis. Next, we discuss simulation modeling as the main systems science tool to achieve these goals and call for more simulation modeling research on opioid misuse.

Simulation Modeling and Analysis

Systems science tools can be employed to develop models for simulating and analyzing the behavior of the system. They can help analyze the actual impact of the policies and identify potential unexpected consequences. In particular, health outcomes and cost-effectiveness of alternative policies for prevention and treatment can be measured. Given that public health resources are always limited, these models are especially helpful for resource allocation: how to allocate resources to prevention or treatment strategies that optimize outcomes and are cost-effective.

Also, although data is currently available to some limited extent (e.g., the numbers of dispensed prescriptions and fatal overdoses reported by the Centers for Disease Control and Prevention), there is lack of data for essential mechanisms (e.g., transitions across the trajectory of OUD development). Through calibrating a model to available data, unknown variables of the model can be estimated which helps understand the behavior of previously unknown mechanisms.

Another benefit of simulation models is to conduct sensitivity analysis: changing a variable in the model (e.g., prescription rate for high dose opioids) and monitoring the outcome of interest over time (e.g., the number of overdoses). This helps not only to estimate the short- and long-term effects of policy options, but also to analyze the tradeoffs of benefits and risks and to pinpoint leverage points for most effective policies. Through the sensitivity analysis, the application of simulation models goes beyond the analysis of alternative strategies (policy evaluation) and can suggest opportunities for developing new policies (policy design). For instance, this type of analysis can address questions such as: How would supporting (or restricting) policies for abuse-deterrent opioids impact opioid misuse and the transition dynamics to heroin? How would new policies on ultra-high dose opioids impact the trajectories of developing OUD and the trends of overdose death? How would the effects of these policies vary across patients in different age groups and genders?

The use of systems science also goes beyond prediction to uncover the complexities of the system and understand the root causes of the problems. For example, some behavioral questions to analyze could be: How would social contagion (e.g., through connections with people who use or misuse opioids) impact the exposure of opioid-naïve individuals to opioids? How would the changes in the rates of overdose affect physicians' perception of opioid safety, and how would their perception impact their prescribing behavior and, accordingly, the number of overdoses in the long-term (closing the loop)? Mechanisms to answer these and many other social questions are often absent in statistical and

epidemiological studies due to the lack of quantitative data. In the complete absence of such data, qualitative systems methods (e.g., causal loop diagrams and subsystem diagrams) can enhance our intuitions and overcome the impediments to learning the complexity of the system—see[103] for more discussion. In fact, system science tools have assisted learning in many complex social problems that key variables cannot be readily quantified or optimized.[104,105] If limited data are available with high uncertainties, which is a common case in opioid research, simulation modeling can inform policy development through sensitivity analysis, as discussed above.

Overall, simulation modeling helps answer "what-if" policy questions and expand and refine the mental models of policy-makers. Also, from the perspective of policy-makers, no one solution can solve this public health problem (e.g., short-term harm reduction interventions for individuals with OUD may not be fully effective without follow-up for the treatment of OUD). To address this concern, simulation modeling can be employed to provide insights on what combinations of interventions, policies, and resource allocation strategies can best achieve the desired goals. Hence, simulation models can replace the short-term, narrow, and static understanding of the problem with a long-run, broad, and flexible outlook fit to address the public health crisis. See Figure S1 in the supplementary document for the general steps for developing a simulation model.

Moving Forward to Address the Opioid Crisis

Systems science and simulation modeling have been widely used in public health;[106-108] however, their applications have been very limited in opioid research. There have recently been initial modeling-based studies on opioids focusing on educational interventions,[6] tamper-resistant formulations and informal sharing of opioids,[7] interventions targeting prescription opioid misuse,[8] and health outcomes of several prevention and treatment policies.[9] However, these models have limitations in their scope, so there remains a need for more models to unveil the complexities of the crisis. In fact, no one simulation model for opioids can answer all research questions. In other areas of research, such as obesity,[110] infectious diseases,[109] and HIV/AIDS,[111,112], a stream of systems science research helped policy development. For instance, NIH's Models of Infectious Disease Agent Study program, started in 2004, created a network of over 20 universities to develop infectious disease epidemic models, which has resulted in impactful strategies to prevent infectious diseases or minimize their impact. There are also over 200 simulation-modeling reports in the literature informing HIV treatment decisions.[113] A similar investment in systems science research is needed to inform policy development in opioids.

Particularly, simulation models that are grounded in the literature and data, reported with a clear presentation of all assumptions, presented with detailed sensitivity analyses on assumptions, and developed with a minimum number of assumptions are needed—a model based on a mountain of assumptions would be more harmful than helpful. Hence, future research should employ system science tools and study the dynamic interconnections of the major factors in opioid misuse to develop effective interventions and policies.

Conclusion

The primary goal of this article was to emphasize that the opioid crisis is a multi-faceted and ever-evolving issue, which requires consideration of numerous interacting factors in developing interventions and evaluating their effectiveness. These factors intersect with several disparate stakeholder groups, including healthcare providers, government and

regulatory agencies, insurers, and law enforcement and criminal justice, among others. The development of effective opioid prevention and treatment interventions requires a broad analysis of the factors that arise from multiple contexts (individual, interpersonal, community, and society). We conceptualized this complex system using the social-ecological framework presented in Figure 1.

