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Calculating prescription rates and addiction probabilities for the four most commonly prescribed opioids and evaluating their impact on addiction using compartment modelling

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In 2016, more than 11 million Americans abused prescription opioids. The National Institute on Drug Abuse considers the opioid crisis a national addiction epidemic, as an increasing number of people are affected each year. Using the framework developed in mathematical modelling of infectious diseases, we create and analyse a compartmental opioid-abuse model consisting of a system of ordinary differential equations. Since 40% of opioid overdoses are caused by prescription opioids, our model includes prescription compartments for the four most commonly prescribed opioids, as well as for the susceptible, addicted and recovered populations. While existing research has focused on drug abuse models in general and opioid models with one prescription compartment, no previous work has been done comparing the roles that the most commonly prescribed opioids have had on the crisis. By combining data from the Substance Abuse and Mental Health Services Administration (which tracked the proportion of people who used or misused one of the four individual opioids) with data from the Centers of Disease Control and Prevention (which counted the total number of prescriptions), we estimate prescription rates and probabilities of addiction for the four most commonly prescribed opioids. Additionally, we perform a sensitivity analysis and reallocate prescriptions to determine which opioid has the largest impact on the epidemic. Our results indicate that oxycodone prescriptions are both the most likely to lead to addiction and have the largest impact on the size of the epidemic, while hydrocodone prescriptions had the smallest impact.

Keywords: opioid epidemic; prescription drug addiction; SIR compartment model; sensitivity analysis.

1. Introduction

During the past several decades, the impact of opioids has been catastrophic with opioid related deaths averaging nearly 130 people per day in the USA (National Institute on Drug Abuse, 2018). While cultivation of the opium plant dates to the earliest years of human civilization, the relatively newer development of synthetic opioids has led to a drastic increase in addiction rates and overdoses (Centers of Disease Control and Prevention, 2019). The opioid epidemic is widely considered to have begun in the 1990s when pharmaceutical companies falsely advertised that opioids were non-addictive, encouraging large amounts of opioid prescriptions to be written (Alpert *et al.*, 2019). Today, despite its addictive nature, opioids continue to be prescribed in alarming numbers. For example, in 2017, Alabama and Arkansas filled more opioid prescriptions than people with 107.2 and 105.4 prescriptions per 100 people, respectively (Centers of Disease Control and Prevention, 2017). This problem of over-prescribing opioids has led to extreme misuse, with estimates that upwards of 30% of all opioid prescriptions are misused (National Institute on Drug Abuse, 2018).

While there has been recent work applying the framework of SIR-type compartmental models to better understand drug abuse, only a few of these models incorporate a compartment for prescription opioids, which is a key driver of abuse. Furthermore, we were unable to find any existing research that broke down the prescription compartment by individual opioid type. White & Comiskey (2007) modelled heroin addiction by creating a three-compartment model that included a compartment for susceptibles and for heroin users both in and out of treatment. They found that targeting addiction rates specifically for heroin is a more efficient way to reduce the size of this epidemic than improving treatment. Mushanyu & Nyabadza (2018) modelled the flow of people from low- and high-risk susceptibility to using opioids to treatment and finally to high- and low-risk recovery. They concluded that more knowledge about relapse and how best to maintain sobriety would best combat the epidemic. Battista *et al.* (2019), on the other hand, created a model that allowed for addiction both through prescription and directly from susceptible. After performing a sensitivity analysis, they concluded that better and more effective treatment regimens, fewer prescriptions and an increase in access and motivation for treatment would be best to prevent the crisis from worsening. Similarly, Caldwell *et al.* (2019) constructed a Vicodin-abuse compartmental model that demonstrated the flow of prescription Vicodin use beginning from acute medical use, escalating to chronic use, followed by abuse and entrance into treatment. Infectious disease models have also been used to better understand co-infection. Orwa & Nyabadza (2019) modelled alcohol-methamphetamine co-abuse by creating a model composed of two submodels: the methamphetamine submodel and the alcohol submodel. They determined that keeping the reproduction number for the alcohol epidemic model below 1 is necessary to control the alcohol epidemic and subsequently the co-use epidemic of methamphetamine and alcohol.

