8-2024

Opioid Overdose Epidemic Modeling

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A Dissertation
Presented to
the Graduate School of
Clemson University

In Partial Fulfillment
of the Requirements for the Degree
Doctor of Philosophy
Industrial Engineering

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by
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August 2024

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Abstract

The opioid overdose crisis in the United States has led to thousands of lost lives and thousands more people struggling with opioid dependence. Disease modeling allows researchers to examine the course that the disease may take and to investigate policies to determine the effects they may have. Disease models can be used to model non-communicable diseases and have been used to study opioid use disorder. Many types of disease models exist with their own inherent benefits and drawbacks.

In this dissertation, we provide a scoping review of the disease models that have been used to study the opioid overdose epidemic. The scoping review identified 85 articles that developed at least one disease model of the opioid overdose epidemic. The review showed that most disease models are compartmental models (78), and a majority of the models only modeled heroin (49). Fifty-seven were more theoretical and only forty-four used data to inform their modeling. There were three major gaps identified during the scoping review. Most models used country-wide data or no data, only considered heroin use, and were primarily one model type.

Based on the gaps identified in the scoping review, we developed an agent-based model (ABM) of the opioid overdose epidemic. The model addresses gaps in previous research by including using multiple types of opioids, having a criminal justice system influence, modeling different opioid potencies, and including individual characteristics. The ABM has two agent types: human agents, who can misuse opioids, and opioid agents, who supply opioids. The model was run over a five-year time frame and was calibrated to historical data. The agent-based model produced results that are similar to historical averages in overdoses and overdose deaths as well as people who use opioids.

We used the agent-based model to test possible interventions and supply changes. Increasing amounts of fentanyl in drugs has led to higher overdoses and overdose deaths. We chose to model an environment with increasing fentanyl presence, including in other opioids. Due to the increased

fentanyl presence, we modeled increased distribution of naloxone, an opioid overdose reversal drug. Distributing naloxone allows bystanders to reverse overdoses, reducing the fatality rate. Results from the model show that the increased proliferation of fentanyl increased overdose deaths while increased naloxone distribution reduced overdose deaths. When both scenarios were simulated, high levels of naloxone mitigated many of the overdose deaths caused by the higher levels of fentanyl.

Dedication

I dedicate this dissertation to my loving family and friends. Your unwavering encouragement and support have been my strength throughout this journey.

Acknowledgments

I am deeply grateful to my advisor, Dr. Mary E. Kurz, for her invaluable advice, patience, and guidance throughout this journey. Her unwavering support and willingness to help, especially during the challenging period of changing dissertation topics, have been pivotal to the completion of this work.

I would also like to extend my sincere thanks to my committee members, Dr. Thomas C. Sharkey, Dr. Bryan Lee Miller, and Dr. Kevin M. Taaffe. Their expertise, insightful feedback, and encouragement have significantly enriched this dissertation. A special mention is owed to Dr. Sharkey and Dr. Miller who met with me regularly and greatly improved this research.

A special thank you goes to my family and friends, whose support and understanding have been a source of strength and motivation. Their belief in me has been instrumental in reaching this milestone.

Lastly, I am grateful to all those who have contributed to this dissertation in various ways. Your assistance and encouragement have not gone unnoticed, and I am deeply appreciative of your support.

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Chapter 1

Background and Motivation

1.1 Opioid Overdose Epidemic

In 2022, 81,806 people died in the United States due to opioid overdoses [166]. The number of fatal overdoses has increased significantly since 2000 as shown in Figure 1.1. While males comprise a higher number of the overdose deaths, the rate for females is increasing as well. There was a plateau in overdose deaths from 2017 to 2019, but this was followed by a large increase in 2020 and another increase in 2021.

The current opioid overdose epidemic in the United States began in the 1990s with many contributing factors. In the 1980s, the World Health Organization discussed acute pain and pain caused by cancer that was often not adequately treated which led to multiple publications about pain's under-treatment [97]. To address the under-treatment, Dr. James Campbell proposed that pain should be considered as the fifth vital sign in 1995, and health organizations began to adopt this suggestion [148]. These two developments are believed to have increased the number of prescriptions written for opioids since doctors were focused on reducing and treating patients' pain [19], and opioids are strong analgesics that can manage discomfort [140].

Additionally in 1995, Oxycontin was introduced to the market as a safe, long-acting pain reliever that was unlikely to cause addiction [78]. While the active ingredient in Oxycontin, oxycodone, has been used for nearly a century, the time-release capsule to deliver pain relief for twelve hours was novel. Oxycontin was heavily marketed as less addictive, but the time-release capsule could be crushed allowing a stronger dose to be released initially which could lead to addiction.

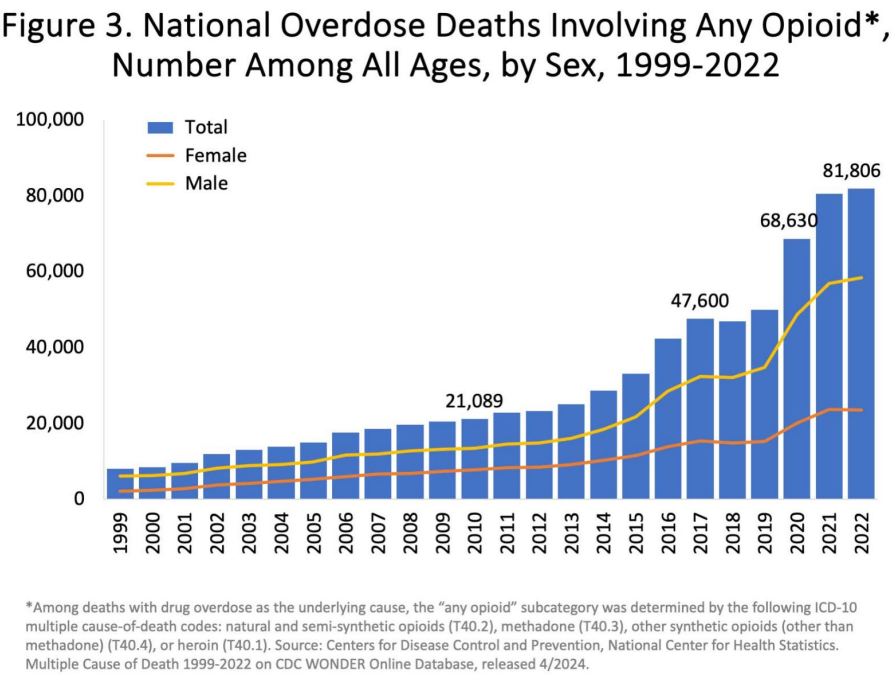

Figure 1.1: Opioid Overdose Deaths in the United States [166]

Addiction can include both psychological dependence from habits and repeated behavior as well as physical dependence that elicits physical withdrawal symptoms [182].

Pharmaceutical companies contributed to the opioid overdose crisis through their marketing [97]. The manufacturer of Oxycontin, Purdue Pharma, gave funding to the American Pain Society, which developed guidelines for opioid use in both chronic and acute pain [27]. The company also aggressively marketed Oxycontin even after realizing that crushing the pills would release more than half of the oxycodone immediately [78]. Purdue Pharma spent $200 million promoting Oxycontin leading to a 10-fold increase in the number of prescriptions of the drug written in 2002 and has been accused of misleading physicians and downplaying the risk of addiction to Oxycontin [199].

The number of opioid prescriptions written increased more than 300% from 2000 to 2010 [199]. The increase in the amount of opioid prescriptions written also coincided with a fourfold increase in overdose deaths from 1999 to 2008 [97]. Since 2011, the rate of prescription opioid use has decreased gradually, but this reduction was balanced by a sharp increase in heroin use [196]. While illegal, heroin is easier to find and less expensive than illicit prescription opioid pills [48].

Synthetic opioids, such as fentanyl, are another complicating factor in the opioid epidemic [187]. Synthetic opioids were originally developed by pharmaceutical companies working to discover

a non-addictive pain reliever, but most were not approved for human use [189]. These drugs can be purchased on the internet and are often combined with other opioids or recreational drugs [189]. Synthetic opioids are typically highly potent causing overdose deaths to occur quickly [88]. In addition, these opioids are often sold to users who believe they are purchasing heroin or similar drugs [127]. From 2013 to 2019, the overdose death rate involving synthetic opioids increased 1,040% [139]. Figure 1.2 shows the drug overdose deaths by drug type which shows the sharp increase in synthetic opioid deaths.

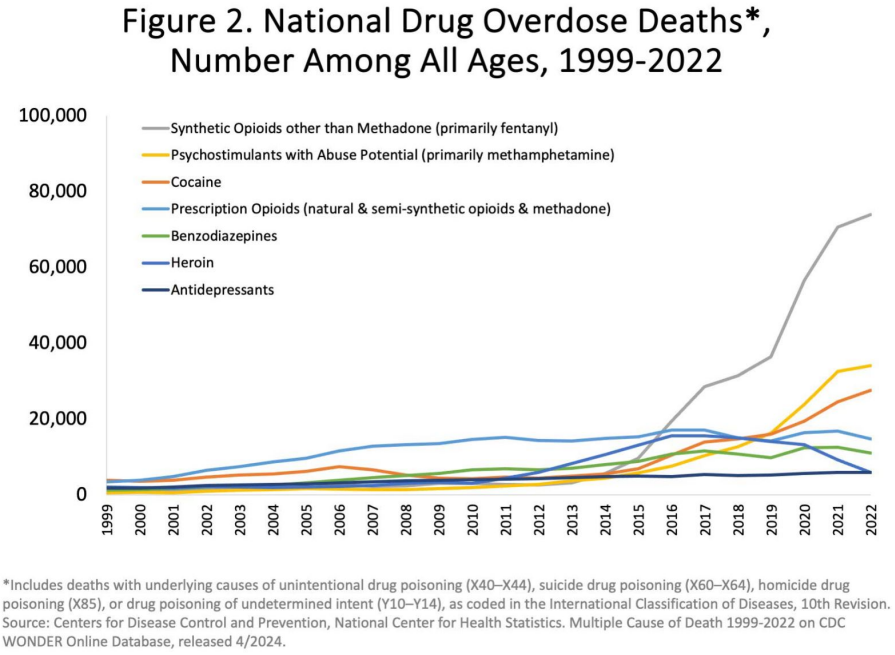

Figure 1.2: Drug Overdose Deaths in the United States [166]

Novel prescription drug policies have been enacted around the country due to the severity of the opioid overdose epidemic with the aim of reducing opioid misuse. One epidemic-related policy that focuses on reducing opioid prescription rates and ensuring that opioid prescriptions are not diverted is the prescription drug monitoring program (PDMP) [67]. Additional drug interventions work to reduce opioid users' harm; these programs include tamper-resistant pill formulations, medication-assisted treatment (MAT), and naloxone distribution [159]. While new policies have been enacted, thousands of people in the United States continue to die each year [166].

Because of the loss of life, decision makers are continuing to develop policies that they hope will be beneficial. Evaluating the effectiveness of interventions and the interactions between them

can help decision makers allocate limited resources, such as funds, space, or staffing. One tool that can aid in evaluating policies is disease modeling.

1.2 Disease Modeling

Disease modeling allows reality to be simplified and helps researchers understand how different inputs affect outcomes [213]. One of the first and most well known disease models is the susceptible-infected-removed (SIR) model developed by Kermack and McKendrick in 1927 [184]. In this model, individuals fall into one of three groups. Healthy individuals are susceptible (S) to the disease, infected individuals (I) can pass the disease to susceptible individuals, and infected individuals are removed (R) and unable to become infected again after the disease has run its course [106]. The original SIR model was formulated using differential equations and straightforward assumptions about a disease's nature [106].

The SIR model has been expanded to include other scenarios. The susceptible-infected-susceptible (SIS) model can be used when recovering from the infection does not provide immunity, while the susceptible-infected-recovered-susceptible (SIRS) model functions when individuals gain temporary immunity before becoming susceptible again [15]. Other models contain latent periods where a person is exposed to the disease but not yet infected, including the susceptible-exposed-infected-removed (SEIR), susceptible-exposed-infected-susceptible (SEIS), and susceptible-exposed-infected-recovered-susceptible (SEIRS) models [15].

Techniques for disease modeling beyond differential equations include decision trees, Markov models, discrete event simulation, and agent-based modeling (ABM) [34]. The model techniques differ on the interaction level of individuals in the system, whether population averages or individual values are used, and whether the model is considered "memory-less" [34]. Each of the models can provide useful information depending on the disease being considered, the data available, and the questions that need to be answered [34].

While the initial disease models were focused on communicable diseases, noncommunicable diseases (NCDs) accounted for over 60% of the world's deaths in 2010 [213]. NCDs are caused by factors that are influenced by an individual's behavior, genetics, and interactions with other individuals or the environment and include diseases such as cancer, heart disease, and substance abuse [155]. Epidemiological model structures can be applied to NCDs and used to estimate the

benefits of interventions [34]. These models can help researchers and policymakers understand how changes in risk factors or behaviors will affect health outcomes [213].

1.2.1 Modeling the Opioid Overdose Epidemic

One of the first models of the opioid overdose epidemic was created in 2007 [19]. An SIR model was adapted into an S-U_1-U_2 model where S represents the susceptible population, U_1 represents drug users not in treatment, and U_2 represents drug users in treatment [217]. Heroin is the only drug modeled, and the population is considered to be homogeneous [217]. This model has been modified to become more robust and is further discussed in Chapter 2.

In 2017, prescription opioids were modeled following the previous model's structure. This model contains four user populations [19]:

- S (susceptible) - individuals who are susceptible to opioid addiction and are not currently using opioids. They may be prescribed opioids at rate α.
- P (prescribed users) - individuals who are currently prescribed opioids and are not addicted to them. Individuals become addicted to their prescriptions at rate γ and finish their prescriptions without addiction with rate ϵ.
- A (addicted) - individuals who are addicted to opioids regardless of whether their drugs are prescribed. Individuals can enter the addicted state due to prescription-induced addiction γ, interactions with addicted users or drug dealers β_A, or the presence of opioid patients who may have unsecured or extra drugs β_P. Addicted individuals enter treatment at rate ζ
- R (rehabilitation/treatment) - individuals who are in treatment for their addiction. Individuals fall back into addiction at rate σ and return to being susceptible at rate δ.

Four continuous-time differential equations govern the model.

$$\dot{S} = -\alpha S - \beta_A SA - \beta_P SP + \epsilon P + \delta R + \mu(P + R) + \mu^* A \tag{1.1}$$

$$\dot{P} = \alpha S - (\epsilon + \gamma + \mu)P \tag{1.2}$$

$$\dot{A} = \gamma P + \sigma R + \beta_A SA - \beta_P SP - (\zeta + \mu^*)A \tag{1.3}$$

$$\dot{R} = \zeta A - (\delta + \sigma + \mu)R \tag{1.4}$$

Additionally, the summation of S, P, A, and R is set to 1 so that each letter represents the mean expected population for their class. Importantly, the model considers different routes by which a person can become addicted. However, neither heroin nor synthetic opioids are incorporated into the model.

System dynamics (SD) modeling, which also uses differential equations, has been used to study the opioid overdose epidemic. An SD model was built to simulate the use of prescription opioids with a primary focus on opioid overdose fatalities [204]. The model contained five primary feedback loops concerning populations of opioid users and the supply and demand of opioids. The model was developed in conversation with a panel of experts and contained 49 parameters. Key results suggest that tamper-resistant opioid pills are likely to reduce overdose deaths if there is not an increase in prescription rate.

Researchers have developed a dynamic compartmental model to evaluate policies in the opioid overdose epidemic which considered overdose deaths and quality-adjusted life years as metrics of success [171]. A dynamic compartmental model allowed populations to flow between predetermined compartments or states based on set mathematical equations. This model did account for the fact that policies that reduce access to prescription opioids will cause some users to switch to heroin, increasing heroin-related deaths. Due to the uncertainty of parameter values related to the opioid overdose epidemic, ten base case models with differing parameter values were used. By comparing the results from the base cases, estimates were drawn based on expected values. The results from this model indicated that any single policy is unlikely to substantially reduce deaths over the course of a decade.

Another approach to modeling the opioid overdose epidemic has been to use economic theory. Researchers created a model informed by economic theory where the goal of the each individual was to maximize their expected lifetime utility [196]. Lifetime utility was determined using an equation and considered the price of the drug, importance of pain relief, amount of pain experienced, and perceived susceptibility to addiction. Based on the expected utility, individuals chose whether to use opioids. Results from the model show that communities can become stuck in higher levels of opioid use if perceived susceptibility to addiction is low in model initiation even after the belief is adjusted as the model runs [196].

Examinations of opioid overdose epidemic models have been conducted. In one scoping review, fourteen papers were identified, and the modeling techniques in the research included system

dynamics simulation modeling, mathematical modeling, conceptual modeling, and agent-based modeling [187]. Major findings from the models suggest that preventing opioid initiation has a stronger effect on health outcomes than treatment strategies and that interventions can be both beneficial and harmful. None of the studies considered the role that age or geographic location may play in health outcomes.

Researchers are beginning to study the combined effects of policies, since these interventions can cause conflicting outcomes. For instance, reducing the number of opioid prescriptions written will reduce the amount of opioids pills available but may cause people with substance use disorders to switch to cheaper and more readily available heroin [48]. Models have been developed to review the combined impact of interventions [95] and to project reductions in overdose fatalities [17].

1.3 Agent-Based Modeling and its Application to Modeling the Opioid Overdose Epidemic

Agent-based modeling is another modeling technique that can be adapted to disease modeling. Agent-based models are especially useful simulation tools when [31]:

- Behavior is nonlinear.
- Individual behavior is not memory-less.
- Agents interact heterogeneously.
- Using population averages negatively affects the system.

These characteristics make agent-based modeling well-suited to simulating the complexity of the opioid overdose epidemic. The behavior of human systems as a whole likely cannot be determined solely by understanding the behavior of the system's individual parts [182]. Applying this simulation method allows researchers to view the ways that individuals' behavior and feedback loops affect the system [155].

Agent-based modeling is historically linked to complex adaptive systems (CAS) [129]. Complex systems are comprised of individual agents whose interactions can yield unpredictable behavior [155]. Properties of CAS include aggregation, non-linearity, and diversity [129]. ABM's lineage can be traced to Von Neumann's cellular automata, Conway's Game of Life, and Holland's genetic

algorithms [198]. Agent-based modeling is flexible [31] and can capture population-level phenomena that differs from what would be expected on an individual level [198]. They have become more popular due to the increase of available computational power [198].

ABMs are comprised of agents, agent relationships, and the environment [155]. Agents have individual attributes and behaviors [155], and each model has a set of rules that define the way elements in the model interact [136]. These rules include how agents update their internal states, interact with other agents, and move in and interact with the environment [136]. Rules can contain nonlinear components and feedback loops [136]. Average outcomes can be estimated by running a model simulation multiple times and observing the outliers [136]. Multiple modeling software systems exist for ABMs, such as SWARM, Repast, and NetLogo [182].

When defining agent-based models of diseases, four major taxonomy components have been defined: disease, society, transportation (movement), and environment [94]. When creating a model, a specific or general disease can be programmed. Likewise, a specific city or region may need to be modeled while in other situations a generic society is preferable. The agents' movement and the environment setting can also vary based on the question being asked; transportation and movement can be programmed to occur generally or be modeled using an environment built with maps and populated with location data from cell phones or other sources. In some cases, the taxonomy components are related. For example, location data or maps cannot be used without considering a specific society.

Agent-based models have been used to model both communicable and noncommunicable diseases. An ABM examined the spread of an H1N1 outbreak in Mexico using cell phone records to model the agents' movements [74]. Similarly, another study of the spread of a contagious disease modeled agents' movement by integrating a geographic information system [168]. An increasing number of ABMs are being developed to model NCDs because the relationships between individuals and feedback over time can affect disease progression [198]. ABMs can be used to gain insight into risky behaviors and potential interventions to reduce those behaviors [198]. These models also allow researchers to explore unintended consequences of interventions [198].

An ABM was used to model heroin use in Australia by incorporating dealers, people who use heroin, overdoses, and the surrounding environment [182]. This model has been expanded to differentiate between user and non-user drug dealers and people who use drugs who are addicted as opposed to recreational users . Police and treatment workers were also included in the model [182].

A different ABM was used to estimate the effect of naloxone distribution to bystanders and was built using data collected from a qualitative study [103]. For the qualitative portion of the study, interviews were conducted with substance use treatment providers and people with high risk for opioid overdose. The ABM considered social contact, opioid use, overdose, administration of naloxone, confidence administering naloxone, and confidence calling emergency response. Overall, the study showed that community-based naloxone distribution lowered the opioid overdose death rate in the simulation.

1.4 Gaps and Contributions

In this section we discuss the gaps in the literature and the research questions that will be addressed with this study. Next, we discuss the contributions of this dissertation.

1.4.1 Gaps

Because the opioid overdose crisis has taken many lives, researchers and policymakers are working to identify and address issues. However, little research exists to examine disease models of the opioid overdose crisis. Understanding the models that have already been developed can help researchers decide where to focus their attention. Some opioid overdose epidemic models have been discussed in this chapter, and we plan to extend this research.

1.4.2 Research Questions

1. What types of models have been developed to simulate the opioid overdose crisis? Based on the models that have been developed, is there a model that we could develop to fill any gaps?

2. What insights can be gained from using an agent-based model to evaluate the current opioid overdose crisis?

3. What further insights can be gained by using an agent-based model to explore changes in the environment on interventions that are implemented?

1.4.3 Contributions

We present a scoping review of the disease models of the opioid overdose crisis. The scoping review discusses the types of models used, the opioids that are modeled, the data sources used, and the model calibration and validation. The review also allowed us to identify gaps in the literature.

Based on the gaps identified in the scoping review, we chose to develop an agent-based model of the opioid overdose crisis. Because most models were found to be compartmental models, an agent-based model that focused on individual characteristics addresses a research gap. The ABM incorporates phenomenon that are acknowledged in the literature but are rarely seen in models such as "bad", or highly potent, batches of opioids and the effect of being released from jail or prison on overdose rates. The model also includes different types of opioids, addressing another gap. The ABM is focused on a specific area, South Carolina, and is parameterized to its population.

Using the ABM, we tested possible interventions and opioid supply scenarios to examine overdose and misuse outcomes. We specifically considered scenarios with increased fentanyl in the opioid supply and increased distribution of naloxone. This contribution shows the uses of an ABM in providing guidance for policymakers.