The dynamic environment in which the opioid crisis is embedded indicates the importance of utilizing systems science research (e.g., qualitative and quantitative simulation tools) that provides information on system diagnoses and performance changes of the crisis. Using these tools, researchers can develop models to measure and analyze the interconnections among the risk factors to better understand the complexities of the crisis. Critically, these models can also be used to conduct trade-off analysis and evaluate the effectiveness of ongoing (and new) policy efforts to provide evidence to inform where to focus efforts and allocate limited resources. Overall, these tools effectively examine and can help experts comprehend the underlying complexities and interconnections of variables to better establish effective prevention and treatment solutions.

While the interest in the application of systems science in public health and health policy has been increasingly growing, application to opioid research has been slow. The shortage of effective models for addressing the opioid crisis indicates an urgent need for systems science tools, and we encourage researchers and experts in systems science and opioids to develop and utilize systems science tools to address the crisis, which will require intensive interdisciplinary research and more attention and support from state and federal agencies.

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Supplementary document for

The Opioid Crisis: A Contextual Framework and Call for Systems Science Research

Our use of the term "framework"

We presented our conceptualization of the opioid crisis and called it a 'framework', not a 'model.' It should be noted that a 'model' is a tool used to generate hypotheses, explain findings, and assess whether hypothesized relationships can be confirmed or disconfirmed with empirical data. Accordingly, we do not intend to call our framework a model, as a model that includes everything may be comprehensive, but it may also be unhelpful for modeling analyses. Instead, we called it a contextual framework and used it to illustrate the complexity of the crisis and stimulate discussions for future research and model-based studies.

Simulation modeling and analysis tools

Several tools are utilized to incorporate into decision-making processes of policy intervention designs. These tools include but are not limited to causal loop diagrams and stock and flow diagrams. Causal loop diagrams help conceptualize the complexity and the interconnections between different elements. This qualitative method is widely used in the public health domain (e.g., see [114-116]) and incorporates positive and negative feedback loops to illustrate the different causal aspects of the problem that perpetuate, reinforce, and balance the system. Stock and flow diagrams and system archetypes are quantitative models which capture the movement and behavior of the elements within the system (e.g., see [117-120] for applications in public health and health policy). See [121] for more information about systems science tools used in public health.

Steps of the modeling process

Figure S1 presents the steps of the modeling process. This process is not a linear sequence of steps and is iterative. One needs to start from step one (problem articulation) and follow the cycle but the results of any step can increase the understanding of prior steps; accordingly, any earlier step can be revised. See [108] for more information about each step and guidelines to develop a proper model.

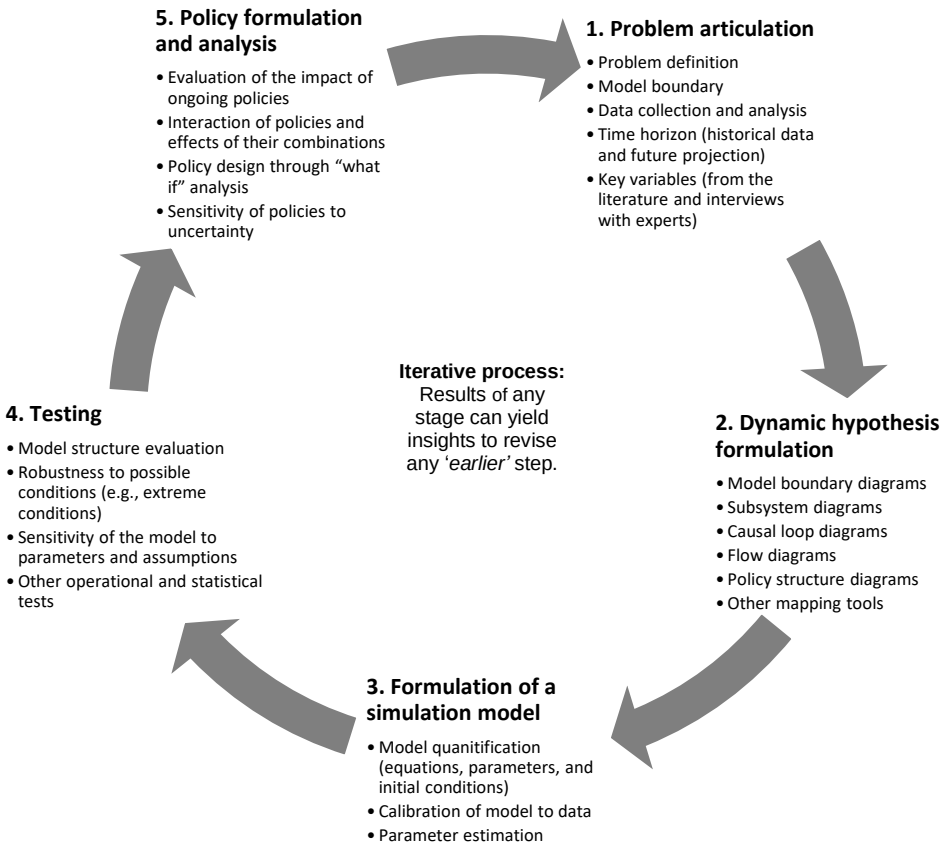

Figure S1: Modeling process (adapted from [108])