We focus on the relative role that different prescription opioids play into the current crisis. Each of the four opioids we are evaluating have different chemical makeups, so we do not a priori assume that their addiction probabilities are equal. For example, tramadol, a synthetic opioid, was synthesized in the 1970s and was initially thought to have no addictive qualities. It was thus prescribed in very high quantities and was listed as a schedule IV substance according to the Controlled Substances Act (Addiction Center, 2019). Most other painkillers, including the opioids hydrocodone and oxycodone are schedule II substances and codeine is schedule III (generally speaking, the higher the substance number, the less addictive the drug is thought to be). According to data collected by the Substance Abuse and Mental Health Services Administration (SAMHSA), the four most commonly prescribed opioids are hydrocodone, oxycodone, codeine and tramadol. They made up 87% of all prescriptions from 2015 to 2016 and accounted for 40% of all opioid overdoses (Substance Abuse and Mental Health Services Administration, 2017b). In this manuscript, we combine data from the SAMHSA, which tracked the proportion of people who used or misused one of the four commonly prescribed opioids, with data from the Centers of Disease Control and Prevention (CDC), which counted the total number of prescriptions, to estimate prescription rates and probabilities of addiction. We calculate the prescription rates and addiction probabilities specific to each of these four opioids and evaluate whether there is a theoretically 'safer' or 'more dangerous opioid' in terms of driving the addiction epidemic.

The paper is organized as follows. In Section 2, we expand on the other models mentioned above by creating a seven-compartment model that includes a compartment for susceptible individuals, the four most common prescriptions, addicts and drug users in treatment. We write our model as a system of differential equations and estimate the associated parameters from the data and from the existing literature. In Section 3, we compute the equilibrium and perform a sensitivity analysis on the prescription rates and reallocate the number of prescriptions to evaluate the relative role of each prescription opioid in the epidemic. We find that oxycodone has the largest effect and hydrocodone has

the smallest. In Section 4, we discuss the implications of these results and outline ways in which this research could be expanded upon.

2. Model

Between the 1999 and 2017, the number of prescription overdose deaths rose from 3,442 to 17,029 deaths per year (National Institute on Drug Abuse, 2019). In order to better understand which prescriptions contribute the most to the overall crisis and how changing the prescription rates affect the addicted population, we create an opioid addiction model that includes prescriptions as a gateway to addiction. We focus on the relative role that prescriptions have on the opioid epidemic, so we choose to expand on Battista *et al.* (2019) prescription opioid model. They used a four-compartment model with a compartment for susceptible, prescription, addiction and recovery. In addition to the susceptible, addiction and recovered populations, we subdivide the prescription population into four compartments corresponding to the four most frequently prescribed opioid populations: hydrocodone, oxycodone, codeine and tramadol; see the schematic in Fig. 1 and the differential equations in (1).

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda N + \eta \sum_{i=1}^{4}(1-\beta_i)P_i - \mu_1 S - S\sum_{i=1}^{4}\alpha_i \\
\frac{dP_1}{dt} &= \alpha_1 S - (1-\beta_1)\eta P_1 - \beta_1 \eta P_1 - \mu_1 P_1 \\
\frac{dP_2}{dt} &= \alpha_2 S - (1-\beta_2)\eta P_2 - \beta_2 \eta P_2 - \mu_1 P_2 \\
\frac{dP_3}{dt} &= \alpha_3 S - (1-\beta_3)\eta P_3 - \beta_3 \eta P_3 - \mu_1 P_3 \\
\frac{dP_4}{dt} &= \alpha_4 S - (1-\beta_4)\eta P_4 - \beta_4 \eta P_4 - \mu_1 P_4 \\
\frac{dA}{dt} &= \eta \sum_{i=1}^{4}\beta_i P_i + \delta R - \omega A - (\mu_1+\mu_2)A \\
\frac{dR}{dt} &= \omega A - \delta R - \mu_1 R
\end{aligned} \tag{1}$$

The susceptible population, S, consists of all Americans over the age of 18 years not currently prescribed opioids, addicted or in recovery. The four prescription compartments are distinguished based on the type of opioid they are prescribed: P_1 represents hydrocodone, P_2 represents oxycodone, P_3 represents codeine and P_4 represents tramadol. The prescription compartment is defined as those who are properly following the instructions of their prescribed opioid. We choose to not incorporate prescriptions that include combinations of multiple opioids and assume the average prescription length is $1/\eta$. Prescription length is defined as the following: the number of days a prescription is written for without refills. Consider the scenario where a chronic pain patient is prescribed hydrocodone for 18 days and the prescription is continued for the next 30 years. The prescription length is 18 days, and in our model, the patient's 30 years of taking his/her prescribed hydrocodone would count as multiple repeated prescriptions and not as one prescription. Individuals enter the prescription