1.5 Dissertation Organization

This dissertation is organized as follows. Chapter 1 introduces the history of the opioid overdose epidemic in the United States and provides a background on disease modeling methods. It discusses relevant infectious disease models and some disease models that have been used to study the opioid overdose epidemic. Chapter 1 concludes with research gaps related to opioid overdose epidemic modeling and contributions presented by this dissertation.

Chapter 2 provides a scoping literature review of disease models of the opioid overdose epidemic. The literature review discusses metrics of interest, including different model types and opioids modeled. Additionally the chapter presents the notable models and interventions that can be employed in an environment. Based on the results, research gaps are identified and discussed.

Chapter 3 presents an agent-based model developed to simulate the opioid overdose epidemic. The rationale behind the model creation, model calibration, and results are discussed. The chapter is concluded with limitations of the ABM.

Chapter 4 tests an opioid overdose epidemic intervention and an opioid supply change to

predict the possible overdose and misuse outcomes. The ways that the initial model was modified to implement the interventions are discussed, and the results of the simulations are presented.

The final chapter summarizes the contents of the dissertation and possible future work directions.

Chapter 2

Scoping Literature Review of Disease Modeling of the Opioid Overdose Crisis

The work presented in this chapter is published in [191].

2.1 Introduction

In 2020, 77% of drug overdose deaths in the United States (US), accounting for 75,785 people, involved opioids, including prescription opioids, heroin, and synthetic opioids [158]. In the early 2000s, prescription opioids and heroin were responsible for most opioid-related overdoses. However, synthetic opioids, such as fentanyl, have become a major factor in the opioid overdose epidemic [187].

Synthetic opioids are typically highly potent causing overdose deaths to occur quickly [88]. These opioids can be purchased online and are frequently combined with other opioids or recreational drugs [189]. In addition, they are often sold to people who use drugs (PWUD) without their knowledge such as those who believe they are purchasing heroin [127]. From 2013 to 2019, the overdose death rate involving synthetic opioids increased 1,040% [139], and as of 2020, 83% of opioid overdoses involved synthetic opioids [153]. Figure 2.1 shows the opioids that are responsible for

overdose deaths from 2000-2020 in the US [153].

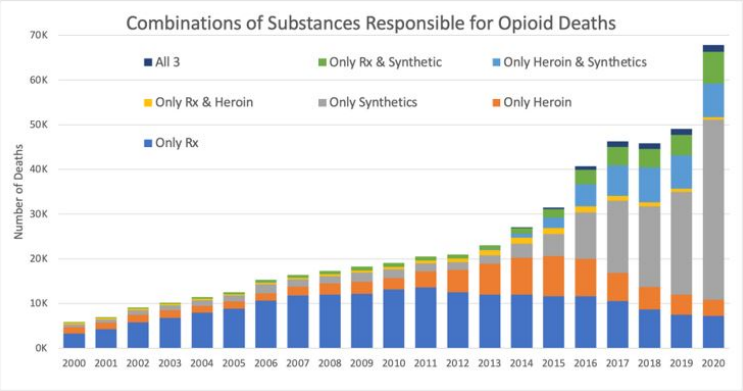

Figure 2.1: Opioids Responsible for Overdose Deaths in the United States [153]

2.1.1 Disease Modeling

Disease modeling, developed in the 1900s for application to communicable disease spread, can be used to track the spread of opioid use and misuse. One of the most well-known disease models is the susceptible-infected-removed (SIR) model developed by Kermack and McKendrick [184]. Healthy individuals are susceptible (S) to the disease, infected (I) individuals can pass the disease to susceptible individuals, and infected individuals are removed (R) after the disease has run its course. The original SIR model was formulated using differential equations and simple assumptions about a contagious disease's nature [106].

Although initial disease modeling predominately considered communicable diseases, disease modeling is useful for noncommunicable diseases (NCDs). NCDs are influenced by an individual's behavior, genetics, and interactions with other individuals or environments and include diseases such as cancer, heart disease, and addiction [155]. Epidemiological model structures can be applied to NCDs and used to estimate the benefits of interventions [34]. NCD models can also help researchers understand how changes in risk factors or behaviors will affect health outcomes [213].

The spread of heroin use has shown epidemic characteristics, including rapid diffusion and clear geographic boundaries [131], and the medical community has considered heroin addiction an epidemic since the early 1970s [76]. This scoping literature review analyzes articles that model or simulate the disease-like spread of opioid use and misuse through a community. These models are a subset of general simulation models of the opioid overdose epidemic specifically focused on disease

spread.

2.1.2 Other Literature Reviews

The severity of the opioid epidemic has prompted researchers to develop models aimed at addressing various aspects of the crisis. Barbosa et al. focused on the costs of interventions in the opioid epidemic [18]. A majority of the studies considered incremental cost per quality-adjusted life years. They found that the eighteen studies they identified only considered one method to care for those with opioid use disorders which may miss interactions between interventions. Only ten of the studies they described conducted validation [18].

Beaulieu et al. focused on studies that simulated the economic costs of strategies to address the opioid epidemic [20]. Of the 23 studies identified, methadone and buprenorphine maintenance treatments were most commonly evaluated, and naloxone distribution was the only harm reduction technique modeled. The studies identified consistently found that interventions such as methadone maintenance or naloxone distribution were cost effective [20]. One article that appears in [18] and [20] is included in this scoping literature review.

Sharareh et al. investigated models that evaluate policies about the opioid overdose epidemic (14 articles) [187]. These papers used system dynamics, mathematical, conceptual, or agent-based modeling to suggest strategies to improve health outcomes surrounding the opioid epidemic. Major findings include that prevention of opioid addiction is better than treatment, analysis of strategies should include harms and benefits, and short-term benefits from interventions may be counterproductive in the long-term. The authors report that most studies focused on prescription opioids and did not consider the transition from prescription opioids to heroin [187]. Seven of these articles are included in our literature review.

Cerda et al. completed a systematic literature review of simulation models addressing the opioid overdose crisis (88 articles) [44]. The authors found similar model types as [187]. They evaluated model calibration, validation, and data sources. Of the studies, 61% were calibrated using empirical data, and 31% validated the modeling process. Common data sources were the US Census, National Survey on Drug Use and Health (NSDUH), vital statistics data from the Centers of Disease Control and Prevention (CDC), published literature, and small cohort studies or ethnographic data. Eleven articles from the study are included in this review.

The current study is the first scoping literature review to focus on modeling the disease-like

spread of opioid use.

2.2 Methods

The goal of this scoping literature review is to collect papers that model opioid use and misuse spread in an area. We follow the PRISMA extension for scoping reviews methodology, and in this section, we discuss the eligibility criteria, search strategy, and screening methods. Figure 2.2 shows the number of articles found at each stage of the search process.

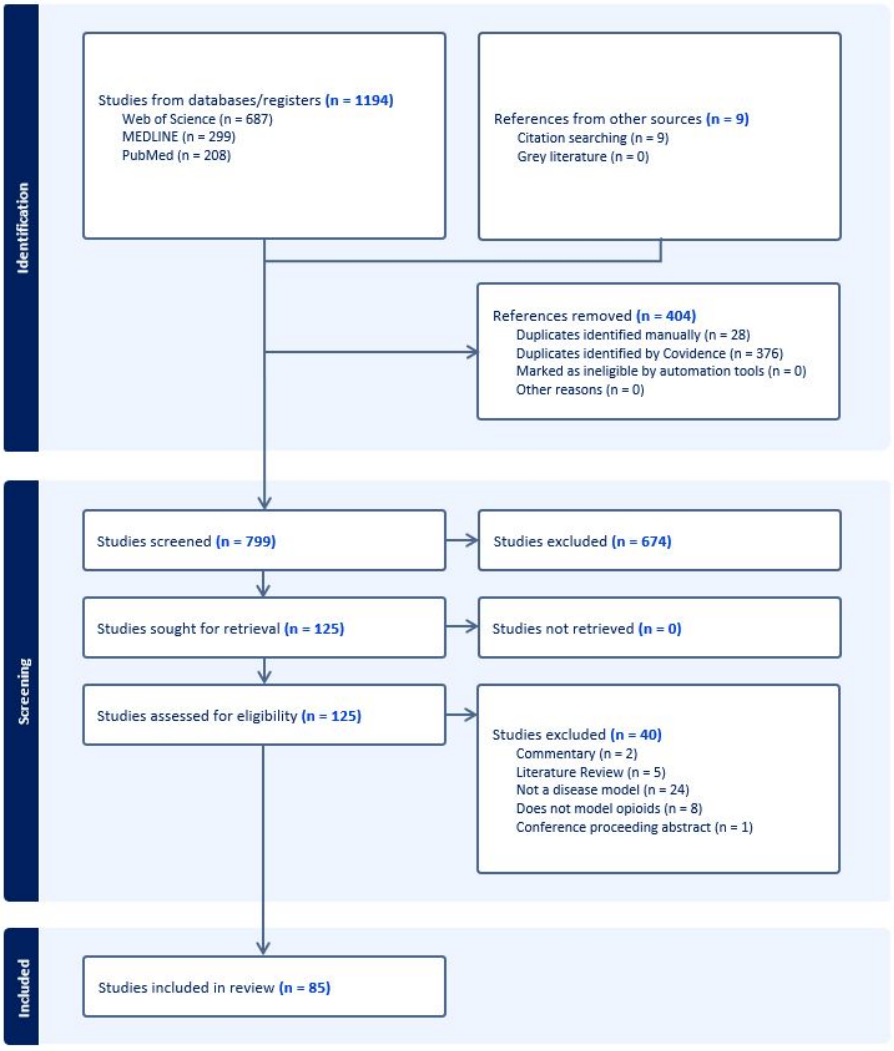

Figure 2.2: PRISMA Diagram

2.2.1 Eligibility Criteria

Studies published in English between January 1, 2000 and December 31, 2022 were included if they modeled the disease spread of opioid use and misuse through communities. Studies were excluded if they were literature reviews, conference abstracts, or did not model any opioids. We excluded studies that contained variations of animal models or were pharmacological in nature.

2.2.2 Search Strategy

We searched Web of Science, PubMed, and MEDLINE. A research librarian created tailored search strings for each database. Key search terms include opioid, heroin, and model, and key exclusion terms are rat, animal, placebo, and neurons. Search strings for each database are available in Appendix A. A total of 1,194 papers were identified.

2.2.3 Screening Methods

After removing 404 duplicates, the remaining papers were screened based on their title and abstract by two reviewers using Covidence. The two reviewers independently reviewed the title and abstract. Any differences in decision were discussed and resolved before the full review. A total of 125 papers were fully reviewed independently; 40 did not meet the eligibility criteria. Exclusion rationales can be found in Figure 2.2. An additional nine papers were found by reviewing the citations of the included papers. Eighty-five papers were collected for the analysis portion of the scoping literature review.

2.2.4 Assessment

Each article was assessed for the opioids that were modeled, the type of modeling that was used, what data sources were used, and whether the model was validated.

2.3 Results

Here, we highlight key findings of our scoping review.

2.3.1 Opioids Modeled

We categorized each model by the types of opioids discussed, and a graph of the results is shown in Figure 2.3. Article citations for these categories are listed in Appendix B.

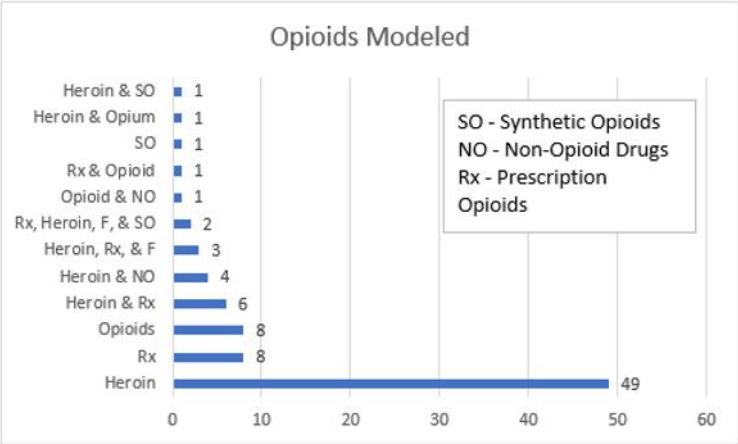

Figure 2.3: Opioids Modeled in Articles Included in Scoping Review

Of the studies, 49 only included heroin while prescription opioids and unspecified opioids were tied for a distant second, including eight each. Fentanyl and unspecified synthetic opioids were only included in seven models. Fourteen (16%) models included more than one opioid, and nineteen included more than one drug. Eleven models considered the transition from prescription opioid use to heroin use, and five modeled the transition from heroin to prescription opioids.

2.3.2 Model Types

The types of models employed were evaluated and are shown in Figure 2.4. We differentiate between theoretical compartmental models (primarily focused on theorems or lemmas, in 57 of the published articles) and applied compartmental models (required data to define system parameters, used to simulate drug use in a system, and often examined policies, in 21 of the studies). Applied compartmental models include system dynamics models. Cellular automata models, agent-based models, Markov models, Monte Carlo simulation, and optimal control models comprise the rest. Additional information about the model types can be found in Appendix C.

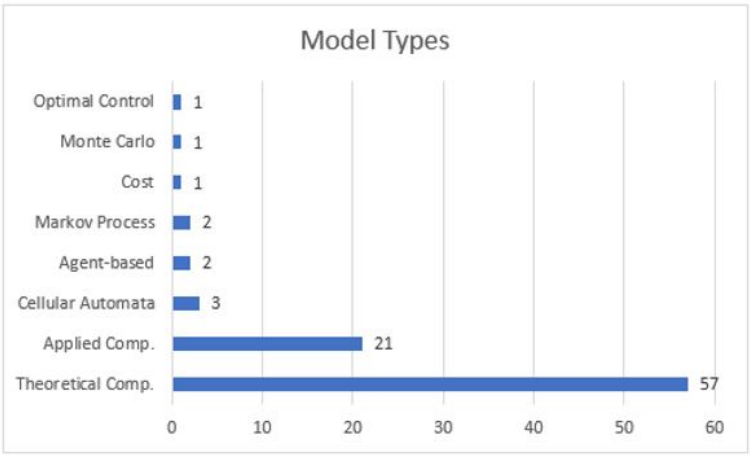

Figure 2.4: Model Types in Articles Included in Scoping Review

2.3.3 Data Sources

Data informed 44 of the models while the other 41 relied solely on equations for theoretical results. The data sources are shown in Figure 2.5. Published articles were the most common data source (38 articles), closely followed by panel or expert consensus (31 articles). Common government sources (21 articles) include the US census, CDC, Substance Abuse and Mental Health Services Administration, and NSDUH data.

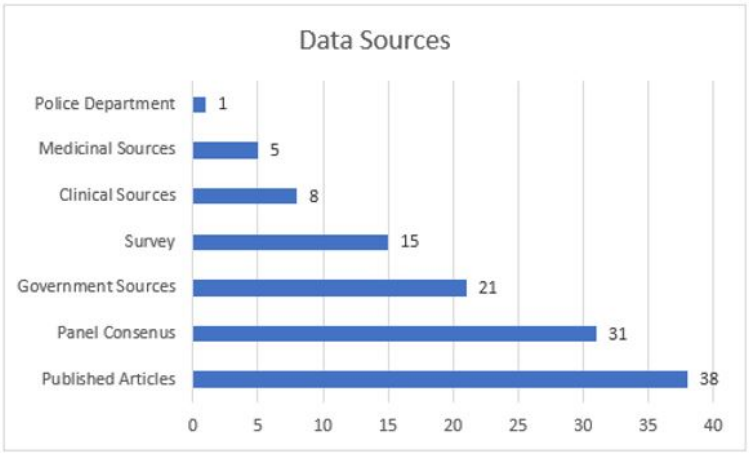

Figure 2.5: Data Sources in Articles Included in Scoping Review

2.3.4 Model Calibration and Validation

Of the 85 articles, 48 discussed calibrating the models or verifying the accuracy of their results. Thirty checked the assumptions of their theorems by setting initial conditions and verifying that the results supported the theorems. Of the remaining 18 papers, seven calibrated models. Tatara et al. described the algorithm used to calibrate [197], while Pitt et al. mentioned that the model was calibrated without describing the process [171]. Eight articles compared the model results to historical data as their validation method, and three models used error metrics. Of the 37 models that did not offer any validation, 27 were theoretical compartmental models. Thirty articles used sensitivity analysis to determine the effect of the model parameters.

2.3.5 Funding Sources

Sixty-four (75%) of the studies reported receiving financial support, with fifty-five receiving government funding, eleven receiving university funding, ten receiving non-profit funding, and seven receiving for-profit funding. Studies could receive funding from multiple sources. If many of the papers were funded by for-profit industries, it could be a sign of possible existing bias. This is especially true surrounding opioids because the pharmaceutical industry has been implicated in exacerbating the opioid epidemic [78], but for-profit bias does not seem to be a concern for these articles.

Agencies in China and the United States supported 28 and 25 research articles respectively. Agencies in Algeria and Japan contributed to three articles each, and agencies in Austria, Australia, India, and Qatar contributed to two papers apiece. Canada, Iran, Ireland, Portugal, Saudi Arabia, Serbia, and Slovakia each funded one article.

2.4 Discussion

2.4.1 Theoretical Compartmental Models (TCMs)

White and Comiskey created one of the first disease spread models of the opioid epidemic in 2007 [19]. An SIR model was adapted into an S-U_1-U_2 model where S represented the susceptible population, U_1 represented drug users not in treatment, and U_2 represented drug users in treatment [217]. The model was formulated using differential equations and an unchanging population size.

They found that preventing addiction to heroin is more beneficial to stopping the epidemic than curing PWUD. We refer to the base model presented by White and Comiskey as the "WC model". Mulone and Straughan used the WC model to determine conditions for stability of the drug free and endemic equilibrium [151]. The WC model was modified to allow the system population to vary [210]. Additional TCM disease models are described below.

2.4.1.1 Time Delays

Time delays represent the time it takes for a person to move between states in the model. The WC model was modified to include a delay to simulate the time it takes to become a person who uses heroin (PWUH) and time variation in population size and epidemiological parameters [183]. Abdurahman et al. developed a discretized heroin epidemic model (HEM) with a delay in moving from the susceptible population to drug use [4]. The delay was further explored by including different stages of drug use (casual or addicted drug use) [3].

Liu and Zhang included a relapse delay to account for the transition from being in treatment to heroin use [119]. This model was later analyzed to determine global stability [93]. Zhang and Wang added a delay to simulate the recovery time required for treatment before moving to a recovered state [228]. Kundu et al. extended the HEM of [128] by adding a time delay to represent the time between entering treatment and becoming susceptible again [110].

Fang et al. included multiple delays, one to move from the susceptible population to PWUD and another to move from PWUD in treatment to PWUD not being treated [65].

2.4.1.2 Rate Changes

Rate changes have been added to the WC model because time in a state can affect the likelihood of staying in the state. The rate changes are typically simulated using integrals in the given compartmental equation. In the initial WC model, susceptible people became PWUD at a constant rate. Fang et al. developed a model of heroin use where initiation of drug use depends on the individual's age [66]. Ma et al. incorporated the observation that a person is likely tempted at least twice before becoming a PWUH by using a bilinear incidence rate [128]. Djilali et al. expanded a HEM to further consider a generalized nonlinear incidence function with a time delay [57].

Fang et al. incorporated a relapse rate related to how long the person has been in treatment [64]. Yang et al. analyzed a heroin model with a nonlinear incidence rate and a relapse rate that

changed based on treatment time [223]. Djilali et al. used a nonlinear rate to model how the length of treatment influences the likelihood of returning to drug use [58]. Other articles included a treatment-dependent structure that allowed the time in treatment to affect the likelihood that the individual will relapse [62] and a rate change based on the length of time in treatment combined with withdrawal symptoms [25]. Bentout et al. developed a HEM with focus on the ways that relapse, simulated as a relapse rate change, can affect the spread of heroin use [26].

Chekroun and Nor Frioui developed a heroin-cocaine epidemic model where individuals could move between heroin use and cocaine use but not both at the same time [45]. The recovery rates were dependent on the time an individual used the specific drug.

Some models included multiple rate changes. Liu and Liu proposed a HEM where an individual's susceptibility and relapse is dependent on the time that an individual has spent in their current state [120]. Din and Li developed a HEM that considers the length of heroin use when determining the likelihood of ceasing drug use without treatment and the likelihood to influence others to use drugs [56], while the time spent in the susceptible and recovered states was considered in another model [107].

2.4.1.3 Multi-Group Models

Liu et al. analyzed a delayed multi-group HEM to describe the spread of heroin use in heterogeneous populations [121]. Multi-group HEMs have been developed with nonlinear incidence rates and delays [152], where the time in a category influences the likelihood that an individual will move from that category [209], and with nonlinear incidence rates and delays that model relapse, which is shown by changing states from treated to untreated [125].

2.4.1.4 Stochastic Models

Researchers have added stochastic perturbation to simulate random variance among PWUD and changing environments [123]. Liu and Wang created a stochastic non-autonomous HEM [118], and Wei et al. created a stochastically perturbed HEM [215]. Improvements to the TCMs include adding environmental stochasticity [124], creating a stochastic HEM [175], and creating a stochastic HEM with two delays [100]. Additionally, Li et al. (2018) included Levy jumps in a HEM to simulate sudden environment changes [113].

2.4.1.5 Reaction-Diffusion Models

TCMs have been adapted to include a spatial component. Wang and Sun developed a reaction-diffusion HEM to account for spatial heterogeneity [208]. Xu and Geng used this model to study the case where the average number of cases caused by each PWUD, also called R0, equals one [221]. Zhang and Xing developed another reaction-diffusion HEM with five compartments, which differs from the three to four compartments common in previously discussed models [227]. The additional states include people who have used drugs but are not currently using drugs and people who never use drugs or have successfully completed treatment [227].

2.4.1.6 Network Models

Utilizing a network model, Yang et al. created a HEM with a scale free complex network where the nodes of the network linked the individuals [223].

2.4.1.7 Intervention Models

Interventions modeled have included the effects of educational campaigns about the dangers of heroin [142], incarceration [143], the limited availability of treatment [211], and both preventive education and drug treatments [190]. Duan et al. modeled a hypothetical heroin vaccine that could minimize heroin misuse and the time that an individual is in treatment [60]. Duan et al. built on this model by considering imperfect vaccination, where vaccine efficacy wanes [59].

2.4.1.8 Unique Analysis Methods

Rashid et al. developed a HEM using the Atangana-Baleanu fractional-order derivative in the Caputo sense [177]. The authors captured relapses during and after treatment as well as persistent immunity after treatment [177]. Raza et al. developed a HEM and designed a nonstandard finite difference method (NSFD) for computational analysis [178]. They analyzed the model using two standard computational analysis (Euler and Runge-Kutta methods) and the NSFD [178].

2.4.1.9 Prescription Opioid Models

Befekadu and Zhu created a dynamical mathematical model with random perturbation to investigate the prescription opioid epidemic [22]. Befekadu developed an SIR model to minimize the

asymptotic exit rate of a stochastically perturbed prescription opioid epidemic [21].

2.4.1.10 Other Opioid Use Models

Memarbashi et al. developed an opioid epidemic model of heroin and prescription opioid use [141]. People could switch between heroin and prescription opioid use but could not use both simultaneously. Similarly, Cole and Wirkus altered the WC model to include individuals with illicit OUD [52]. They allowed individuals to move out of the OUD state without treatment and modeled limited treatment availability in a US medium-sized city [52]. Liu and Zhang developed both a deterministic and stochastic synthetic drug epidemic model with an added category for recovered individuals [122].

Pourhosseini and Memarbashi created an epidemic model of drugs that can and cannot be quit [172]. Individuals can switch from drugs that can be quit into treatment and from treatment to drugs that cannot be quit or a recovery state [172]. Li et al. developed a co-epidemic non-linear model of smoking cigarettes and using heroin, and individuals could stop use of either drug without treatment [114].

2.4.1.11 Opioid Use and HIV

Duan et al. developed a simultaneous model of the spread of heroin use and HIV infection and found the disease-free equilibrium of the system which was based on the reproduction numbers of individual epidemics [61]. Gupta et al. created a network model of HIV infection and opioid addiction, determining the basic reproduction number for both epidemics and found conditions for a stable disease-free equilibrium [79]. The researchers built on their work to discuss the relationship between the two epidemics [80]. They determined the equilibrium of the individual epidemics as well as the co-epidemic and suggested that control strategies that prevent people who use opioids (PWUO) from contracting HIV were most beneficial [80].

Table 1 summarizes the characteristics of the TCMs. The last row contains summary data.

Citation	Addiction Delay	Relapse Delay	Recovery Delay	Addiction Rate Change	Relapse Rate Change	Treatment Rate Change	Recovery Rate Change	Multi-Group	Stochastic
[217]	No	No	No	No	No	No	No	No	No
[151]	No	No	No	No	No	No	No	No	No
[119]	No	Yes	No	No	No	No	No	No	No
[183]	Yes	No	No	No	No	No	No	No	No
[210]	No	No	No	No	No	No	No	No	No
[93]	No	Yes	No	No	No	No	No	No	No
[4]	Yes	No	No	No	No	No	No	No	No
[65]	Yes	Yes	No	No	No	No	No	No	No
[64]	No	No	No	No	Yes	No	No	No	No
[66]	No	No	No	Yes	No	No	No	No	No
[121]	Yes	Yes	No	No	No	No	No	Yes	No
[125]	No	Yes	No	Yes	No	No	No	Yes	No
[152]	Yes	Yes	No	Yes	No	No	No	Yes	No
[223]	No	No	No	Yes	Yes	No	No	No	No
[224]	No	No	No	No	No	No	No	Yes	No
[58]	No	No	No	Yes	Yes	No	No	No	No
[128]	No	No	No	Yes	No	No	No	No	No
[211]	No	No	No	Yes	No	Yes	No	No	No
[60]	No	No	No	No	Yes	No	No	No	No
[113]	No	No	No	No	No	No	No	No	Yes
[3]	Yes	Yes	No	No	No	No	No	No	No
[21]	No	No	No	No	No	No	No	No	Yes
[22]	No	No	No	No	No	No	No	No	Yes
[118]	No	No	No	No	No	No	No	No	Yes

[120]	No	No	No	Yes	Yes	No	No	No	No
[123]	No	No	No	No	No	No	No	No	Yes
[124]	No	No	No	Yes	No	No	No	No	Yes
[142]	No	No	No	No	No	No	No	No	No
[175]	No	No	No	No	No	No	No	No	Yes
[209]	No	No	No	Yes	Yes	No	No	Yes	No
[215]	No	No	No	No	No	No	No	No	Yes
[228]	No	No	Yes	Yes	No	Yes	No	No	No
[45]	No	No	No	Yes	No	No	Yes	No	No
[56]	No	No	No	Yes	No	Yes	No	No	No
[61]	No	No	No	No	No	No	No	No	No
[62]	No	No	No	No	Yes	Yes	No	No	No
[100]	Yes	Yes	No	No	No	No	No	No	Yes
[143]	No	No	No	No	No	No	No	No	No
[208]	No	No	No	Yes	Yes	Yes	No	No	No
[227]	No	No	No	Yes	Yes	Yes	No	No	No
[25]	No	No	No	No	Yes	No	No	No	No
[26]	No	No	No	No	Yes	No	No	No	No
[57]	No	Yes	No	Yes	No	No	No	No	No
[59]	No	No	No	Yes	No	No	No	No	No
[107]	No	No	No	Yes	Yes	No	No	No	No
[190]	No	No	No	No	No	No	No	No	No
[221]	No	No	No	Yes	Yes	Yes	No	No	No
[52]	No	No	No	No	No	No	No	No	No
[79]	No	No	No	No	No	No	No	No	No
[80]	No	No	No	No	No	No	No	No	No

[110]	No	No	Yes	Yes	No	No	No	No	No
[114]	No	No	No	No	No	No	No	No	No
[122]	No	No	No	No	No	No	No	No	Yes
[141]	No	No	No	No	No	No	No	No	No
[172]	No	No	No	No	No	No	No	No	No
[177]	No	No	No	No	No	No	No	No	No
[178]	No	No	No	No	No	No	No	No	No
Total	**7**	**9**	**2**	**20**	**13**	**7**	**1**	**5**	**10**

Table 2.1: Theoretical Compartmental Model Summary

2.4.2 Applied Compartmental Models (ACMs)

2.4.2.1 Opioids Modeled

While TCMs focused primarily on heroin, ACMs considered multiple types of opioids, shown in Table 2.2. The two largest categories were prescription opioids (6) and prescription opioids and heroin (4). Five models included fentanyl or synthetic opioids. Some studies included transitions

Opioids Modeled	Total	Citations
Prescription Opioids	6	[19], [156], [181], [204], [205], [206]
Prescription Opioids and Heroin	4	[23], [171], [176], [202]
Heroin, Prescription Opioids, and Fentanyl	3	[92], [170], [201]
Illicit Opioids	3	[117], [133], [149]
Unknown Fentanyl	3	[92], [115], [195]
Heroin, Prescription Opioids, Fentanyl, and Synthetic Opioids	2	[115], [195]
Heroin	2	[41], [42]
Heroin and Opium	1	[174]

Table 2.2: Applied Compartmental Models' Opioids

between opioids. Because interventions can encourage people to switch drugs, capturing use changes can improve model accuracy [10]. The opioid transitions, shown in Table 2.3, considered were prescription opioid use to heroin (8 models), heroin use to prescription opioid use (3 models), and opium dependence to heroin dependence (1 model). Eleven of the studies modeled only one type of opioid.

Transitions	Total	Citations
Prescription Opioid to Heroin	8	[92], [115], [170], [171], [176], [195], [201], [202]
Heroin to Prescription Opioids	3	[23], [115], [195]
Opium to Heroin	1	[174]

Table 2.3: Applied Compartmental Models' Opioid Transitions

When only one or two opioids are modeled, the effects of price changes and the substitutability of opioids are not captured.

2.4.2.2 Locations Modeled

Seventeen articles modeled the United States, two modeled Australia, and one each modeled Iran, North America, and Ukraine. The articles that modeled each country are listed in Table 2.4.

If countries are modeled using averaged data, the differences between socioeconomic groups or urban and rural centers are not captured. Examples of specific locations being modeled include

Country	Total	Citations
United States	17	[19], [23], [42], [92], [115], [117], [156], [170], [171], [176], [181], [195], [201], [202], [204], [205], [206]
Australia	2	[41], [42]
Iran	1	[174]
North America	1	[133]
Ukraine	1	[149]

Table 2.4: Locations Modeled in Applied Compartmental Models

Perry County, Kentucky and Massachusetts [23], Tennessee [170], and Massachuesetts [117]. Rafiemanesh et al. (2021) modeled a generic area in Iran [174], while Morozova et al. (2020) modeled three cities in Ukraine [149].

Nineteen of the twenty-two ACMs included at least one location in North America. This finding could be influenced by only accepting papers written in English.

2.4.2.3 Outcomes Modeled

There are different ways to assess the harms of opioid use or the effectiveness of interventions. The most common outcome measures were overdose deaths (14 models), prescribed users (12 models), and drug users (10 models). Outcome measures that were used in the applied compartmental models are shown in Table 2.5.

Different outcome measurements can affect how interventions are viewed. An intervention may reduce overdose deaths but increase overdoses. Expanding measures to include life-years or quality-adjusted life-years (QALY) can aid in determining the effects of the intervention on general health. Incorporating policy costs and incremental costs per QALY may support the evaluation of interventions in terms of cost [149].

2.4.2.4 Interventions Modeled

Interventions tend to fall into harm reduction or use reduction categories. Harm reduction interventions reduce the likelihood that harm will come to PWUD, while use reduction interventions work to reduce the number of PWUD.

Harm reduction interventions in the ACMs are listed in Table 2.6. Frequent harm reduction interventions were naloxone availability and use (7 models), medication-assisted treatment (6 models), and tamper-resistant prescription opioid formulas (6 models). A common goal of harm

Outcomes	Total	Citations
Overdose deaths	14	[19], [23], [92], [115], [117], [171], [174], [176], [195], [201], [202], [204], [205], [206]
Prescribed Users	12	[23], [92], [115], [156], [170], [171], [176], [181], [195], [201], [202], [205]
Drug Users	10	[23], [41], [42], [92], [133], [171], [174], [201], [204], [206]
Non-medical opioid users	9	[23], [92], [156], [171], [176], [201], [202], [204], [205]
People with OUD	8	[92], [115], [117], [171], [176], [195], [201] [202]
Users in treatment	7	[19], [117], [171], [174], [176], [181], [202]
Overdoses	5	[92], [117], [171], [176], [201]
Addicted Users	4	[19], [170], [174], [181]
Life-years	4	[92], [171], [176], [201]
QALY	3	[149], [171], [176]
R_0	3	[19], [170], [176]
Recovered Users	3	[115], [174], [195]
Injection Drug Use (IDU) Initiations	1	[133]
Assisted IDU Initiations	1	[133]
Policy Costs	1	[149]
Incr. Cost/QALY	1	[149]

Table 2.5: Outcomes Modeled in Applied Compartmental Models

reduction is to reduce the risk of overdoses or fatal overdoses. For example, increasing the tamper-resistance of extended-release prescription opioids may reduce the risk of overdose, and increasing naloxone availability may reduce the risk of fatal overdoses. Some articles focused on generic treatments while others selected a specific type. Harm reduction can also include other health goals, such as reducing the risk of infectious disease transmission through needle exchanges.

Interventions	Total	Citations
Naloxone availability and use	7	[92], [117], [170], [171], [176], [195], [201]
Medication-assisted treatment (MAT) usage	6	[92], [117], [171], [174], [195], [201]
Tamper resistance prescription opioid formulas	6	[156], [171], [176], [202], [204], [206]
Expanded access to psychosocial treatment	4	[171], [174], [176], [195]
Expanded access to pharmacotherapy	3	[170], [176], [195]
Needle exchange availability	2	[171], [176]
Opioid agonist therapy (OAT)	2	[133], [149]
Generic harm reduction	1	[41]

Table 2.6: Harm Reduction Interventions in Applied Compartmental Models

Use reduction interventions are shown in Table 2.7. Reductions in prescribing of prescription opioids (5 models) and prescription drug monitoring programs (3 models) are intended to reduce the available supply of prescription opioids for misuse. However, this reduction can cause individuals

to seek other opioids, like heroin [10]. Supply reductions can also occur through excess prescription opioid disposal (4 models). Educational programs may raise awareness of doctors, patients, and the public about the dangers and addictive nature of opioids, specifically prescription opioids. Other strategies were vague, simply mentioning reducing the incidence of PWUO.

Interventions	**Total**	**Citations**
Reductions to prescription opioid diversion	5	[92], [156], [195], [201], [202]
Excess prescription opioid disposal	4	[156], [171], [176], [195]
Reduced prescribing	4	[171], [176], [181], [195]
Prescription drug monitoring programs (PDMPs)	3	[171], [176], [204]
Strategies to reduce drug initiation	3	[41], [156], [195]
More restrictive drug scheduling	2	[171], [176]
Patient-level opioid education programs	2	[195], [205]
Prescriber education programs	2	[205], [206]
Reducing the popularity of opioids	2	[204], [205]
Programs that reduce rates of medical user-related abuse	1	[206]
Reduced chronic pain prescribing	1	[23]
Reduced incidence of prescription opioid misuse	1	[195]
Reducing supply of drugs other than cannabis	1	[41]

Table 2.7: Use Reduction Interventions in Applied Compartmental Models

Determining whether to implement harm or use reduction strategies can be difficult. Caulkins et al. developed one model of Australian injection drug use and one model of cocaine use in the US to collect data to inform policy decisions, finding that harm reduction policies that marginally increase use can be problematic if the number of PWUD is at a tipping point between two equilibria [42].

Wakeland et al. found that tamper-resistant formulations and interventions to reduce informal sharing could reduce nonmedical user populations and overdose deaths in the long term [202], and Nielsen et al. suggested that reducing informal sharing of leftover medicine could significantly reduce initiation and nonmedical use [156]. However, Wakeland et al. found that it may be difficult to minimize overdose deaths without adversely affecting the degree to which chronic pain patients can access treatment [206].

As heroin use increased, modelers noted that some interventions may cause increased harm. Interventions that reduce supply may increase heroin overdoses if not combined with treatment or social interventions [23].

Harm reduction strategies have shown benefits. Marks et al. found that increasing OAT coverage causes a decline in the population who use injection drugs [133]. Rafiemanesh et al. sug-

gested that small reductions in the current levels of treatment may lead to relatively large negative impacts over the course of 30 years [174]. Rao et al. tested many interventions and found that expanding naloxone availability had the largest impact on reducing fatal overdoses [176].

Combining interventions is likely necessary because of the complex nature of the opioid epidemic. Linas et al. used a dynamic state-transition model to assess how changes in different medication treatments and increased naloxone distribution may affect opioid overdose mortality in urban and rural counties in Massachusetts [117]. The researchers found that no single intervention could reduce overdose mortality by 40%, but combining interventions could achieve that goal [117]. Pitt et al. and Homer and Wakeland similarly found that more than one intervention will be needed to significantly reduce deaths ([171], [92]). Wakeland and Homer built on their previous model by using a method for analyzing the effects of parameter uncertainty, believing that the uncertainty intervals provided by this method may increase the value of simulation models [201].

Stringfellow et al. used SOURCE (Simulation of Opioid Use, Response, Consequences, and Effects), a national-level model of the US, to assess the effects of eleven intervention strategies on overdose deaths and the prevalence of OUD [195]. They found that reducing the overdose risk involving fentanyl, increased naloxone distribution, and recovery support strategies saved the most lives [195].

2.4.3 Cellular Automata

Cellular automata models are often used to simulate regional spread and evolution of a phenomenon [23]. Such models have been used to predict drug abuse and infer spread characteristics of drug abuse, including heroin and synthetic opioids, in five states in the US [222]. Gao et al. described opioid spread in five US states [75]. The authors simulated opioid propagation through counties based on a geographic network and a Susceptible-Infected-Susceptible framework, and they used support vector regression to predict the drug reports in each county [75]. Benneyan et al. (2017) used a cellular automata model to analyze the opioid epidemic in Massachusetts [23].

2.4.4 Additional Model Types

A Monte Carlo simulation of one million people was used to determine the cost effectiveness of drug treatment programs, balancing the costs of treatment, crime, incarceration, and healthcare

with the financial benefits of employment [226]. An optimal control model of the opioid epidemic was used to examine whether eradication or accommodation is the best policy for an illicit drug epidemic, confirmed results for the deterministic version, and applied Skiba sets to a stochastic version of the problem [37].

Alexander et al. developed a dynamic Markov model of the opioid epidemic in the US, which demonstrated a lag of many years between initiation of medical opioid use and overdose death [10]. Ballreich et al. designed a decision analytic dynamic Markov model using US data to project 10-year overdose deaths and prevalence of OUD, simulating a reduction of prescription opioids, increased naloxone distribution, and expanded treatment [17].

A social network analysis model, a type of agent-based model, was developed in which nodes represent individuals connected via arcs that are weighted by adjacency or relationship strength [23]. Licit and illicit drug use levels are simulated at each node [23]. The Justice-Community Circulation Model, an agent-based model that can simulate OUD in individuals involved in the criminal justice system, was used to study the effects of interventions, like providing naloxone on release, on overdose deaths [197].

2.5 Conclusions

This scoping literature review identified and examined 85 papers concerning modeling of opioid misuse spread. Theoretical and applied compartmental models comprised 93% of the models identified in this study. We compared the opioids modeled in each of these model types to US opioid overdose deaths in 2020 by opioid using overdose data from [153], as shown in Figure 2.6.

Despite most opioid overdose deaths in 2020 in the US being attributed only to synthetic opioids, only one TCM and five ACMs specifically considered synthetic opioids. The seven articles that considered synthetic opioids were published since 2019.

Three major research gaps were identified during the review. First, most models either used generic country-wide data or no location data. Generally, data to inform the models is lacking, as noted in previous research [186] and verified in this review.

Second, and possibly influenced by the previous gap, most of the models used differential or difference equations which do not allow for individuals to be tracked throughout the system. Individuals may have risk factors that make them more likely to begin using opioids or relapse.

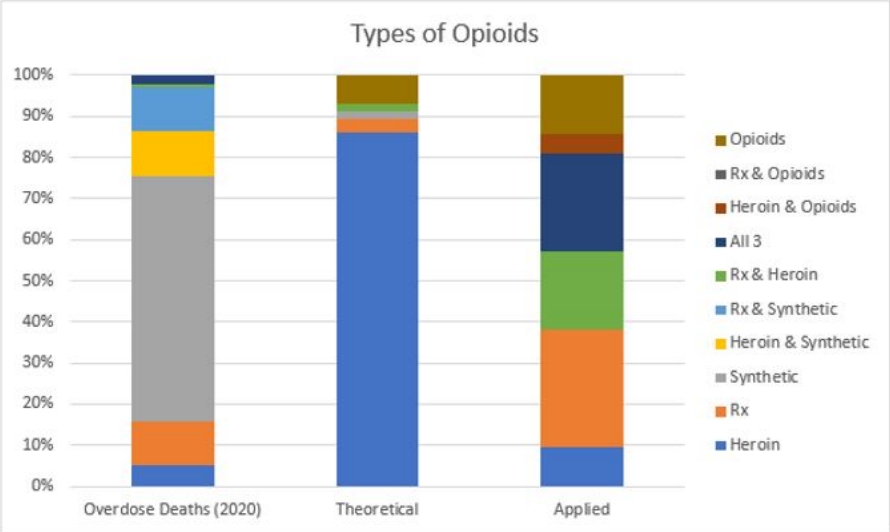

Figure 2.6: Opioids Involved in Overdose Deaths and Used in Compartmental Models

Using other modeling techniques could reveal new insights and may be better suited to evaluating different policies to reduce the severity of the opioid overdose epidemic.

Third, most models focused on heroin with a smaller number including other opioids. Since fentanyl is more potent than other opioids, its presence increases overdose risk, and PWUD may unknowingly use fentanyl in adulterated heroin or in counterfeit prescription opioids tablets.

Some models are beginning to address these gaps. Stringfellow et al. considered prescription opioids, heroin, fentanyl, and other synthetic opioids in their national-level model and simulated eleven strategies to reduce deaths and OUD prevalence [195]. Homer and Wakeland expanded a system dynamics model to include counterfeit fentanyl pills in addition to prescription opioids and heroin [92]. Tatara et al. incorporated individual's characteristics and history to inform their agents' use of opioids and involvement in the criminal justice system in the Chicago area [197].

Based on the results and current state of the opioid overdose epidemic, future research should incorporate synthetic opioids into their work alongside heroin and prescription opioids. Since most deaths in the US can be attributed to synthetic opioids, having effective research including them is vital. Additional studies that discuss how people transition between different types of opioids will be beneficial for policymakers. Addressing these gaps will allow researchers to better assess factors in the opioid crises, construct more accurate models, and inform how interventions could impact the severity in a community.

Chapter 3

Development of Agent-Based Model of the Opioid Overdose Crisis

3.1 Introduction

Agent-based modeling has its roots in complex adaptive systems (CAS) [129]. CAS can be defined as systems with many parts that interact. These systems also tend to evolve and show aggregate behavior [91]. Although simulation is often thought of as a recent phenonomon, these systems were theorized about as early as the 1700s. In 1759, Adam Smith proposed his "theory of the invisible hand" which stated that individuals that acted according to their interests could produce societal benefits [109]. As the individuals in the society interact according to their own behaviors, a phenomenon emerges that none of the individuals were directly working towards [86].

Work with complex adaptive systems was supported by computer processing. ABMs and cellular automata (CA) are both bottom-up approaches to simulate CAS [50]. CA is similar to agent-based modeling but with its own specific distinctions. CA uses a grid of cells that can be a given set of states, and each cell is a part of a neighborhood, typically with eight neighbors that surround it on the grid [50]. The cells can change states based on rules that typically involve the cells own characteristics along with its neighbors' states [50].

Two well-known examples of complex adaptive systems are Conway's "Game of Life" and Schelling's study in segregation. Conway's game of life uses CA. In Conway's model, the cells could be black or white and would change states based on three rules. Based on the initial states, sometimes shapes would emerge and appear to move across the grid [86]. Further research has been done since the base game was introduced, and research has shown that the Game of Life can emulate a universal Turing machine [50].

In 1971, Schelling introduced a model of segregation that allows agents to relocate based on their surroundings [84]. The agents are assigned to two different groups. The agents check their neighbors and find that some percentage of them are of the same type. If that percentage is below a defined threshold, the agent will relocate to a cell with a percentage above the threshold. Otherwise, they will stay. The model shows that a relatively low required percentage (33%) will cause segregation [84]. Figure 3.1 shows the initial and final state of a Schelling model.

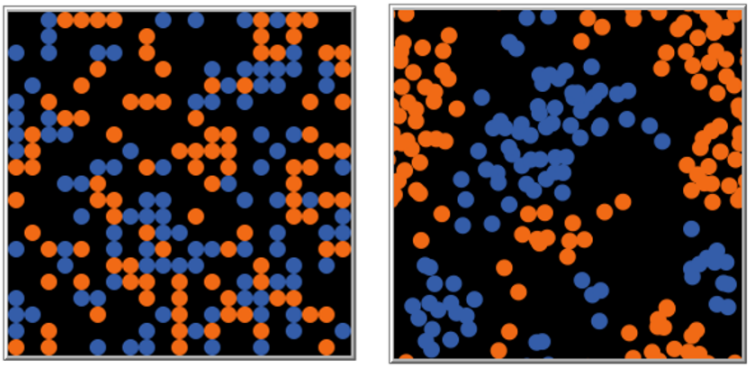

Figure 3.1: Example of Initial (Left) and Final (Right) State of a Schelling Model

ABMs have been used to examine public health phenomenon. ABMs can model infectious disease spread well, but research has found that the models are being applied to NCDs and other public health behaviors [198]. In 2015, Nianogo et al. found 22 articles featuring ABMs that modeled different types of NCDs [155].

Relevant work is discussed in Section 3.2. The research contributions and model purpose are presented in Section 3.3. The structure of the model, data included, and decisions made to develop the model are discussed in Section 3.4. In Section 3.5, the results are presented. Further discussion and limitations of the model and study are shown in Section 3.6, and the chapter is concluded in Section 3.7.

3.2 Related Work

ABMs have been developed to examine many aspects of the opioid overdose crisis, not all directly related with disease spread. This section will cover a selection of related work. Some were previously mentioned in Chapter Two but have more explanation here.

Hoffer et al. created one of the first ABMs related to opioid use and utilized ethnographic data to populate the model [90]. The model was of Denver's Larimer open-air heroin market, and its goal was to investigate the role of heroin users who facilitated transactions and how police activity influenced the market. The model had six types of agents. Customer agents were heroin users who needed to purchase heroin and could be satiated, craving, or in withdrawal and used, searched for, and purchased heroin. Broker agents used heroin and interacted with customers. Seller agents did not use heroin but sold their supply of heroin over the course of a shift. Private dealer agents sold heroin like sellers but did not work in the open-air market. They only interacted with customers and brokers that they knew. Police agents patrolled the area and arrested agents with heroin. Homeless agents populate the market and do not use heroin but provide "noise" for the police.

This model did not consider how people became PWUD but focused on how brokers facilitated sales. The presence of brokers increased the number of sales, but the increase did not continue linearly with 25 and 50 brokers producing similar transactions. Drug busts by police can dampen transactions initially but brokers tended to transfer customers to private dealers so sales return to the previous level over the course of a few months [90].

Hoffer et al. continued their work with the ABM with a focus on how the individual reactions to heroin affect and are affected by the heroin market by incorporating withdrawal and tolerance effects [89]. If people who use heroin did not at least use their "habit" amount, they would eventually enter withdrawal. The agent types were constant from the previous paper. The customer agents could maintain their drug habit or use more heroin to get high and would attempt to avoid entering withdrawal. If users consistently used more than their habit to get high, going back to their habit would cause them to have withdrawal symptoms for a set amount of time until their body adjusts. In the model, some agents experienced periods of bingeing and crashing, some increased or decreased more gradually, and others had stable addiction levels. The model did not account for new opioid users or the spread of opioid use [89].

Benneyan et al. developed three different types of opioid overdose epidemic models: dif-

ferential equations, cellular automata, and social network analysis (SNA) [23]. The eventual goal was to integrate the separate models to harness their strengths. The CA model updated cells based on their neighbors, influenced by adjacency or relationship strength. In the SNA, individuals were represented by nodes and connected to one another by arcs that are weighted by closeness or relationship strength, similar to the CA model. The agents could use licit or illicit drugs and were updated based on their neighbors' influences as well as internal characteristics. The authors said that both the CA model and SNA were beginning to produce face-validity when compared to Massachusetts epidemic growth and spread patterns. However, little was included in the article about how the models were parameterized and what agent characteristics were included. They did perform sensitivity analysis to determine key parameters but did not elaborate on what the parameters represented. The authors used MATLAB and Python to implement the models, although it was not clear which models were implemented with which programs or if they used both programs [23].

Bobashev et al. developed an ABM in NetLogo to model pain patients [30]. Pain patient agents can seek treatment for their pain and may be prescribed opioids. The patients develop a tolerance over time, and some patients begin to use larger doses than prescribed. These patients may choose to visit other physicians, emergency departments (EDs), buy from other patients or dealers, or switch to heroin. The other agents in the model are the physicians, drug dealers, pharmacies, and EDs. Physicians, pharmacies, and EDs could choose to provide opioids (based on patient records), and dealers will provide opioids but only have a limited amount. The agents are linked to each other, with patients having links to at least one physician, friends who may also be patients or dealers, and pharmacies. The simulation was run for five years with a daily time step. The authors modeled four possible interventions: reduced initial dose, improved PDMP compliance, improved tamper-resistant pill compliance by pharmacies, and high naloxone availability. The outcomes of concern were number of heroin users, PO and heroin overdose rates, and PO and heroin death rates [30].

Decreased initial dose was shown to increase heroin use but decrease rates of overdose and opioid death. Similarly, more tamper-resistant medication increased heroin use and also increased overdose rates. Improved naloxone availability decreased death rates from overdoses. Partial PDMP compliance showed marginally higher rates of heroin users, while full compliance did lead to a significant decrease in PO overdose rates [30].

Keane et al. collected qualitative data to use in their ABM to determine how community-

based naloxone distribution to bystanders would affect opioid overdose deaths [103]. For the qualitative studies, they conducted interviews with substance use treatment providers and recent or current injection drug users. Participants in the interviews generally thought that providing bystanders with nalaxone would be beneficial and would not change their risk assessment. Their ABM contained PWUO (approximately 11,000 agents) and a much larger population (1 million) that does not. The group who used opioids was further divided into a smaller group of 1,000 that was more likely to overdose and 10,000 PWUO that were not as likely to overdose although they may. Another agent type was emergency medical providers who would respond to calls of overdoses [103].

The agents could visit randomly distributed sites to pick up naloxone kits. The number of kits distributed per visit and the number distribution sites were varied (1 or 10) and the resulting overdose deaths were compared. Individuals with multiple kits could give the kits to other agents who did not have a kit. Another set of simulations was run distributing naloxone kits from syringe exchange sites even though PWUO may not visit them often. Bystanders were considered to be people with opioid use disorders, and they were the only ones capable of administering naloxone with the exception of the emergency medical providers [103].

The time step for this model was one minute during the eight hours of awake time set per day. The agents would move on average once every fifty minutes and could interact with their neighbors. The model was run for a six month time period. Providing one kit from one site reduced the baseline level of opioid overdose deaths by only 6%. Increasing the number of sites to 10 reduced the overdose deaths by 37.5%. If agents were not allowed to distribute the kits to other agents, increasing the number of kits that could be received per visit did not greatly reduce the number of overdose deaths (37.5% to 39.9%). Allowing secondary distribution with multiple kits being provided at each site showed a 61.1% reduction in overdose deaths [103].

Tatara et al. developed an ABM called the Justice-Community Circulation Model (JCCM) using Repast4Py software to simulate individuals in the CJS who have an OUD [197]. Criminal justice involved (CJI) people who have an OUD are more likely to overdose shortly after release from incarceration. This ABM has one type of agent, the person. Agents have demographic characteristics and characteristics that vary over time like opioid use and criminal justice involvement. The agents can be in three states: no opioid use, non-injecting opioid use, and injecting opioid use. The agents will transition between these states based on their characteristics and location. When using opioids, agents can overdose which may lead to overdose death. CJI individuals who are incarcerated do not

update their state transition model. Therefore, the JCCM does not consider opioid use in jails or prisons but allows PWUO to begin using once they are released [197].

To calibrate the model, the authors used the IMABC algorithm, which is an approximate Bayesian version of adaptive importance sampling. This algorithm helped determine the parameters to be calibrated. The model was calibrated based on overdoses and overdose deaths in their area and was run for one year. Two considerations for the study were the percentage of the general and previously jailed population that had naloxone, which if administered reduced the chance of overdose by 95%, and mass jail release where 1/3 of the incarcerated population was released at once. The model showed that the mass jail release caused spikes in overdose deaths when it occurred, but the severity was reduced when both the general and previously jailed population were given high levels of naloxone [197].

Shojaati and Osgood developed an agent-based model to test how changes in prescribing opioids affected opioid misuse [188]. Agents who were prescribed opioids could take more or less than prescribed. Taking less than prescribed led to excess availability that could be given to agents who had taken more. Agents who had taken more could also obtain illegitimate prescriptions or buy illicit opioids. The model was implemented using AnyLogic with a one day time unit. Before beginning any calibration or experimentation, a five-year burn-in period to populate the agents with previous histories of use was enacted. Calibration was done on model parameters that were sensitive during the sensitivity analysis [188].

The authors studied multiple interventions, including reducing the baseline opioid prescription dose, reducing baseline prescription length, creating a PDMP to prevent overlapping prescriptions, and combinations of the interventions. Results showed that lowering the baseline prescription dose had the most beneficial impact over five years [188].

Lönn et al. modified an existing agent-based model of drug (not specifically opioid) use programmed in C++ [126]. Further explanation of the existing model (Framework for Reconstructing Epidemiological Dynamics) can be found in [77]. The model considered three states of use: no lifetime use, current use, and prior but not current use. The agents in the model were representative of the population of a region of southern Sweden. Characteristics that could influence drug use were age, school achievement, genetic risk, parental separation, sex, and socioeconomic status [126].

The simulated intervention provided additional help to students and has been shown to improve average student grades. The improved student success was theorized to lead to less drug

use later in life. The model was run from 2010-2018 and showed mild to moderate reductions in drug use disorder cases among males but little reduction among females [126].

3.3 Model Purpose and Contributions

This agent-based model was designed to allow researchers and policymakers to assess how interventions may affect opioid use and overdose deaths in a state or community. By viewing the changes of key metrics in the model, we can anticipate how those changes would affect the community. The ABM focuses on individual characteristics and decisions to determine how individuals move throughout the simulation. The contributions of this study are as follows:

- This chapter addresses a gap identified in the previous chapter by providing a disease model of the opioid overdose epidemic using a different model type. Since only two ABMs were identified in the scoping review, this agent-based model provides research in a less studied area.
- The ABM allows agents to use four different types of opioids (prescription opioids, counterfeit prescription opioids, heroin, and fentanyl). The addition provides more granularity to the simulation than one or two opioid types. Additionally, the opioids have potencies which can be used to simulate differing levels of fentanyl mixed into other opioids.
- We incorporate more states of opioid use than most models previously identified. With three stages of opioid misuse and a treatment state, we can use data for people who use recreationally as well as those with mild/moderate and severe opioid use disorders.
- We include three different routes of administration for opioid use (oral, smoking, and injection). How the opioids are administered are important to consider in a model because they can affect a person's chance to overdose. Also, some interventions may only affect people who inject opioids, so having that group identified may be important for future work.
- The ABM uses a unique way to model opioid supply. There are many ways to get opioids (from friends or family, excess prescriptions, and people who supply drugs). In this model, the opioids are supplied from a specific agent type and represents supply as supposed to determining where the supply comes from. To the best of our knowledge, this is a novel way to model opioid supply.

- We include two different treatment modalities in the model as well as involvement with the criminal justice system (CJS). Both treatment and the CJS influence how PWUO move through the environment and can change how they use opioids.

3.4 Model Structure

3.4.1 Model Setting

Because ABMs require data for individual characteristics, we had to select a location of interest. We chose to model South Carolina because it is where the research team is based and where the area experts have contacts. The model setting can be updated by changing the community and individual data to a different location of interest.

3.4.2 Agent Types

This ABM has two types of agents: people and opioids. The human agent (h-agent) type is the primary model focus and has the largest number of characteristics. The opioid agent (o-agent) type supplies opioids to the h-agents. The following sections will discuss the characteristics for the two agent types, the data used to inform the characteristics, how the agents move through the model, and how the agents interact.

3.4.3 Opioid Use States

In the model, each h-agent is in one of seven opioid use states shown in Figure 3.2. The arcs in the model show how h-agents can move from and enter a state.

Each of the seven states is described as follows:

- No Use (State 0) - The h-agent is not currently using any opioids although they may have in the past.
- Medical Use (State 1) - The h-agent is currently receiving and using legally acquired prescription opioids.
- Recreational Use (State 2) - The h-agent is using opioids not as prescribed occasionally or socially. If the h-agent was forced to stop using opioids, they would not suffer any major

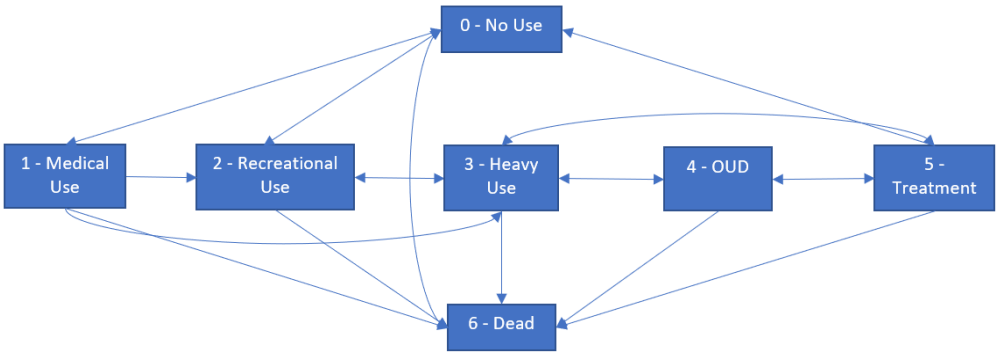

Figure 3.2: ABM Opioid Use State Diagram

physical withdrawal symptoms.

- Heavy Use (State 3) - The h-agent is using opioids regularly. In this state, being unable to use opioids would cause physical withdrawal symptoms. However, the opioid use is not significantly affecting the h-agent's family and job responsibilities, similar to a "functional alcoholic" [24].

- OUD (State 4) - The h-agent is using opioids regularly and meets the diagnosis of opioid use disorder as covered by the DSM-5 [220]. The opioid use is causing negative consequences that make it difficult for the h-agent to meet their responsibilities.

- Treatment (State 5) - The h-agent is receiving treatment for opioid misuse. Treatment types and how h-agents move through treatment are discussed in 3.4.6.

- Dead (State 6) - The h-agent is dead. This can occur due to natural causes in any state or from opioid overdose if the h-agent is using illicit opioids.

This ABM contains three levels of illicit opioid use, which differs from many of the models discussed in the related work or found in the scoping literature review. Multiple levels of use more accurately describe an h-agent's opioid use patterns and allow us to explore the characteristics that influence reduction and increase of use on a more granular scale.

There are three main influences in the model that move h-agents through the opioid use states: h-agent characteristics and past history, randomness, and neighbors. These influences will be explored in detail in the following sections.

3.4.4 Initialization of H-agents

H-agents are initialized with characteristics that affect their chance to move through the opioid use states. Their characteristics may be static, such as race and gender, or variable, such as the time since visiting the emergency room. The characteristics were selected because research shows that they influence the way that an agent moves through opioid use states or the criminal justice system. We cover the characteristics that are included, how the values were determined, and any sources used in this section.

An h-agent's age is determined using census data from South Carolina based on age ranges [1]. The last age range (80+) was assigned an upper limit of 90. Only 4% of South Carolina's population is 80 or older, so an even smaller number would be older than 90, and we chose to not include that population in the model [1].

H-agents are given a binary value to represent early alcohol use. Early alcohol use has been shown to be a risk factor for future opioid misuse [194]. Early alcohol use is defined as alcohol use before fourteen [108]. Based on this definition, the lifetime rate of alcohol use of children thirteen or younger from NSDUH 2022 (8.7%) was used to inform the probability that an h-agent has previously engaged in early alcohol use [164].

H-agents are assigned a race that influences their chance of entering the criminal justice system. The chance that an h-agent is assigned a race was determined using census data from South Carolina [2]. We chose to use two racial categories, white and non-white. These categories were selected because census data makes it difficult to separate and correctly account for multiple races including multiracial people. Additionally, criminal justice system data may not include all races or multiracial people. After consulting with a criminal justice expert, we chose to use two categories to simplify the model and minimize incorrect assumptions about the percentage of people of different races. Based on the South Carolina census, 63.5% of the h-agents are assigned the race white and 36.5% non-white [2].

Gender affects how an h-agent moves through the opioid use states and the criminal justice system. The chance that an h-agent is assigned to be female is 51.3% and male is 48.7% with the values coming from census data from South Carolina [2].

Further characteristics that the h-agents have, the chance that an h-agent will have the characteristic, and the source for the chances are listed in Table 3.1. The way these characteristics

affect opioid use will be discussed in the following sections.

Characteristic	Chance	Source	Citation
Previous substance misuse	0.181	NSDUH	[164]
Anxiety disorder	0.232	SAMHSA	[5]
Mood disorder	0.37	SAMHSA	[5]
Low back pain	0.13	Journal Article	[193]
Renal impairment (age 18-44)	0.06	CDC	[68]
Renal impairment (age 45-64)	0.12	CDC	[68]
Renal impairment (age 65+)	0.38	CDC	[68]
Painful neuropathy (age 40+)	0.135	Journal Article	[87]

Table 3.1: Initialization Characteristics

In Table 3.1, renal impairment is assigned based on the age of the h-agent because it has different prevalence rates based on age [68]. Likewise, the chance of painful neuropathy is only given to h-agents forty and older based on previous research [87].

3.4.5 Changing Opioid Use States

Multiple data sources were used to support how the h-agents change opioid use states because opioid use and dependence is influenced by multiple factors. This section covers the data sources that were used and decisions that were made to inform how the h-agents move through the opioid use states by looking specifically at the arcs from Figure 3.2.

3.4.5.1 Medical Use

H-agents can move from no use to medical use. H-agents do not move from illicit use states to medical use. In reality, people illicitly using opioids may receive a prescription for legitimate reasons, but this is not accounted for in the model because that h-agent is already using opioids. It is unlikely that medical use of opioids would cause the h-agent to stop illicit use. In this scenario, any possible medical use could be considered a different supply for an h-agent in illicit use states.

If an h-agent is in the no use state, they can receive a prescription for opioids to move to the medical use state. The rates for opioid prescriptions are based on prescription opioid data from South Carolina. The number of unique patients and prescriptions over the course of two years is provided in [163]. The prescription opioid data also provides the number of patients who receive a prescription by age bracket [163]. As people age, they are more likely to be prescribed opioids, and we chose to assign a daily probability to receive a prescription opioid based on the age of an agent

to more accurately reflect the data [163].

We first found a yearly probability to receive at least one prescription regardless of age by dividing the number of patients by two and dividing that number by the number of people living in South Carolina [2]. We assumed that the number of patients is roughly the same in both years which appears accurate based on the data. We also assumed that the only patients receiving opioid prescriptions were from South Carolina. The yearly probability was converted to a daily probability by determining the chance that a person in South Carolina is not prescribed an opioid over the course of the year, and we used binomial probabilities to solve for this daily rate. Binomial probabilities require two mutually exclusive events where one is deemed a success and the other a failure [169]. In this case a success is considered as not receiving an opioid prescription. We then subtracted this number from one to find the probability of receiving an opioid prescription on a given day. Further explanations of the binomial probability calculations can be found in Appendix D.

To account for differences in age-related prescriptions rates, we determined the number of people living in South Carolina in the given age ranges using census related age data [1]. We divided the number of people who received prescriptions in the age range per year by the number of people in that age range to get a yearly percentage chance to receive an opioid prescription. We used the same methodology to find daily chances to receive a prescription opioid by age bracket as we did to find the overall daily chance to receive an opioid prescription.

Another important component for opioid misuse is the length of time a person is using an opioid prescription [55]. We used data from [163] to determine the average number of prescriptions per patient. We determined this value based on the number of prescriptions divided by the number of unique patients and found than an average of 4.4 prescriptions were given to each patient. Based on that value, we created a range of prescription amounts (1, 3, and 8) that an h-agent could be assigned when they moved to the medical use state. We assumed that a single prescription was likely for acute pain. In South Carolina, the prescription length for acute pain is typically seven days [162]. For three and eight prescriptions, we assumed that the person was receiving regular monthly (30 day) prescriptions. The h-agent's prescription length is based on the number of prescriptions they are assigned. The chance to receive one of the three prescription amounts was determined by solving for percentages that would average to 4.4 prescriptions per person per year.

If an h-agent is the medical use state, after they finish their set of prescriptions they will move to another state. Research from [179] informed the rates at which h-agents move from the

medical use state to illicit use states. From [179], the following characteristics will increase the chance that h-agents will misuse opioids: being younger than 30, having an emergency room visit in the past 30 days, having previous substance misuse, having an anxiety or mood disorder, having low back pain, having renal impairment, and having painful neuropathy. These characteristics do not all have equal effect on the chance to increase to opioid misuse and the effect amounts were taken from [179].

All h-agents start with a characteristic that tracks the time since their last emergency room (ER) visit and is initialized at 30 days to avoid triggering the penalty since most people have not been to ER in the past 30 days [71]. The daily chance for an ER visit was taken from the yearly ER visit data from the CDC [71] and was solved for using binomial probabilities.

Based on calculations from [179], the h-agent is assigned a probability to move to an illicit use state. Using the h-agent's probability, chance decides whether the h-agent moves to the no use state or an illicit use state. The length of the h-agent's prescription determines which illicit use state an h-agent moves into if they move into illicit use. If an h-agent has a prescription length that is longer than 30 days, the h-agent enters heavy use, otherwise they enter recreational use. Research shows that longer prescription lengths are more likely to lead to an opioid use disorder than shorter prescription lengths [55]. If the h-agent does not move to illicit use, they move back to the no use state.

3.4.5.2 Illicit Use States

H-agents in the no use, recreational use, heavy use, and OUD states change states based on the characteristics in Table 3.2. The sources informed which characteristics to include and whether they would increase or decrease the likelihood of opioid use. The chance values were arrived upon based on expert opinion.

Some of the characteristics (gender, early alcohol use, previous mental health diagnosis, age, and previous substance use disorder) are set at the model initialization. The other characteristics develop as the model runs.

Randomness, which is not included in Table 3.2, is used to account for static and variable risk factors that are not directly modeled. Static risk factors for opioid use disorder include genetics [85] and adverse childhood events [144] which will not change over time. In the model initialization, a susceptibility value for the h-agent is randomly generated as a value between 0 and 0.25 and simulates

Characteristic	Chance	Source	Citation
Male gender	+0.05	Journal Article	[12]
Early alcohol use	+0.05	Journal Article	[51]
Previous state OUD	+0.3	Journal Article	[214]
Previous state heavy use	+0.2	Journal Article	[214]
Previous state recr. use	+0.1	Journal Article	[214]
Previous mental health diagnosis	+0.05	Journal Article	[214]
Age (49+)	-0.1	Journal Article	[214]
Peer influence	+ or - 0.05	Technical Report	[6]
Previous substance use disorder	+0.2	Journal Article	[12]

Table 3.2: Characteristics that Adjust Opioid Use Chance

static risk factors. The lower the susceptibility is, the less susceptible the h-agent is considered to be to opioid misuse. The numeric values were chosen based on expert opinion.

Variable risk factors for opioid use disorder include living in a disadvantaged community [105] and stress [116] which can change over time. Variable risk factors are modeled by creating daily random values between 0 and 0.25 and are affected by the h-agent's susceptibility. The daily random values are created using a triangular distribution with the susceptibility value as the mode. The daily value is averaged with the average of the previous seven days' values. In the initialization of the model, seven values are created using the same triangular distribution as the daily values to create a week's worth of values.

An h-agent's neighbors also affect an h-agent's state and are incorporated in the characteristic peer influence [6]. In the grid structure, the h-agents can share a cell with each other. To simulate the effect of peer influence, the h-agent considers the average state of all h-agents with whom they share a cell. If the average is higher than the h-agent's state, the h-agent is given a characteristic that increases the chance that they begin or increase use. If the average is lower, the h-agent's characteristic is changed to be more likely to decrease their use, and if the average is the same, the characteristic remains neutral.

All of the chances and randomness are summed. Depending on the h-agent's current opioid use state and the summation, they can increase or start opioid misuse, reduce or stop opioid misuse, or stay in their current state. However, if an h-agent has increased their opioid misuse in the past 14 days, they will not increase their misuse regardless of the summation value. The delay slows ascent to higher use because it does take time to develop opioid dependence. In the no use state, there is only a boundary to move to misuse, and in the OUD state there is only a boundary to reduce use.

The boundary values were determined during calibration.

3.4.6 Opioid Use Disorder Treatment

Two different treatment types, in-patient and out-patient, are incorporated into the model. In-patient treatment means that the person stays in a residential treatment center while receiving treatment while attendees of out-patient treatment go home each day [43]. Each of the treatment types could incorporate different therapy methods, including medication assisted treatment (MAT), psychotherapy, group therapy, or a combination of those methods. In speaking with an expert, we chose to focus on the setting in which the therapy is delivered as opposed to the specific therapy methods. The decision reduces model complexity because people in recovery may be involved in different therapy methods at the same time.

H-agents who are in the opioid use disorder or heavy use states have a random daily chance to enter treatment. The daily chance comes from the 2022 NSDUH survey [164] where people report if they thought they needed treatment, and if they believed they need treatment if they had it in the past year. The daily rate is higher for h-agents in the OUD state based on the self-reported values.

When h-agents enter treatment, they have an equal chance of starting in-patient or out-patient treatment. The treatment types are given equal weight because the NSDUH survey shows that roughly the same number of people entered in-patient as out-patient treatment for opioid misuse [164]. The treatment lengths for each treatment type were found from [43]. In-patient treatment was assigned a length of 60 days while out-patient was assigned 135 days [43].

If an h-agent goes to in-patient treatment, after finishing that treatment they will begin an out-patient treatment program. Upon speaking with an expert, out-patient treatment typically follows in-patient treatment, like a "step-down" model. We chose to not include the "step-up" version where a person goes from out-patient to in-patient, often due to struggles in out-patient treatment, because in-patient treatment capacity may be limited, and people may not want to attend or be able to afford more intensive treatment.

Research has been done to predict whether people will relapse while in treatment [192]. In the ABM, relapse is influenced by criminal justice involvement [192], the treatment type [192], and previous treatment attempts [49]. Approximately 36% of all treatment events end in treatment discontinuation, and we used this value to determine a daily chance to discontinue treatment [192]. If an h-agent relapses, they return to their previous opioid misuse state. The h-agent also has a higher

chance to overdose the first time they use opioids after leaving treatment because their tolerance has been altered [197]. After successfully completing treatment, the h-agent moves to the no use state.

H-agents who are in treatment are at an increased risk of relapse if they share a cell in the ABM with another h-agent who is misusing opioids. H-agents in treatment check if their neighbors' are misusing, and if they are the h-agent's risk of relapse is increased.

3.4.7 Preferred Opioids and Route of Administration

The h-agent's past opioid use influences their preferred opioids and route of administration. H-agents begin opioid misuse by misusing either prescription opioids or counterfeit prescription opioids. If an h-agent is transitioning from the medical use state, they will continue to use prescription opioids. Otherwise, h-agents have an equal chance to use prescription opioids or counterfeit prescription opioids.

H-agents change the type of opioid they prefer over time. Every time an h-agent uses opioids, they have a small chance to begin using a more potent opioid. For the model's purposes, counterfeit prescription opioids are more potent than prescription opioids, heroin is more potent that counterfeit prescription opioids, and fentanyl is more potent that heroin. In general, potency of opioids are measured in morphine equivalent doses (MEDs). Heroin typically has an MED between 2 and 5 while fentanyl can be between 50 and 100 depending on the amount and purity [180].

If an h-agent moves out of the opioid misuse states, their preferred opioid type is carried with them. If they begin to use again, they will start with their preferred opioid type.

There are three routes of administration that are built into the model. H-agents can use orally, through smoking, or through injecting. In the case of the model, oral use of prescription opioids or counterfeit prescription opioids also includes insufflation (snorting). Insufflation of pills can be used to remove an extended release coating as well as produce a faster high [200].

H-agents begin opioid misuse through an oral route. As they use opioids, they have a small chance to begin using a route that produces a more efficient high. For this model, oral use is less potent than smoking, and smoking is less potent than injection [225].

3.4.8 Criminal Justice System

People who are misusing opioids are at higher risk of entering the criminal justice system (CJS) than those who are not [219]. A key reason to include the CJS in a model counting opioid overdoses is because reduced tolerance that can occur after time in the CJS can lead to unintentional overdoses [197]. Because we are focused on the result of exiting the CJS and then using opioids, only h-agents who are misusing opioids enter the CJS. Additionally, because the chance of entering the CJS is so low, h-agents only have a chance to enter every 30 days.

H-agents' chance of entering the CJS is based on their race and gender. H-agents who are white or female have a lower likelihood of entering the CJS. The chance that h-agents enter the CJS was based on the number of unique jail admissions in South Carolina. According to [28], 1,783 unique individuals are admitted to jail per 100,000 state residents each year. From this value, an overall monthly chance of 0.15% was found to be sent to jail. The monthly value was adjusted for race and gender by considering the proportion of the population currently in the CJS that is in the four categories (white male, non-white male, white female, and non-white female) [161] and the percentage of the overall population that is in those four categories [2]. The ratio of the percentage of the CJS population to the overall population percentage was multiplied by the monthly chance to be sent to jail to get four monthly values.

If the h-agent enters the CJS, they can be sent to jail, prison or treatment court, and the chance to be sent to each option was influenced by the number of unique jail admissions in South Carolina [28] and the number of people currently in prison [161]. Little is published about the number of people who begin treatment court in South Carolina. Based on unique jail admissions, current people in prison and expert opinion, we decided on the percentage chance to enter each part of the CJS. 85% of the h-agents go to jail, 10% go to prison, and 5% go to treatment court. The length of a jail sentence in the model was 33 days [146], a prison sentence was 46 months [150], and drug treatment court was 18 months [165]. Release from jail or prison can increase the risk of overdose because people's tolerance has changed which has been incorporated into the model [197].

If an h-agent is sent to jail or prison, they do not move through opioid use states during their sentence. When they finish their sentence, the h-agent exits with the same opioid use state as they entered the CJS. In treatment court, the h-agent receives court-mandated treatment and moves to the treatment state instead of going to prison or jail [36]. The treatment process for h-agents in

treatment court is the same as other h-agents but does last for longer. If an h-agent is unable to complete their treatment court process, they are sentenced to prison [36].

People who are involved in the CJS once are more likely to be involved again. In the model, after an h-agent has entered the CJS, they have a higher chance of re-entering the CJS. To determine this chance, the three year recidivism rates from South Carolina were used [161]. The rates were only provided for males and females so no racial component was added [161].

3.4.9 Opioid Agents

The opioids that h-agents use are the second agent type. We chose to model opioids as opposed to dealers or pharmacies because there are many ways that people get opioids to misuse. People who want to use opioids can reach out to friends and family with leftover prescriptions, dealers, or pharmacies. Modeling only the availability of the supply itself simplifies the model and removes bias against people who may be involved in supplying opioids.

The o-agents can supply one of four types of opioids: prescription opioids, counterfeit prescription opioids, heroin, and fentanyl. Counterfeit prescription opioids are pills that are not made by pharmaceutical companies but are made to look like legitimate prescription opioids [167]. Each o-agent has a supply of forty units on-hand. This value came from an interview with law enforcement and was validated by an expert. The agents can be resupplied weekly if they have two or fewer units. Otherwise, they wait to receive more opioids.

The supply that the o-agents receive has three possible levels of potency: low, medium, and high. Research shows that there is high variability in the potency of opioids since the market is unregulated [7]. The changes in potency will simulate how overdoses can be related to "bad", or unexpectedly strong, batches of opioids [16]. In the model, 20% are low potency, 20% are high, and the remaining 60% are medium.

The percent of the o-agents that are allocated to each of the four types was determined based on the types of opioids that the h-agents were expected to use from the 2022 NSDUH. Of the o-agents, 41.65% supplied prescription opioids, 41.65% supplied counterfeit prescription opioids, 11.1% supplied heroin, and 5.5% supplied fentanyl.

3.4.10 Interaction between Agent Types

The agent types interact to supply the h-agents with opioids. If an h-agent wants to use opioids, they first look at their own supply. If the h-agent has more than one unit of their preferred opioids, they use the opioids that they have. Otherwise, the h-agent looks at the o-agents available in the model. If the h-agent has one unit of opioids, the h-agent only looks for o-agents that match their preferred opioid type. If they find their preferred opioid type, they buy two units if the o-agent has the supply to support that and one otherwise.

If the h-agent doesn't have any supply, they look for o-agents that have their preferred opioid type or are less potent. If the h-agent is in the heavy use or OUD state, then they also look for more potent opioids if less potent ones are not available. After a list of o-agents that meet the h-agent's requirements are found, the h-agent chooses the closest o-agent to get the supply.

3.4.11 Overdoses and Overdose Deaths

Any h-agents who are misusing opioids can experience an overdose. Opioid overdoses occur primarily due to respiratory depression, which can lead to hypoxia [218]. Overdose likelihood is influenced by opioid batch potency [73], route of administration [212], and lowered tolerance due to release from jail or prison or relapse from treatment [197]. Tolerance to respiratory depression is also likely developed more slowly than the tolerance to the euphoria produced by the opioids which can present another risk [218].

Not all overdoses are fatal overdoses. An opioid overdose has an 18% chance to lead to an overdose death [40]. Research showed that in 2020 there were approximately four non-fatal overdoses to every fatal overdose for people who are using opioids [40].

3.4.12 Natural Population Growth and Death

H-agents may die naturally as well as due to opioid use. Daily chances of dying by age were determined using the United States Social Security Actuarial Tables [8]. These tables provide the probability that a person dies in a year based on their age. The yearly probability was translated to a daily probability using binomial probabilities.

To keep a stable population, h-agents must be added to the model. H-agents are added to represent people turning eighteen based on the birth rate in South Carolina in 2005 from the CDC

[81]. This year was chosen for the birth rate because it will more closely simulate the rate that people turn eighteen in 2023 instead of the rate that people are born in 2023. The new h-agents are generated with the same chance of characteristics as the original agents with the exception that all of the new h-agents' ages are set to eighteen.

3.4.13 ABM Pseudo Code

In the model, every day each h-agent and o-agent has actions that may be taken depending on their characteristics and states. Algorithm 1 shows the pseudo code for each day for the h-agents, called the step function. H-agents are not removed from the model after their death for accurate record keeping so the code must begin by checking if the h-agent is alive.

Algorithm 1 ABM Step Function Pseudo Code

```
1: if h-agent is alive then
2:     Increment h-agent's time
3:     Check for natural death
4:     if h-agent is alive then
5:         if h-agent is in jail or prison then
6:             Continue movement through CJS
7:         else if one year has passed then
8:             Increase h-agent's age
9:             Move the h-agent
10:            Check h-agent's neighbors' opioid use states
11:        else
12:            Check h-agent's neighbors' opioid use states
13:        end if
14:        if h-agent is in treatment then
15:            Check for neighbor-influenced relapse
16:        end if
17:        Check for ER visit
18:        Run h-agent opioid use status function
19:    end if
20: end if
```

The function that runs in line 18 of Algorithm 1 is related to an h-agent's opioid use state including possible updates to the h-agent's opioid use state. All of the opioid use states have different update functions for the h-agents. Pseudo code for the recreational use state is shown in Algorithm 2.

The o-agents also have code that runs each day. Algorithm 3 describes what each o-agent does each day, called the step function.

Algorithm 2 Recreational Use Update Pseudo Code

```
Update h-agent's time in the state
Use chance to see if the h-agent wants to use opioids
if h-agent wants to use opioids then
    Update time misusing and time since use
    Seek and use opioids
    if h-agent has a fatal overdose then
        Update status
    else
        Check if h-agent changes state
        if if h-agent changes state then
            Update state
        else
            Check if route of administration or preferred opioid changes
        end if
    end if
else
    Update time since use
    Check if h-agent moves to a lower state
    if h-agent changes state then
        Update state
    end if
end if
if h-agent is not in the CJS then
    Check for CJS entrance
end if
```

Algorithm 3 O-Agent Step Function Pseudo Code

```
Increment the time since the o-agent has been supplied
Move o-agent
if o-agent time since resupply is high and o-agent supply is low then
    Resupply
end if
if o-agent is empty and has been resupplied then
    Remove o-agent from model
end if
```

3.5 Methods

3.5.1 Mesa

We have chosen to use Mesa, a Python module, to program the ABM. Mesa's goal is to be a Python-based alternative to other ABM programs [102]. Mesa provides access to Python's other packages and has clear components for model development, analysis, and visualization [102].

3.5.2 Population and Grid Size

The model population is based on the population of South Carolina. According to the census, South Carolina has a population of 5.37 million people [2] and 78.5% is 18 or older [1] giving a population of 4.2161 million people who are 18 or older in South Carolina. We chose to model one percent of the population and created 42,161 h-agents.

The model grid space is a square. To determine the number of h-agents per square, we considered the social connections that the average person has which will inform the peer influence value. The number of social connections was based on close friends and family size. On average, Americans have 4.1 close friends (not including family) [53] and households have 3.1 family members [63]. We determined the number of total cells in the grid by dividing the population by the total number of connection (7.2). We took the square root of that value and got a grid size of 76 cells by 76 cells.

The number of o-agents initialized in the model was determined based on the expected number of h-agents misusing opioids that was determined for model calibration. Based on an interview with law enforcement, each of our o-agents can supply around five h-agents. We expect that opioid demand is generally being met, so the model needs approximately one-fifth the number of o-agents as h-agents who are using. Since we anticipate 1,350 h-agents to be misusing opioids based on the NSDUH survey over the course of the year [164], we modeled 250 o-agents.

We also had to decide the percent of o-agents that would supply each opioid type. These percentages were based on the opioids that people reported using from the NSDUH survey [164]. When initialized the o-agent has a 41.65% chance to supply prescription opioids, 41.65% to supply counterfeit prescription opioids, 11.1% to supply heroin, and 5.5% to supply fentanyl.

3.5.3 Model Calibration and Validation

The model was manually calibrated to historical values of overdose deaths, the types of opioids that h-agents are using, the h-agents routes of administration, and the number of h-agents in different opioid use states. For calibration, we primarily used information from 2022. At the time of model creation, these were the most recent validated numbers and survey results available. In 2022, 2,204 people died from unintentional opioid overdoses in South Carolina [160]. Since the ABM models 1% of the population, we calibrated the opioid overdose deaths to be 22 per year.

We chose to anticipate that opioid overdose deaths would remain stable. Overdose deaths appear to be leveling off after a rapid increase in 2020 and a smaller increase in 2021 [166]. The cause or causes of the increase of overdose deaths in 2020 and 2021 can not be definitively stated although COVID-19 likely played a role [157].

Opioid overdose deaths were roughly the same in 2022 as in 2021 nationally [166] with a slight increase between the two years in South Carolina [160]. Provisional reports show that in 2023 opioid overdose deaths decreased for the first time since 2018 including synthetic opioid overdose deaths [70]. For these reasons, we believe it is reasonable to calibrate the number of overdose deaths to 22 without including increases. Changing opioid supply and use patterns can be updated and tested if further supply changes are anticipated.

The values for the other metrics were found using historical data from the 2022 NSDUH survey. The number of h-agents expected in opioid use states was taken from the 2022 past year types of illicit drug use and people with opioid substance use disorders in 2022 [164]. The percentage of h-agents expected to be using each opioid type was taken from 2022 past year types of illicit drug use [164]. Finally, the expected route of administration was taken from 2022 past year needle and heroin use [164].

The calibration was done by adjusting variables to meet the historical estimates. Validation of ABMs can be difficult since they function differently than other model types. For validation of the ABM, we relied on the judgement of domain experts to ensure that the model structure and results are logical and working as expected [173].

3.5.4 Model Parameters

The model has a time step of one day and each agent has code that runs once per day. The model starts with all h-agents in state 0. To allow the h-agents to move into illicit opioid use states and minimize any initialization bias, we used a burn-in period to allow the h-agents to develop a history [101]. We ran the model until the h-agents reached an equilibrium [101]. For this ABM, equilibrium was reached after running for ten years. After the burn-in period, the model was run for five years to generate results. The model was run thirty times with different number seeds, and the results from each simulation run were averaged.

3.6 Results

This section covers the results from the ABM and how they compare to historical values.

3.6.1 Overdoses and Overdose Deaths

A critical test for the ABM is to be able to accurately produce overdoses and overdose deaths since they are an important measure of the severity of the opioid overdose epidemic and a key component when considering harm reduction policies. Table 3.3 lists the historical values and average number of overdose deaths and total overdoses over the course of the five year simulation. The table also contains the lower-bound and upper-bound values produced using a 95% confidence intervals for each of the categories.

Category	**Historical**	**Average**	**Lower-Bound**	**Upper-Bound**
Fatal Overdoses	110.2	109.6	106.3	112.9
Total Overdoses	589.3	598.9	588.5	609.3

Table 3.3: H-Agents Overdose Results

The number of fatal overdoses is close to the historical expected number of overdoses over the course of the five years. The average number of fatal overdoses per year from the simulation was 21.93, compared to the historical value of 22.04.

The historical value of total overdoses was calculated assuming the ratio of fatal to nonfatal overdoses given in [40]. With the historical number of overdose deaths known, we calculated an assumed number of total overdoses.

There was a varied amount of fatal overdoses each year over the simulations as shown in Figure 3.3. The box and whisker plot shows that the yearly average is similar over the five years that the model runs.

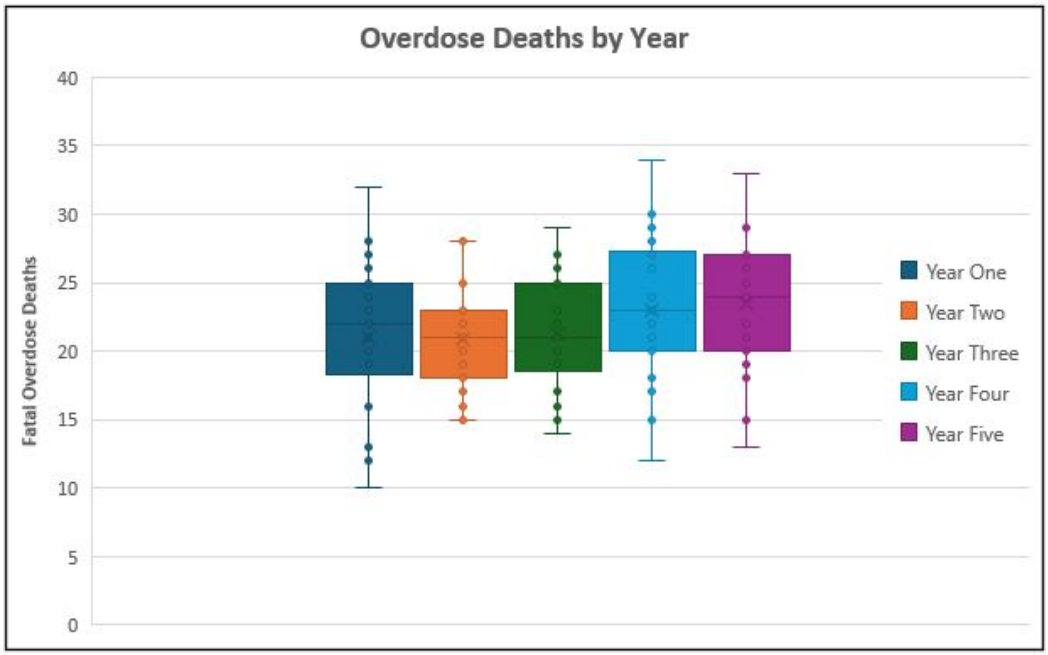

Figure 3.3: Fatal Overdoses by Year

3.6.2 Opioid Use States

Another important metric in the model is how many h-agents are misusing opioids. Figure 3.4 shows the number of h-agents in each of the three opioid misuse states (recreational use, heavy use, and opioid use disorder) over a five year period. There are small changes in the number of h-agents in the heavy use and opioid use disorder states over the course of the simulation. The recreational use state shows an increase over the course of the five years. In total, there is a small increase in the total number of PWUO over the five year simulation.

Values for daily use are sparse in the literature, so we used NSDUH survey data that reports last year use of opioids and people who have been diagnosed with opioid use disorder. The total number of h-agents that misused opioids in the last year is compared to the expected historical values in Table 3.4. In this table, the h-agent is counted to have misused opioids if they were in states 2, 3 or 4 over the course of the year. We also separate between recreational use and daily use

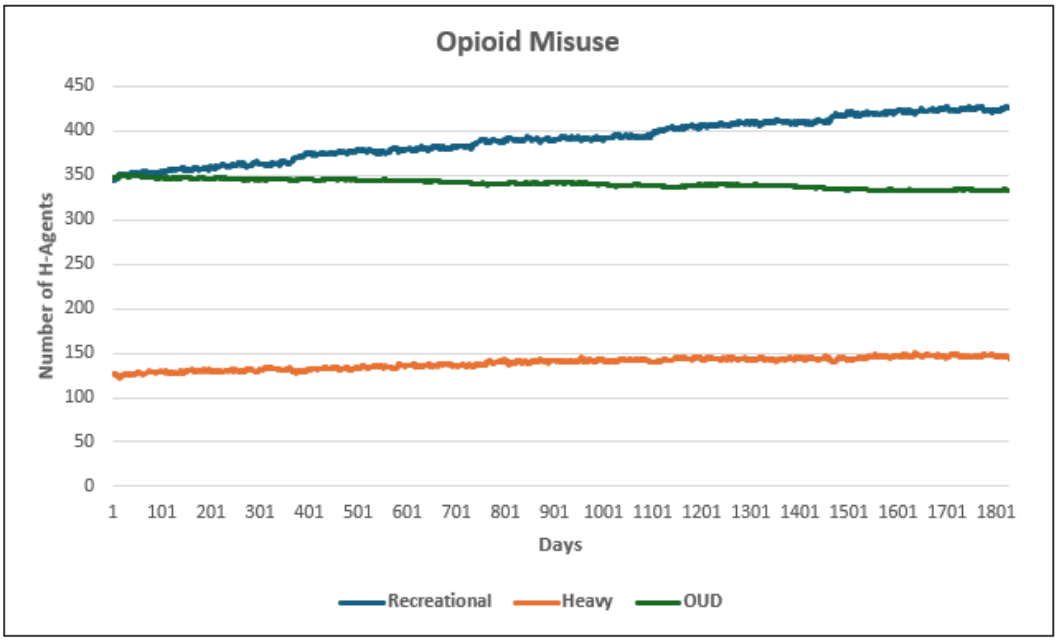

Figure 3.4: H-agent Misuse States

which includes states 3 and 4. To count the number of h-agents in a specific state we consider the highest opioid use state that they reached in that year. For example, if an h-agent spent time in states two and three over the course of the year, they would be included in both the total misusing and states 3 and 4 category because they did misuse opioids and spent time in heavy use. An h-agent who only spent time in state 2 would only be counted in the total misusing category.

Category	Historical	Yearly Total	Lower-Bound	Upper-Bound
Total Misusing	1349.0	1312.9	1288.5	1337.3
States 3 and 4	969.0	1057.9	1040.0	1075.8

Table 3.4: H-Agents Misusing During One Year

The confidence intervals for both categories are relatively narrow. While the historical values do not fall in the bounds, they are close to the yearly total the model produced. The yearly total misusing is 2.7% lower than the historical average, and the value of states 3 and 4 is 9% higher. Differences in the category definitions and the NSDUH survey questions could cause some of the variation between the historical and model values.

We also considered the h-agents in the other states. On average, there were 2,673 h-agents who were using licit opioids in state 1 (prescribed opioids) each day. Over the thirty runs, an average of 8,178 h-agents were prescribed an opioid in the last year. Using South Carolina data, we expected

18.4% of the population to receive at least one opioid prescription in a year [163]. In our model, 19.4% of the population received at least one opioid prescription in a year.

Licit prescription opioids have led some people to subsequent opioid misuse and this mechanism is accounted for in the ABM. Over the five years, an average of 218 h-agents moved from licit use to illicit opioid use when their prescription ended.

On average, 45.5 h-agents were in state 5 (treatment) on a given day. There were an average of 961.5 treatment visits over the course of five years. This value includes h-agents who entered in-patient or out-patient treatment and who entered treatment court due to their involvement in the CJS system.

The h-agents had an average treatment completion success rate of 61%. Since research has shown that approximately 36% of treatments ended in premature discontinuation, the success rate is similar to previous research values [192].

3.6.3 Preferred Opioid

Another metric for the model is the opioids that the h-agents preferred in the past year. The historical values came from the NSDUH survey that reported the opioids used by people in the past year [164]. The historical values for prescription opioids and counterfeit prescription opioids are combined because the NSDUH only reports values for misuse of pain relievers. For the model results, if an h-agent preferred either prescription opioids or counterfeit prescriptions opioids in the past year or both, they are counted once. The yearly average and historical values are in Table 3.5 along with the 95% confidence interval lower-bound and upper-bound.

Category	Historical	Average	Lower-Bound	Upper-Bound
PO and CPO	1264.8	1182.7	1167.6	1197.9
Heroin	168.6	147.2	142.0	152.4
Fentanyl	84.3	80.6	76.5	84.8

Table 3.5: H-Agents Preferred Opioids During One Year

The historical fentanyl value falls within the 95% confidence interval bounds, and the heroin average value is close to the historical average (12% lower). The prescription opioid and counterfeit prescription opioid category has the largest absolute difference and is 6% lower than historical values. One possible reason for the difference is that the pain relievers category in the NSDUH may include people who use pain relievers that are not opioids which could increase that historical value. Another

reason the model values may be lower is that the model tracks preferred opioids and not opioids that were used. People who prefer heroin may use prescription opioids if they are available.

3.6.4 Preferred Route of Administration

We also assessed the h-agent's preferred route of administration. The historical values were again found using the NSDUH survey and specifically considering past year values [164]. Values are available in the survey for injection use, smoking, and insufflation of heroin, but no survey questions are asked about oral use or insufflation of prescription opioids. We calculated the oral value by subtracting the historical numbers of people smoking and injecting from the historical expected opioid users.

Category	Historical	Average	Lower-Bound	Upper-Bound
Oral	1054.0	1125.1	1110.0	1140.1
Smoke	168.6	173.2	168.8	177.7
Inject	126.5	126.5	122.0	131.0

Table 3.6: H-Agents Preferred Route of Administration During One Year

The number of h-agents who prefer smoking and injecting are similar to the historical averages, with the model producing 2.7% more h-agents who prefer smoking than the historical average. The number of h-agents who use through an oral route are higher in this model (6.7% higher), although this could be because we do not have good values for oral use or insufflation of prescription opioids and counterfeit prescription opioids.

3.6.5 Criminal Justice System Values

The number of h-agents in the criminal justice system was also analyzed. Because only h-agents who are misusing opioids will enter the CJS in this ABM, the number of people involved is fairly small. Based on the number of people who are misusing opioids and the monthly chance to enter the CJS, we expected approximately 24 people to enter the CJS each year. The model produced an average of 23.2 h-agents entering the CJS yearly.

3.7 Discussion and Limitations

As noted in the Chapter 2, data sources continue to be a limitation for models of the opioid overdose epidemic. Regression models have been able to provide some insight into the characteristics that are likely to increase or decrease opioid misuse, but quantifiable data that contains the characteristics that we are using is difficult to find and was supplemented by expert opinion and calibration. Additionally, genetic characteristics that affect how quickly individuals develop a tolerance to opioids and how likely they are to become dependent are still not well documented.

Data sources related to the opioid supply, which include data for the o-agents, are also lacking. While we know that some batches are unexpectedly potent, the exact values are difficult to determine. For our model, the percent range of potencies and amount of supply available was supplemented by expert opinion and previously conducted interviews. Further interviews with law enforcement, PWUD, and people who supply drugs can provide information about the drug supply in the area being considered.

Data limitations also affect treatment data sources. People in treatment may relapse and use opioids but choose to stay in treatment. However, we found little data discussing the daily chance of relapse that would allow the PWUD to stay in treatment and how long attendees can relapse in treatment facilities or programs before their treatment is discontinued. For this reason, the model only considers relapse that leads to treatment discontinuation.

Treatment types in the model are focused on in-patient and out-patient care, but in reality the treatment methods and quality of treatment can vary. Different types of treatment, like medication treatment for OUD, and different treatment qualities can affect outcomes for PWUD [104]. We did not consider these differences in the model because the quality of treatment centers is difficult to quantify and validate.

Predicting who will receive prescriptions for opioids and how they will react to those prescriptions is a challenge. We have compiled state data to make informed decisions like adjusting the chance to get a prescription opioid by age. However, age is a protective factor from opioid misuse and most professionals are not concerned about people who have terminal illnesses developing dependence on opioids. More accurate data for predicting who will receive long-term opioid prescriptions with non-terminal diagnoses could improve model accuracy in predicting who will develop opioid dependence.

The drug seeking and acquiring function has some limitations. H-agents do not use money to purchase opioids but specifically consider how far away the o-agent is. Price and location are both a consideration when making any purchase. Price was excluded from the model because data is difficult to find for the prices of different opioids and the price fluctuates over time and location. Additionally, price may not be involved when prescriptions opioids are sourced from excess supplies from friends or family.

The h-agents also do not have an affinity for an o-agent supply source. People often know the dealers they purchase from, and this relationship can be considered protective if there is trust in quality control measures [39]. H-agents also have access to all of the types of opioids in the model as opposed to a limited subset based on the suppliers the h-agents know. Creating a network of o-agents available to each h-agent is an avenue for future work.

Finally, h-agents consume a fixed amount of opioids each time they use. Agents do not vary the amount that they use over the course of the model, but they can choose to use more potent opioids. In reality, as tolerance builds, people may choose to increase the amount of opioids used [138]. Since tolerance to euphoria seems to increase more quickly than tolerance to respiratory depression, points where people increase the amount they use could be areas where they are at higher risk of overdose [218]. As mentioned previously, the characteristics that affect tolerance are not well documented, so this mechanism is difficult to include currently.

There are limitations related to how agents choose which opioids they prefer to use. The reason people choose opioids and their route of administration is influenced by many factors likely including the way the opioids make the person feel, opioid availability, opioid cost, and any perceived risks of the route of administration or opioid type. Some of these values are difficult to quantify, specifically perceived risks and enjoyment. Determining which opioids people start using is also difficult and may change based on different factors. For these reasons, we chose to use a fixed path of opioid type increases that were informed by expert opinion.

The model has similar limitations related to route of administration for h-agents. Research does show that most people begin using through non-injection methods and primarily oral routes [47]. Due to tolerance increases, PWUD often begin to increase their route of administration because orally taking multiple pills can be expensive and impractical [47]. Other methods can also produce a faster pharmacological onset while using less of the drug [47]. However, PWUD may choose to use multiple routes or reduce the severity of their route of administration [47]. Route of administration may also

differ between urban and rural populations [225]. The model does not allow h-agents to reduce their route or preferred opioid of use. While they cannot reduce their method or preferred opioid of use, the h-agents are able to reduce their state of opioid misuse based on their characteristics.

Poly-drug use or combining different drugs is not included in the model even though in 2020, 68% of stimulant overdose deaths involved an opioid [72]. Most opioid models identified in the literature review did not include stimulants, like cocaine or methamphetamine. Because stimulants are not included, opioid overdose deaths may be over counted in the model. In published data opioid overdose deaths include people who were not intentionally using opioids but encountered other drugs that were laced with fentanyl [72]. Addressing this limitation is a possibility for future work.

The o-agents are currently simple and do not contain internal logic or variety in the supply amounts. These values were not included due to a lack of data about supply variation and logic. As more information becomes available, the o-agents could be updated to vary the amount of opioids they have, the costs associated with the opioids, and the types of opioids they choose to carry.

In the current model, h-agents move in the environment once per year because the primary environmental factor uses neighbors to simulate peer influence. However, this methodology does not capture how people move from work to home to activities in their daily lives. Work colleagues and acquaintances can also influence the opioids a person may decide to use. The method also requires h-agents to change their social connections yearly even though many social connections last longer than that. Similarly, peer relationships are counted as h-agents who share the same square, but the h-agents do not have assigned family relationships with other h-agents who are not local that may affect use.

Currently, opioid misuse does not change an h-agent's chance of natural death. However, opioid use can increase disease burden with rising rates of hepatitis C and HIV among other diseases [112]. Their natural death rate is likely higher than a person with similar characteristics without opioid misuse even without including risk of overdose.

The criminal justice system that has been modeled has limitations. H-agents only spend time in jail, prison, or treatment court with no time spent on parole or probation. People who are on parole or probation would likely require drug testing which could affect their decision to use opioids as well as the consequences of use. The model also does not account for opioid use in prison or jail. Research suggests that about a third of people use drugs while incarcerated [14]. People who are in the CJS for non-opioid related crimes may become exposed to opioids and begin using while

in prison. Likewise, long prison sentences may lead to abstinence upon release. Because we have a relatively small population of incarcerated people and the addition of determining how h-agents would use opioids in prison is complicated, we decided to ignore these uses for now.

Determining who will enter the CJS is done at a coarse level. The model contains four groups with gender and rudimentary racial data. Age and more expansive racial data could be used to better anticipate who would enter the CJS. H-agents are also all initialized with no CJS involvement, even though some of the population has been involved with the CJS. This involvement could make some h-agents more likely to re-enter the CJS than they are in the model. However, this data has been difficult to find which led to the decision to use the current data.

Population growth in the model is focused on minors turning eighteen and does not consider immigration from outside the state or emigration from South Carolina. However, since we are modeling a small percent of the population, changes in the overall population size will not greatly change the number of h-agents that need to be modeled and we decided to keep a steady population size and avoid determining the characteristics for people immigrating to the state.

The model also only includes people who are eighteen and older. The NSDUH shows that some minors misuse opioids which could have some influence over overdoses, deaths, and the number of PWUD [164]. However, the number of minors who misuse opioids is relatively small per the survey, and much of the survey data provides responses of adults separated from minors.

Limitations exist in the data that was used to calibrate the model. The NSDUH was used for most calibration data because it is thorough, covers many questions about type, frequency, and route of administration, and attempts to survey a representative sample of the United States. However, this means the survey provides federal data instead of information specific to South Carolina. Additionally, the NSDUH contains self-reported data of stigmatized information and therefore may be underreported [82]. Even with these limitations, the NSDUH estimates are frequently used and have been tested and found to have moderate clinical validity [98].

3.8 Conclusion

We developed an ABM to model the opioid overdose epidemic in South Carolina. The model had two agent types: h-agents who could use opioids and o-agents who supplied opioids. The model allowed h-agents to move through seven states with differing levels of opioid use and misuse.

The h-agents moved through the states based on their personal characteristics, the characteristics of h-agents close to them, and random chance. The ABM contained a treatment system for opioid use disorder, a criminal justice system, four types of opioids, and three possible routes of administration for the opioids.

The model was calibrated using historical data primarily from 2022, and thirty simulations were run. Because all h-agents are initialized with no opioid use, the models were run for a ten year burn-in period and then for an additional five year simulation period.

Results showed that the model replicated key metrics compared to historical averages. While some historical averages did fall outside of the 95% confidence intervals, overdose deaths and total overdoses did fall with the bounds. An average of 1,312.9 people were misusing opioids in the past year and 21.93 people died per year due to overdoses. As more field research provides supporting data, the values and behaviors of the ABM can be updated to provide more accurate results.

Chapter 4

Policy Evaluation Using Agent-Based Model

4.1 Introduction

The opioid overdose epidemic has affected many people. A survey of US adults found that over 42% of people knew at least one person who had died by an overdose [13]. Opioid use disorder is a complicated disease and the changing opioids involved have made the crisis difficult to adequately address. The use of different types of opioids, primarily prescription opioids, heroin, and synthetic opioids, have shifted as the epidemic has progressed times. The deaths caused by the three "waves" of opioid types are shown in Figure 4.1.

As deaths began increasing in the early 2000s, governments and medical establishments worked to curb access to excess prescription opioids [33]. However, some of the people who were dependent on opioids may have turned to illicit opioids, primarily heroin, to avoid withdrawal [137]. In the mid 2010s, fentanyl became more common likely due to heroin and prescription opioid shortages, fentanyl's lower price point, and fentanyl's increased potency [135]. Fentanyl was also mixed into other drugs, like heroin, which makes the heroin more potent but could lead to overdose if the potency is stronger than the PWUO expects [134].

Some of the interventions enacted by governments and organizations may not have the anticipated effects. Prescribing of opioids was curtailed to correct for over-prescribing, but some

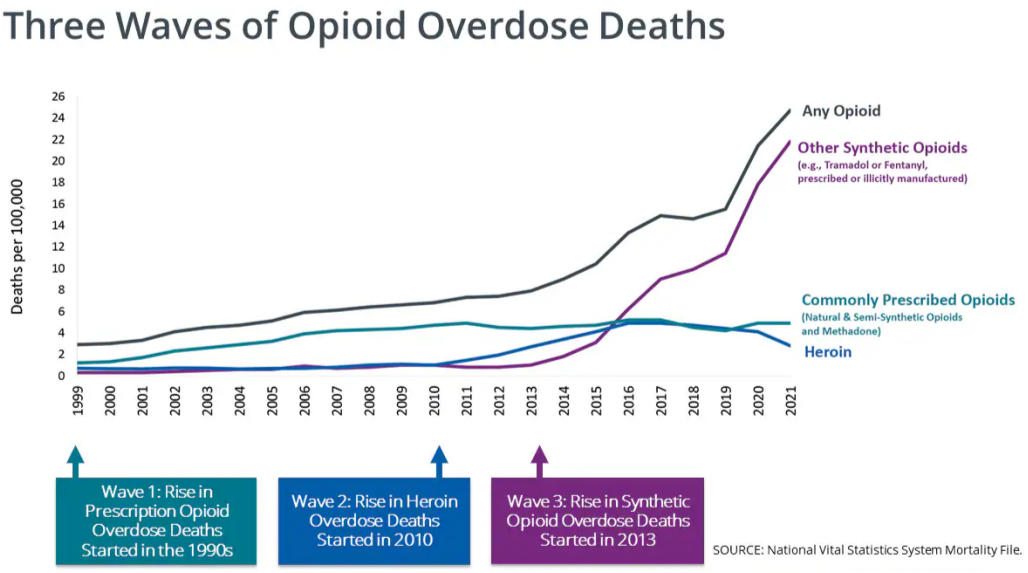

Figure 4.1: Waves of OD Deaths in the US [69]

former patients likely transitioned to other opioids to help manage pain or prevent withdrawal symptoms [196]. The reduced prescribing patterns may have a beneficial effect in the future since it is likely that fewer people are becoming dependent on prescription opioids from licit prescriptions, but the short-term effects did not lead to fewer overall overdose deaths.

Evaluating policies using models can provide guidance so policymakers understand what the likely outcomes are which can allow them to decide how to best allocate limited funding and other resources. Models can also be used to simulate possible changes in supply, demand, or drug use patterns. While models may not have the ability to predict future events, they can allow hypotheses about future events to be tested. In this chapter, we will simulate two possible changes in the opioid overdose epidemic using the agent-based model: increased unknown fentanyl in the opioid supply and increased access to naloxone.

As discussed previously, fentanyl is already mixed into other opioids and drugs, sometimes without the buyers' knowledge. Fentanyl became more common in the drug supply in 2013 and synthetic opioid overdose deaths are still high [69]. There are increasing number of fentanyl analogs that are more potent than fentanyl, including carfentanil [111]. PWUO have a "habit" or standard amount of opioids that they need to use to avoid withdrawal [89]. If PWUO encounter opioids with higher than expected potencies and take their standard habit, they may overdose. People with

lower tolerances are more susceptible to the large differences in potency. For instance, the US Drug Enforcement Administration considers 2 milligrams to be a lethal dose of fentanyl depending on a person's body size and tolerance [9]. However, some PWUO report using one gram per day in interviews. It is reasonable to believe that fentanyl will continue to be present in the opioid supply and will contribute to additional overdose deaths.

Changes in supply and increased overdose deaths would likely cause government and outreach organizations to adopt overdose prevention strategies. Harm reduction strategies aim to reduce the harm to PWUO, while use reduction strategies aim to reduce the number of PWUO [42]. In this simulation, we focus on harm reduction strategies. To mitigate the harm caused by increased fentanyl in the drug supply, naloxone can be provided to PWUD. Naloxone (brand name Narcan) is an opioid antagonist medication that can be used to reverse the effects of an opioid overdose [38]. It can be administered through intranasal or intramuscular routes by people without any prior training [38]. Naloxone previously required a prescription in South Carolina, but in 2016 it became available over the counter to people who are at risk of experiencing overdose and their caregivers [185]. In 2018, data showed that there were bystanders at around 45% of fatal overdoses, but naloxone was only administered in 4% of cases [54]. Bystanders may be hesitant to call emergency services due to fear of arrest, so having naloxone kits can provide life-saving help to people who are overdosing [103].

The chapter is organized as follows. Section 4.2 discusses related work. The contributions and purpose of the work are presented in Section 4.3. The methods that were used to implement the scenarios are discussed in Section 4.4. Section 4.5 details the results of the simulations. In Section 4.6, we further discuss the results and limitations of the model and the scenarios that were modeled. Finally, the chapter is summarized in Section 4.7.

4.2 Related Work

Many models that were identified in Chapter 2 and 3 tested interventions to see the effects on overdose deaths, overdoses, and other metrics. In this section, we discuss some key disease spread models of opioid use that implement interventions.

Pitt et al. developed a dynamic compartmental model of the US that simulated prescription opioid and heroin use and dependence [171]. After model calibration, they implemented eleven

interventions, including reducing opioid prescribing, beginning prescription drug monitoring programs, disposing of excess opioid prescriptions, increasing naloxone availability and needle exchange programs, and expanding treatment [171].

None of the policies were found to substantially reduce opioid related deaths over a five year period, although naloxone distribution did show the largest reduction. Harm reduction policies tended to show gains in life-years and quality of life years (QALYs), while use reduction policies often reduced the number of prescription opioid users but increased the number of heroin users. However, the policies did show larger gains over ten years than may have been expected based on the five year results [171].

Rao et al. extended the previous model and updated the data that was used to consider COVID-19's impact on treatment and the proliferation of fentanyl that has increased the chance to overdose [176]. The model considers pain states, opioid use with prescription, and opioid use without prescription. The authors tested similar intervention types with the updated states and data and found that expanding naloxone availability still had the largest impact on reducing opioid deaths. Combining interventions was found to increase life years, QALYs, and deaths averted [176].

Homer and Wakeland developed a system dynamics simulation model to study the opioid overdose epidemic [92]. After the model was calibrated, the researchers evaluated four interventions over the course of ten years. The interventions considered were reducing prescription opioid dosage, reducing prescription opioid diversion, increasing treatment for PWUD, and increasing naloxone use [92].

Metrics of interest in the article included the number of people with opioid use disorder (PWOUD), overdoses, and overdose deaths. Interventions to reduce dosage and diversion had stronger reduction effects on the number of PWOUD and more modest reductions in overdoses. Expanded treatment and naloxone use increased PWOUD. Increased treatment also reduced overdoses, while naloxone reduced overdose deaths but increased overdoses overall. Combining the four interventions produced reductions in all three metrics [92].

Linas et al. used a dynamic state-transition model to assess how changes in medication treatment may affect opioid overdose mortality in urban and rural counties in Massachusetts [117]. The researchers assumed that physical distancing caused by COVID-19 impacted treatment initiation and retention and tested three durations of physical distancing and two effect sizes. Simulating these changes showed increased overdose deaths, and the deaths remained elevated even in the three month

physical distancing scenario [117].

Lim et al. developed SOURCE (Simulation of Opioid Use, Response, Consequences, and Effects), a dynamic simulation model [115]. The model incorporated social influence on drug use, population perception of the risk of drug use, capacity limits on treatment, supply-side changes in opioid availability, and the competing influences of illicit fentanyl. Varying projections of the future can be made based on trends continuing, pessimistic expectations, or optimistic expectations. The goal of the model was to inform policy planning [115].

Stringfellow et al. simulated eleven interventions using the SOURCE model to determine how changes would affect overdose deaths and prevalence of OUD [195]. The interventions modeled included reducing prescription opioid diversion and prescribing, reducing heroin and prescription opioid misuse initiation, increasing buprenorphine treatment capacity, improving recovery support, increasing naloxone distribution, and reducing overdose risks [195].

Prescription opioid misuse prevention strategies produced small reductions in overdose deaths and OUD prevalence. Reducing heroin initiation, the number of people receiving a prescription, and the development rate of OUD each achieved small reductions (2%) in overdose deaths by 2032. Increasing naloxone distribution and reducing harm from fentanyl produced larger and more immediate reductions in overdose deaths. The researchers used this model to provide insight into possible results from these interventions [195].

4.3 Contributions and Purpose

This chapter uses the ABM developed in Chapter 3. This research contributes to addressing gaps in the following ways:

- We discuss how the base ABM can be adjusted to test changes in the environment or implement policy changes. A model that is able to evaluate different scenarios concurrently is more robust and beneficial to policymakers.

- We simulate changes in the opioid supply composition and possible harm reduction policies. We provide insights into how these changes affect fatal overdoses, total overdoses, and the number of people misusing opioids, comparing them to the base model and each other.

- We evaluate interventions using a model that has filled gaps identified in Chapter 2, including

a different model type and using multiple types of opioids.

The purpose of the model is to provide information about the relative effects of policies compared to the base model as opposed to predict absolute numbers of deaths or PWUD. Understanding relative effects can help policymakers choose how to allocate resources.

The ABM cannot predict surprising events that were not specifically modeled, like the emergence of COVID-19 and how it affected opioid use. However, once the event is known, its effects can be incorporated along with interventions to mitigate harm and the model can provide further insight.

4.4 Methods

Details about the model construction, agent types, and data sources for the base model can be found in Chapter 3. As in the base model, the model has a time step of one day and includes a burn-in period of ten years to allow the h-agents (human agents) to move into opioid use states beside no opioid use and develop a history.

Three different scenarios were evaluated: one with increased unknown fentanyl in the opioid supply, one with increased distribution of naloxone, and one with both increased unknown fentanyl and increased distribution of naloxone.

There were two tiers of increases analyzed in each of the scenarios. The increased unknown fentanyl is simulated by increasing the number of high potency batches in all opioid types. For the first tier, the chance to encounter a high potency batch increased from 20% to 25%. In the second tier, the chance was increased to 30%. The percent of low potency batches was not changed.

Increased naloxone distribution is simulated by reducing the fatality rate of overdoses. Simulating increased naloxone availability or distribution with reduced fatality rates has been used in other opioid overdose disease models [171]. In the first tier, the rate was reduced 10% to 16.8%. For the second tier, the fatality rate was reduced 25% from 18.7% to 14%. We chose relatively minor reductions in expected overdose deaths for two reasons. First, naloxone has been available without a prescription in South Carolina since 2016 and is available to people who want it [185]. Since there is already some market saturation and use of naloxone, very large reductions in overdose deaths due to naloxone distribution seem unlikely. Second, naloxone is only useful in reducing fatal overdoses if another person is available to administer it. If bystanders are present at 45% of overdoses [103],

even if every bystander administered naloxone it would only reduce the fatal overdose rate by 45%.

When both scenarios were simulated together, there was a staggered start to simulate policymakers receiving information and reacting to changes in the opioid supply. The increased unknown fentanyl was started immediately after the burn-in period finished. The increased naloxone distribution was enacted a year after the increased unknown fentanyl appears in the opioid supply. Four separate sets of model parameters were run to account for all combinations of the two tiers of the scenarios. For ease of discussion, the scenarios will be called:

- tier one fentanyl and naloxone distribution - both low
- tier two fentanyl and naloxone distribution - both high
- tier one fentanyl and tier two naloxone distribution - N high
- tier two fentanyl and tier one naloxone distribution - F high

The model was run fifteen times with each set of parameters using different random number seeds for each run. The results from the models were averaged and are presented in the following section.

4.5 Results

4.5.1 Increased Unknown Fentanyl

Table 4.1 lists the total number of fatal overdoses over the course of five years for the three models along with the total overdoses that occurred. The 95% confidence interval lower-bound and upper-bound for the base model is also included.

Category	**Base**	**LB**	**UB**	**Tier One - F**	**Tier Two - F**
Fatal Overdoses	109.6	106.3	112.9	119.1	135.2
Total Overdoses	598.9	588.5	609.3	674.9	743.3

Table 4.1: Comparison of Overdoses - Fentanyl Models

The fatal overdoses and total overdoses of both tiers of increased fentanyl fall outside of the upper-bound of the base model, suggesting that they are statistically different. While they both fall outside the bounds, there were 8% more fatal overdoses in the tier one model and 23% more in the tier two model as compared to the base model.

Figure 4.2 shows a comparison of the yearly overdose deaths of the two tiers of increased fentanyl and the base model. There is some overlap in the boxes of the yearly number of overdose deaths between the base model and the tier one increased fentanyl model. The tier two increased fentanyl model has significantly more overdose deaths than the other models.

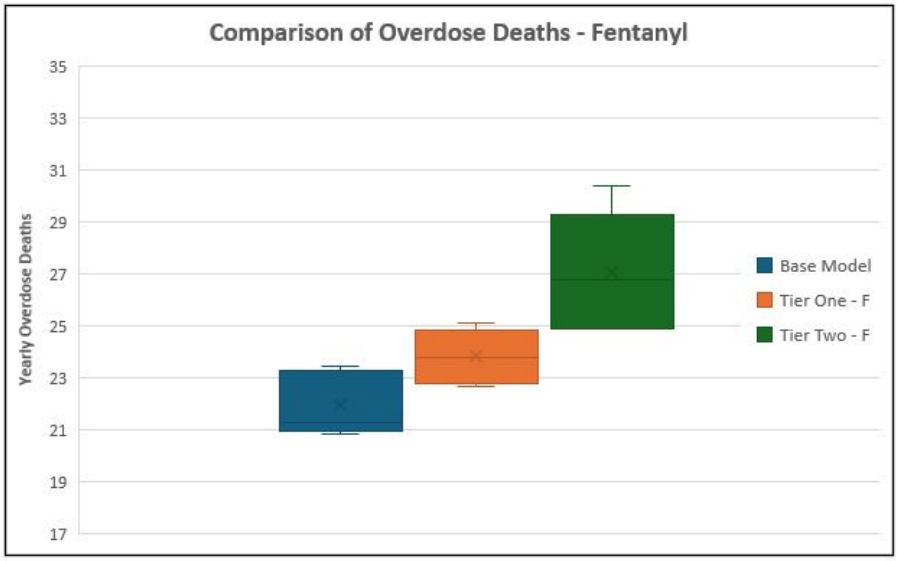

Figure 4.2: Yearly Comparison of Overdose Deaths - Increased Fentanyl

Table 4.2 lists the number of h-agents misusing opioids in the three models. Since the scenario only changed the opioid supply, it is expected that the number of h-agents misusing is similar across the three models.

Category	Base	Low Fentanyl	High Fentanyl
Total Misusing	1312.9	1320.3	1318.3
States 3 and 4	1057.9	1064.5	1063.6

Table 4.2: H-Agents Misusing During One Year in Increased Fentanyl Models

4.5.2 Increased Naloxone Distribution

Figure 4.3 shows a comparison of the yearly overdoses of the two tiers of naloxone distribution and the base model. As in the fentanyl trials, there is some overlap in the yearly number of overdose deaths between the base model and the tier one increased naloxone distribution model. The tier two increased naloxone distribution model has significantly fewer overdose deaths.

Table 4.3 lists the total number of fatal overdoses over the course of five years for the three

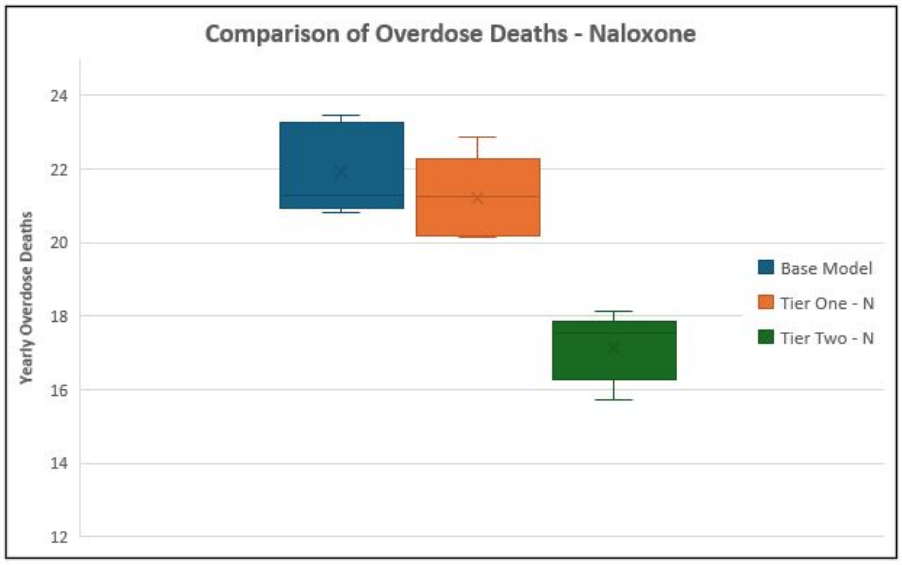

Figure 4.3: Yearly Comparison of Overdose Deaths - Increased Naloxone

models along with the total overdoses that occurred. The 95% confidence interval lower-bound and upper-bound for the base model is also included.

Category	Base	LB	UB	Tier One - N	Tier Two - N
Fatal Overdoses	109.6	106.3	112.9	106.1	85.8
Total Overdoses	598.9	588.5	609.3	602.7	622.7

Table 4.3: Comparison of Overdoses - Naloxone Models

The total overdoses for the tier one naloxone model fall within the bounds of the base model while the fatal overdoses fall slightly outside of the lower-bound. For the tier two naloxone model, fatal and total overdoses fall outside of the bounds of the base model. Fatal overdoses are 3.5% lower in the tier one model and 23% lower in the tier two model as compared to the base model. The total overdoses may be higher when more naloxone is used because agents who may have died due to overdose in the base model will continue to use opioids and may overdose again.

Table 4.4 lists the number of h-agents misusing opioids in the three models. Since the scenario changed the overdose death rate, it is expected that the number of h-agents misusing is similar across the three models. The increased number of people misusing in the tier two naloxone model could be due to people who did not die as a result of overdoses continuing to misuse opioids.

Category	Base	Tier One - N	Tier Two - N
Total Misusing	1312.9	1317.6	1352.8
States 3 and 4	1057.9	1061.7	1082.2

Table 4.4: H-Agents Misusing During One Year in Different Models

4.5.3 Both Scenarios

Figure 4.4 shows a comparison of the yearly overdose deaths of the four scenarios and the base model. The overdose deaths were highest for the scenario where the unknown fentanyl was high and the naloxone distribution was low. In both scenarios where there were high levels of unknown fentanyl in the opioid supply, year one overdose deaths were higher than the base model. As naloxone distribution was started in year two, the overdose deaths fell in both cases.

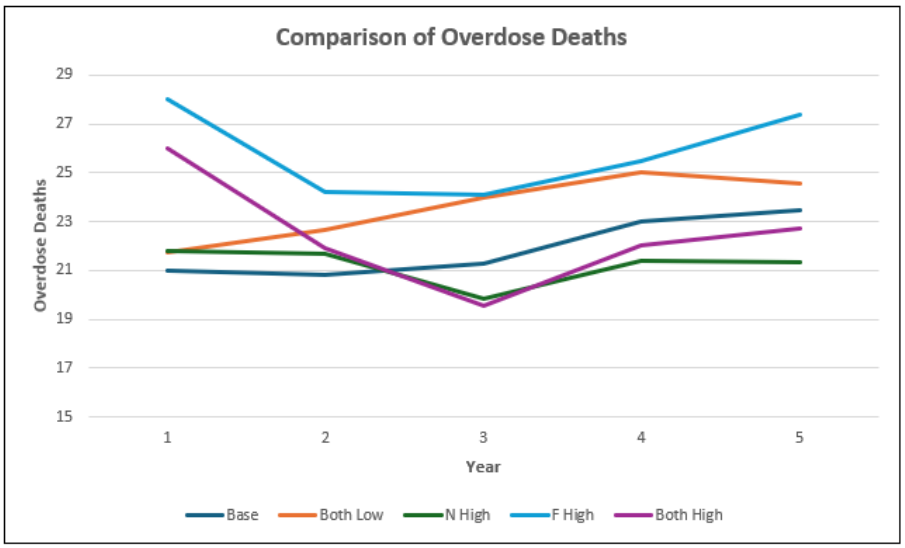

Figure 4.4: Yearly Comparison of Overdose Deaths

Figure 4.5 is a plot of the overdose deaths over the five year run by scenario and can be compared to the base model. In both scenarios with high levels of fentanyl, opioid overdose deaths have high peaks. However, when naloxone distribution is also high, overdose deaths fall to levels similar to the base model and the low proliferation of unknown fentanyl scenario. When fentanyl is increased even at low levels, overdose deaths increased, especially without increased naloxone distribution to combat the increased number of overdoses.

Table 4.5 lists the fatal and total overdoses for each of the scenarios and the base model along with the lower-bound and upper-bound of the base model. When both interventions were

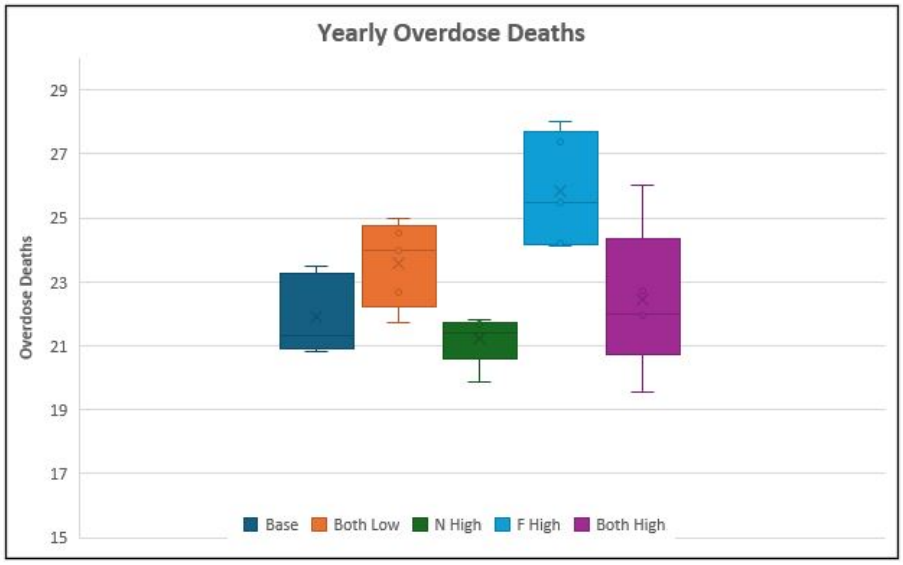

Figure 4.5: Yearly Comparison of Overdose Deaths

at the lower level, both of the metrics fell outside the upper-bound of the base model. When naloxone distribution was high and fentanyl proliferation was low, fatal overdoses fell slightly below the lower-bound of the base model while total overdoses fell outside the upper-bound. When fentanyl proliferation was high and naloxone distribution was lower, both fatal overdoses and total overdoses fell outside the upper-bound. Finally, when both scenarios were high, fatal overdoses fell within the bounds of the base model, and total overdoses fell outside the upper-bound.

Scenario	**Fatal Overdoses**	**Total Overdoses**
Base	109.6	598.9
LB	106.3	588.5
UB	112.9	609.3
Both Low	117.9	677.9
Naloxone High	106.1	699.4
Fentanyl High	129.2	762.2
Both High	112.2	748.7

Table 4.5: Overdoses by Scenario

Figures 4.4 and 4.5 compare the combined scenarios to the base model with no increased naloxone or fentanyl. It is also beneficial to compare the combined scenarios to the individual scenarios. Figure 4.6 has two charts that show the yearly overdose deaths for tier one and tier two fentanyl with differing levels of increased naloxone distribution. These charts show how naloxone affects overdose deaths when the fentanyl level is constant. More naloxone shows reduced overdose

deaths at the different levels of increased fentanyl.

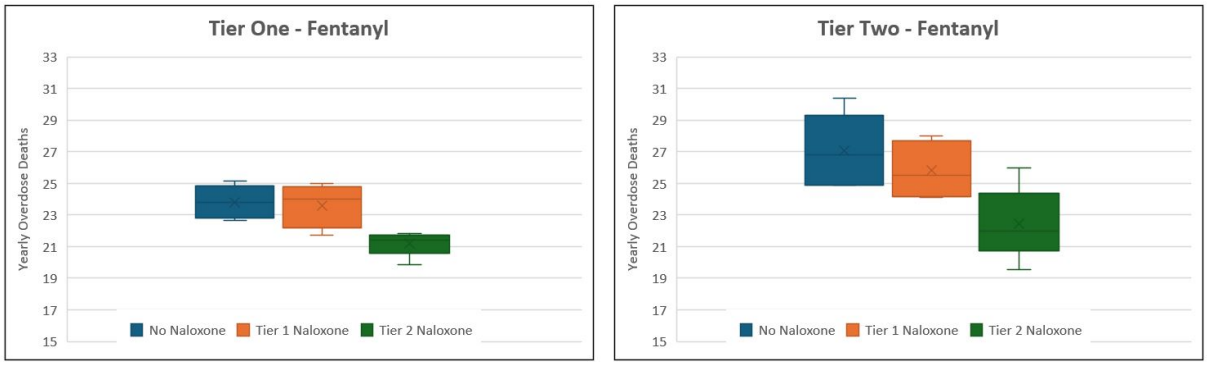

Figure 4.6: Comparison of Yearly Overdose Deaths - Fentanyl

Figure 4.7 details the yearly overdose deaths for the two levels of increased naloxone distribution compared to each level of increased unknown fentanyl including no extra fentanyl. Increased fentanyl increases overdose deaths when the amount of naloxone is constant.

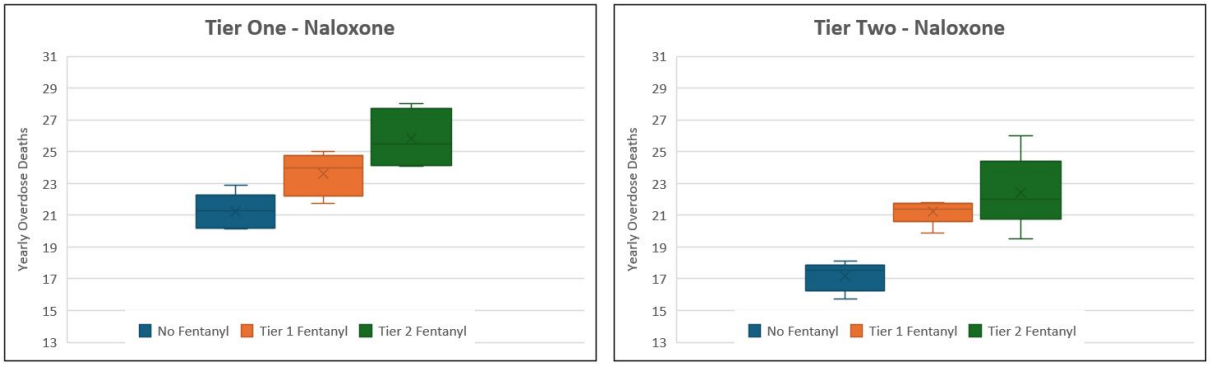

Figure 4.7: Comparison of Yearly Overdose Deaths - Naloxone

The number of h-agents misusing opioids by scenario is detailed in Table 4.6. The lower-bound and upper-bound limits from the base model are also included. The number of h-agents who misused opioids in the last year and who had substance use disorders (states 3 and 4) were within the bounds of the base model for all of the scenarios except when there were high levels of unknown fentanyl in the opioid supply and low levels of naloxone distribution.

Table 4.7 lists the h-agents who preferred heroin and fentanyl and whose preferred routes of administration were smoking and injection. Slightly more h-agents preferred heroin in all of the

Scenario	Total Misusing	States 3 and 4
Base	1312.9	1057.9
LB	1288.5	1040.0
UB	1337.3	1075.8
Both Low	1303.3	1055.9
Naloxone High	1328.3	1068.1
Fentanyl High	1361.9	1100.5
Both High	1307.7	1054.1

Table 4.6: H-Agents Misusing by Scenario

scenarios except when both levels were high, and slightly fewer preferred smoking when both levels were high. None of the scenarios fell outside of the bounds for h-agents who preferred fentanyl and who preferred injection.

Scenario	Heroin	Fentanyl	Smoking	Inject
Base	147.2	80.6	173.2	126.5
LB	142.0	76.5	168.8	122.0
UB	152.4	84.8	177.7	131.0
Both Low	153.4	80.3	168.9	125.9
Naloxone High	155.9	82.3	173.1	129.9
Fentanyl High	155.8	82.1	173.9	130.7
Both High	148.8	78.8	168.1	125.3

Table 4.7: H-Agents Opioid Type and Route of Administration

4.6 Discussion and Limitations

The outcomes from the simulations produced anticipated results. Naloxone distribution reduced overdose deaths compared to the base model while increased unknown fentanyl increased overdose deaths. None of the interventions drastically affected the amount of PWUD, the preferred opioid type, or route of administration. The difference between the tier one interventions and tier two interventions may be larger than expected and could showcase possible multiplicative effects. Additionally increased naloxone distribution can help mitigate overdose deaths to a similar level as the base model even with 30% of opioids being considered highly potent.

The results from the ABM should be interpreted in relative terms as compared to the base model. The model does not attempt to predict the actual number of overdose deaths but can provide information about the relative changes to be expected if a scenario occurs as compared to the base model.

The limitations related specifically to the ABM can be found in Chapter 3. Limitations that apply to the scenarios are discussed further here. There are data limitations in deciding the percentages changed to simulate an increase in unknown fentanyl in the opioid supply and the amount of fatal overdoses that will be averted by increased distribution of naloxone. We managed these limitations by relying on available research and expert opinion.

Additionally, no other changes to the model were made when the fatality rate of overdoses was reduced or when more fentanyl was introduced to the drug supply chain. Harm reduction strategies may cause an increase in PWUD because people believe the opioids are safer to use [42]. H-agents attitudes towards drugs are not modeled and can therefore not be affected based on the way the model is currently developed. Regardless, there is some debate about whether harm reduction strategies meaningfully affect the number of PWUD [130].

More unknown fentanyl in the drug supply would likely affect drugs beside opioids. Poly-substance use, or using different types of drugs concurrently, and opioids being mixed into stimulants like cocaine and methamphetamine has been described as the fourth wave of opioid overdose deaths [46]. Figure 4.6 shows the increase in stimulant overdose deaths that involve opioids (specifically synthetic opioids) over time in US. Stimulant overdose deaths with opioids have risen at a quicker pace than stimulant overdose deaths without opioid involvement. Because stimulant overdose deaths that involve opioids are counted in opioid overdose deaths, the number of opioid overdoses and deaths could be underestimated in this scenario if stimulants are not modeled.

Finally, the metrics we considered focused primarily on overdoses, overdose deaths, and the number of PWUD, but other metrics could be introduced. For instance, none of the scenarios include costs of naloxone distribution which will cost governments or agencies money to purchase as well as distribute it to the people who need it. Including costs and other metrics would provide more information to policymakers.

4.7 Conclusion

In this chapter, we used an agent-based model to simulate scenarios that may occur in the opioid overdose epidemic. The two scenarios evaluated were increased unknown fentanyl in the opioid supply and increased naloxone distribution. The scenarios were tested separately and concurrently. When tested together, the naloxone distribution lagged behind the increased unknown fentanyl by

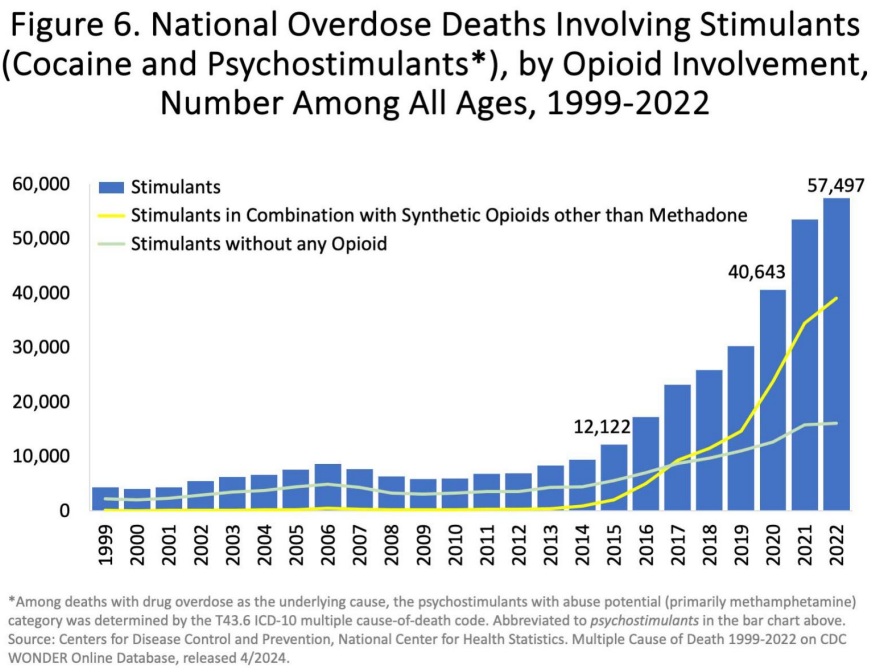

Figure 4.8: Stimulant Overdoses Involving Opioids [166]

one year.

The results showed that increased fentanyl in the opioid supply did increase overdoses and overdose deaths while increased levels of naloxone distribution reduced overdose deaths. In simulations where both scenarios were included high levels of naloxone distribution appeared to mitigate much of the harm caused by additional overdoses due to unknown fentanyl.

Chapter 5

Conclusions and Future Work

In this chapter, we discuss the highlights of the dissertation and potential future research opportunities.

5.1 Summary and Conclusions

Chapter 2 presented our scoping review on disease models of the opioid overdose epidemic. A total of eighty-five articles were evaluated with some articles including multiple models. We identified the types of models that were developed, the types of opioids that were modeled, data sources used, and whether calibration or validation was performed. Seventy-eight of eighty-eight models identified were compartmental models and forty-nine only modeled heroin. We identified three major gaps in the literature:

- Most of the models either did not use data or used country-wide data.
- Most models used differential and difference equations which does not allow the individuals to be tracked through the system.
- Few models included fentanyl which currently is implicated in the majority of opioid overdose deaths.

Based on the gaps identified in the review, we chose to contribute to the current research by developing an agent-based model of a specific state that included multiple opioid types.

In Chapter 3, we presented an agent-based model of the opioid overdose epidemic. The ABM has two agent types: h-agents who represent people who may engage in opioid misuse behaviors and o-agents who supply the opioids. The h-agents can move through different opioid use and misuse states, engage in treatment, and enter the criminal justice system. The o-agents supply one of four types of opioids (prescription opioids, counterfeit prescription opioids, heroin, and fentanyl) with differing levels of potency. The agent types interact to facilitate the transfer of opioids. The model was calibrated using historical data.

Results from the model showed that the ABM is able to reproduce historical results of overdose deaths, number of people misusing, types of opioids used, and route of administration. While some historical averages did fall outside of the 95% confidence intervals, overdose deaths and total overdoses did fall with the bounds. An average of 1,313 h-agents were misusing opioids in the past year and 21.93 h-agents died per year due to overdoses in the model.

We present the following research contributions from Chapter 3:

- We developed an agent-based disease model of the opioid overdose epidemic.
- The ABM incorporated four types of opioids, including synthetic opioids, and three routes of administration for the opioids.
- The ABM differentiates opioid misuse severity into three levels.
- The model shows a unique way to model opioid supply to account for different types of opioid supply.
- The ABM includes two treatment types and a criminal justice system.

Chapter 4 used the ABM developed in Chapter 3 to evaluate two potential scenarios. The first scenario is an increase of unknown fentanyl in the opioid supply which was represented by a larger chance to receive high potency opioids. With increased overdose deaths, a possible policy reaction includes harm reduction. In the second scenario we modeled increased naloxone distribution to combat overdose death rates. Increased naloxone distribution was simulated by reducing the overdose death rate. The scenarios were simulated separately and concurrently.

The results showed that naloxone distribution reduced overdose deaths while more fentanyl increased them. The higher tiers of distribution of naloxone and higher proliferation of fentanyl had much higher overdose deaths or deaths averted than the lower tier. When the scenarios were run

concurrently, higher levels of naloxone distribution appear to mitigate many of the overdose deaths that would be caused by the more potent opioids.

Research contributions from Chapter 4 include:

- a discussion about how to adjust the ABM to test scenarios related to the opioid overdose epidemic
- two scenarios with differing levels that were implemented in the ABM
- an evaluation and comparison of the scenarios

5.2 Future Work

Some key considerations for future research include addressing limitations of the agent-based model. There are four major model additions that could improve the accuracy and validity of the ABM.

First, more realistic movement for both agent types could be incorporated into the model. Currently the h-agents move to simulate changing personal connections. In future work, the h-agents could have social connections built-in and their movement could represent how they travel. Agent-based models have incorporated cellphone records to simulate people's movement [74]. Geographic information systems (GIS) provide another avenue for simulating a more realistic environment [168]. ABMs for contagious disease spread have utilized these systems, so they could be incorporated into a noncommunicable disease model as well [168]. O-agents may be placed in locations based on interviews with law enforcement and people who have previously used opioids.

Next, improving the opioid seeking function and the h-agent's preferred opioids and routes of administration would be beneficial. Allowing the h-agents to have limited access to the o-agents would be more realistic because people do not have full access to the entire opioid supply. Along with access to supply, costs to purchase opioids could be added. Cost is one of the reasons mentioned for why people use more potent opioids or try routes of administration that deliver a quicker and more efficient high [47]. This addition may allow the way h-agents change their preferences to be more dynamic and not primarily related to chance. Cost is also a lever that could be used to simulate reduced supply which often increases costs of products.

Additionally, adding more logic into the function would make the opioid seeking more realistic. If there is not enough supply to meet demand, the o-agents may adjust the price for their supply or the amount of supply they want in their next delivery. If h-agents cannot meet their personal demand, they may take more extreme actions to avoid going into withdrawal.

Tolerance is another metric that may encourage PWUO to change to more potent opioids and routes of administration. Tolerance can be difficult to quantify and is dependent on multiple factors. Additionally, tolerance to euphoric effects often increases faster than tolerance to the respiratory sedation effects [218]. If tolerance could be accurately tracked for h-agents, it could be incorporated when determining how h-agents choose to increase the potency of the opioids that they use or their routes of administration and affect their chance of overdose.

Characteristics that affect an h-agent's chance of overdose could be added to the model. How people respond to opioids is affected by factors including their age, gender, physical health, and genetics [99]. As more research is done to quantify the characteristics' effects on opioid overdoses, future work could include adding these characteristics and how much they affect overdose chance.

Thirdly, incorporating stimulants into the ABM may produce a more robust model. Stimulants and opioids are used together frequently enough that the combinations have street names. Use of cocaine and heroin, known as speedballs, and methamphetamine and heroin, goofballs, can increase the chance of overdose more than the drugs used alone [96]. Even if people who use stimulants do not intentionally use opioids, they can still encounter batches of cocaine or methamphetamine that have fentanyl to increase their potency.

Finally, other harm or use reduction strategies could be evaluated. The only intervention tested in Chapter 4 was increased naloxone distribution. One possible intervention is fentanyl test strip (FTS) distribution. FTS were originally developed to detect fentanyl in urine but were modified to test drug samples for fentanyl [216]. The strips are very sensitive and can detect trace amounts of fentanyl using a small amount of the drug [216]. Studies have shown that PWUDs are typically receptive to using FTS and that using FTS can lead to other protective drug use behaviors ([216], [147]).

However, it is common to find fentanyl in opioids, and FTS do not provide any information on the quantity of fentanyl present which may make them less beneficial to people primarily using opioids. If stimulants were included in the model, FTS could be distributed to h-agents who use stimulants to allow them to check for the unexpected presence of opioids. Other possible inter-

ventions include expanding the number of people in drug treatment court which would allow more people to receive treatment as opposed to punitive measures, increasing treatment quality and medication treatment, which would reduce the chance of treatment discontinuation, and reducing the opioid supply. Testing further interventions would provide more information to policymakers and other agencies.

Appendices

Appendix A Scoping Literature Review Search Strings

The search strings that were used in the systematic literature review are listed in their entirety below for each database used.

A.1 Web of Science Search String

((ALL=(opioid* OR "opioid epidemic" OR heroin OR "opioid crisis")) AND TI=(model* OR simulat*)) NOT ALL=(rat OR rats OR "animal model" OR mouse OR murine OR vivo OR animal* OR molecul* OR vitro OR pharmacological* OR pharmacokinetic* OR pharmacodynamic* OR neuron* OR placebo* OR avian OR receptor* OR manufacturing OR depression OR cognitive OR pregnant OR therapeutic OR skin OR neonatal OR brain* OR porcine OR tumor OR nurse* OR apnea* OR postoperative OR preoperative OR spectral OR liver OR pig OR rodent) NOT TI=(education* OR hepatitis)

A.2 PubMed Search String

((opioid* OR "opioid epidemic" OR heroin OR "opioid crisis" OR (Analgesics, Opioid[MeSH Major Topic]) OR (Opioid Epidemic[MeSH Major Topic]) OR (Heroin[MeSH Major Topic]) OR (Heroin Dependence[MeSH Major Topic])) AND (model*[Title] OR simulat*[Title])) NOT (rat OR rats OR "animal model" OR mouse OR murine OR vivo OR animal OR molecul* OR vitro OR pharmacological* OR pharmacokinetic* OR pharmacodynamic* OR neuron* OR placebo* OR avian OR receptor* OR manufacturing OR depression OR cognitive OR pregnant OR therapeutic OR skin OR neonatal OR brain* OR porcine OR tumor OR nurse* OR apnea* OR postoperative OR preoperative OR spectral OR liver OR pig OR rodent OR (Rats[MeSH Major Topic]) OR (Models, Animal[MeSH Major Topic]) OR (Mice[MeSH Major Topic]) OR (Animals[MeSH Major Topic]) OR (Pharmacokinetics[MeSH Major Topic]) OR (Neurons[MeSH Major Topic]) OR (Placebos[MeSH Major Topic]))

A.3 Medline

(opioid* OR "opioid epidemic" OR heroin OR "opioid crisis" OR (MH "Analgesics, Opioid") OR (MH "Opioid Epidemic") OR (MH "Heroin Dependence") OR (MH "Heroin")) AND TI (model* OR simulat*) NOT (rat OR rats OR "animal model" OR mouse OR murine OR vivo

OR animal OR molecul* OR vitro OR pharmacological* OR pharmacokinetic* OR pharmacodynamic* OR neuron* OR placebo* OR avian OR receptor* OR manufacturing OR depression OR cognitive OR pregnant OR therapeutic OR skin OR neonatal OR brain* OR porcine OR tumor OR nurse* OR apnea* OR postoperative OR preoperative OR spectral OR liver OR pig OR rodent OR (MH "Rats") OR (MH "Models, Animal") OR (MH "Mice") OR (MH "Animals") OR (MH "Pharmacokinetics") OR (MH "Neurons") OR (MH "Placebos"))

Appendix B References for Scoping Review Results

Opioids Modeled	**Total**	**Citations**
Prescription Opioids	8	[19], [22], [21], [156], [181], [204], [205], [206]
Opioids	8	[52], [75], [79], [80], [117], [149], [172], [197]
Heroin and Prescription Opioids	6	[17], [23], [141], [171], [176], [202]
Heroin and Non-Opioid Drugs	4	[41], [42], [45], [114]
Heroin, Prescription Opioids, and Fentanyl	3	[92], [170], [201]
Heroin, Prescription Opioids, Fentanyl, and Synthetic Opioids	2	[115], [195]
Opioid and Non-Opioid Drugs	1	[133]
Prescription Opioids and Opioids	1	[10]
Synthetic Opioids	1	[122]
Heroin and Opium	1	[174]
Heroin and Synthetic Opioids	1	[222]

Table 1: Opioids Modeled Citations (Only heroin not included)

Data Sources	**Total**	**Citations**
Published Articles	38	[17], [19], [21], [37], [41], [42], [52], [79], [80], [92], [100], [107], [115], [117], [120], [122], [133], [149], [156], [170], [171], [174], [175], [176], [177], [181], [190], [195], [197], [201], [203], [204], [205], [207], [211], [222], [226], [227]
Panel Consensus	31	[10], [17], [19], [41], [52], [56], [61], [92], [100], [107], [115], [120], [133], [149], [156], [170], [171], [174], [176], [181], [190], [195], [197], [201], [203], [204], [205], [207], [223], [226], [227]
Government Sources	21	[11], [17], [19], [52], [61], [75], [100], [115], [117], [133], [149], [156], [170], [174], [176], [181], [195], [197], [204], [205], [226]
Survey	15	[10], [41], [52], [92], [100], [115], [133], [149], [156], [170], [176], [195], [201], [205], [226]
Clinical Sources	8	[92], [115], [149], [174], [195], [201], [204], [226]
Medicinal Sources	5	[100], [156], [197], [205], [207]
Police Department	1	[197]

Table 2: Data Sources Citations

Model Validation	**Total**	**Citations**
No Calibration or Validation Mentioned	37	[3], [21], [22], [37], [42], [52], [58], [60], [64], [65], [66], [93], [100], [113], [117], [119], [120], [121], [123], [128], [133], [142], [149], [151], [152], [174], [175], [176], [181], [183], [215], [217], [221], [222], [223], [224], [226]
Checked Assumptions	30	[4], [25], [26], [45], [56], [57], [61], [62], [80], [79], [107], [110], [114], [118], [122], [124], [125], [141], [143], [172], [177], [178], [190], [208], [209], [210], [211], [227], [228]
Compared Results to Historical Data	8	[19], [23], [41], [201], [203], [204], [205], [207]
Calibrated Model	7	[10], [17], [115], [170], [171], [195], [197]
Error Metrics	3	[75], [92], [156]

Table 3: Model Calibration and Validation Citations

Appendix C Simulation Model Types Review

Different modeling (simulation) types exist because they have different strengths and limitations. Common model differences include deterministic (all variables are fixed) versus stochastic (at least one variable incorporates probability) models and static (time is not considered) versus dynamic (passage of time can affect variable interactions) models [132].

Specific to modeling the opioid overdose epidemic, some models, like the theoretical compartmental models, have a stronger focus on proving mathematical theorems. The opioid overdose epidemic models also tended to become more complex over time as they incorporated more real-world characteristics.

Further details are discussed in the following sections.

C.1 Compartmental Models

Compartmental models use a top-down modeling approach with a mathematical formulation based on differential equations [145]. The differential equations describe the rate at which the population enters and leaves the compartments, and the compartments represent the state that a portion of the population will be in.

In the scoping review, many of the theoretical compartmental models are focused on determining equilibrium (when the rates of individuals entering and leaving each compartment are the same) and the basic reproductive number, R0, of the epidemic [29]. The applied compartmental models tended to use data to inform the models and determine how interventions affected the outcomes.

Compartmental models are used widely as can be seen by the number identified, but they do require the model to be described using differential equations which can be difficult for some systems including human behavior.

C.2 Agent-Based Models

Agent-based models represent a bottom-up modeling approach where the behavior of the system is determined by the rules given to the agents and environment, and the mathematical formulation is based on logic [145]. The agents have characteristics that may affect how they interact with other agents or the environment [155].

ABMs are often used in situations where individuals' behavior is nonlinear, individual behavior shows dependence on previous states, and averages smooth out fluctuations that may be amplified [31]. Some drawbacks to ABMs include large computational power requirements and difficulty validating the model because some data is difficult to obtain [31].

C.3 Cellular Automata

Similar to ABMs, cellular automata models are bottom-up [50]. In this model type, agents are placed on a grid and interact with neighbors who are connected geographically [50]. The agents do not move, and it is most beneficial when the transition rates between states are known and stable [50].

C.4 Markov Process

Markov models are a stochastic model type designed with mutually exclusive states and transition probabilities to leave each state and enter another [35]. Markov models can use constant or time-varying transition probabilities [35].

A limitation for Markov models when considering human processes is that the transition probabilities only consider the current state, not the previous states visited or the time spent in the current state [35]. This limitation can be mitigated by creating states that are based on previous states [35].

C.5 Monte Carlo

Monte Carlo simulation is a stochastic modeling method which means it incorporates random variability in the model [32]. To be a Monte Carlo simulation, the sampling distribution of the variables must be defined before the model is run [32]. The sampling distributions are typically one or many probability density functions (PDFs) [83]. The variable parameters are determined by randomly sampling from the PDFs [83]. The simulation runs multiple times creating a set of possible outcomes, the outcomes are examined, and the variability of the model can be analyzed [32].

C.6 Optimal Control

Optimal control models require a model, described using a system of equations, and an objective function [154]. The model aims to adjust controls to optimize the desired result based on the objective function [154]. Optimal control models can use different equation types, including ordinary differential equations and stochastic differential equations [154]. Theorems and principles have been developed to determine whether optimal control exists [154].

Appendix D Binomial Probability Calculation

Binomial probabilities were used in multiple places to determine daily values of events when yearly or monthly values were the more commonly reported probabilities. Here, we present a sample binomial probability calculation to solve for the daily probability of receiving an opioid prescription in the 65+ age range. Binomial probabilities are useful when an event can be classified as either a success or failure [169]. The probability equation is:

$$P = \binom{n}{m} * p^n * (1-p)^{(n-m)} \tag{1}$$

where n is the number of successes, m is the total number of events, p is the probability of a success for an event, and P is the overall probability of receiving n successes and (n-m) failures.

For our example, not receiving an opioid prescription is considered a success. To find the probability that a person does not receive a prescription in a year, they must not receive a prescription 365 days in a row. In the 65+ age range, approximately 270,260 unique people received opioid prescriptions in one year [163]. In South Carolina, there are approximately 1,045,156 people in the 65+ age range [1]. Therefore, the yearly chance to receive an opioid prescription in that age range is 25.86% which means that the yearly chance to not receive an opioid prescription is 74.14%. We can put this value in the binomial probability equation.

$$74.17\% = \binom{365}{365} * p^{365} * (1-p)^{(365-365)} \tag{2}$$

Since there must be zero days receiving a prescription, we do not need to consider the probability related to (1-p) (that will be raised to the 0th power which will equal one).

$$74.17\% = 1 * p^{365} * 1 \tag{3}$$

With this information we can solve for the daily probability to not receive a prescription opioid. In our example, this percentage (p) is 99.918%. Since the events are mutually exclusive, we can solve for the daily chance to receive a prescription opioid by subtracting the chance to not receive an opioid from one. The daily chance to receive a prescription opioid is 0.082%.

This process is repeated for each age range.

One limitation when using this method is that it assumes statistical independence between

each day [169]. While we cannot claim statistical independence between days (whether you have recently been prescribed an opioid may affect your chance to be prescribed again), the method does provide expected yearly values.

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