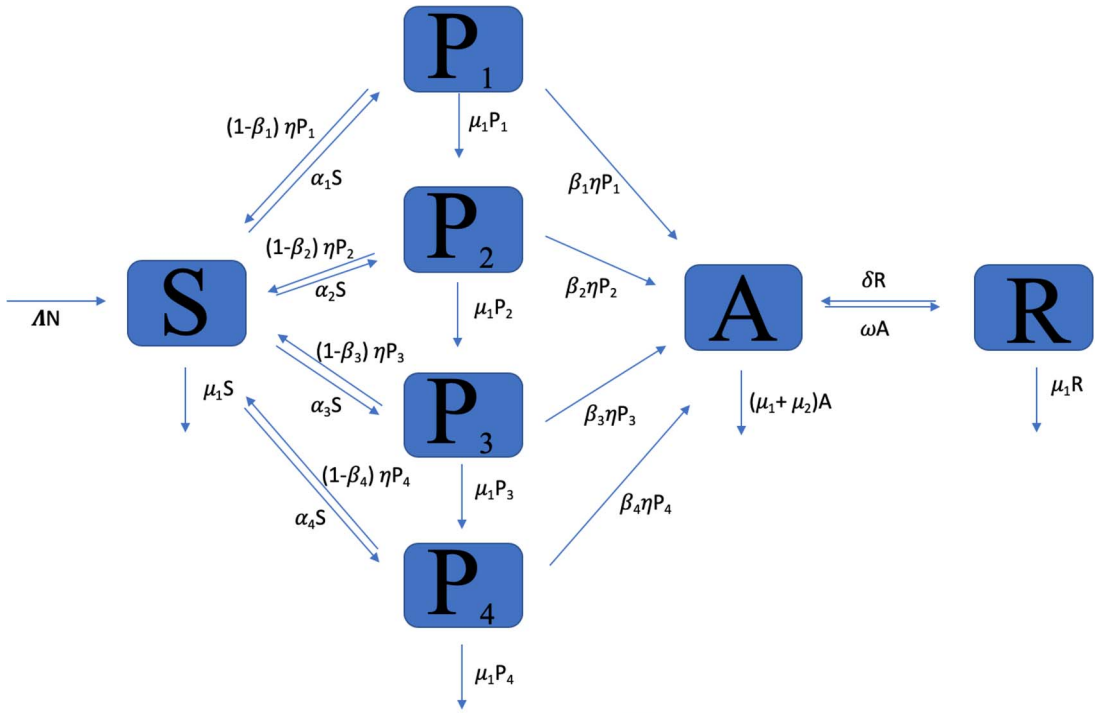

FIG. 1. Schematic of model. Each box represents a compartment and the arrows describe the flow of individuals between compartments. The model contains a susceptible population, S, an addicted population, A, and a recovered or in-treatment population, R. Individuals currently taking legally prescribed hydrocodone, oxycodone, codeine and tramadol prescriptions are classified as in the prescription population: P_1, P_2, P_3 and P_4, respectively.

compartment at rate α_i when they are prescribed one of the four opioids. Once an individual appropriately completes their prescription with no continued use, the individual returns to the susceptible compartment.

We define addiction as any misuse, abuse or dependence of a prescription opioid, i.e. if any prescription opioid use occurs without instruction by a doctor, those individuals are classified as being in the addicted compartment. We classify misuse as any use beyond the said length of prescribed opioid, even though this use is not always considered 'addiction'. Distinguishing between these three behaviours is difficult, especially since they are not clearly differentiated in the public health literature. While some individuals become addicted without first being prescribed opioids, prescription is a major gateway to addiction, and since we focus on the role of prescription, we ignore the direct addiction pathway. The National Institute on Drug Abuse (2018) reports that 75% of non-heroin opioid abusers began their opioid use via prescription opioids and that 80% of heroin users began their opioid use via prescription opioids. This provides strong evidence that the majority of individuals who abuse opioids received a prescription first. Currently, there are no available data that distinguish between the four opioid prescriptions in a direct S to A pathway. Furthermore, our goal is to determine which opioid contributes the most to the addicted population. Without data differentiating direct addiction between these four opioids, incorporating this pathway into the model would not change the ranking order of the opioids in leading to addiction. For these reasons, we assume that the only entry into the

addicted compartments is through an opioid prescription. After completing a prescription, an individual has probability, β_i, of entering the addicted compartment, A, and probability, $(1 - \beta_i)$, of returning to the susceptible compartment. This model structure is in contrast to the model in Battista *et al.* (2019), which has two different rate parameters that describe leaving the prescription compartment. Because the length of a prescription is fixed by the physician and does not depend on whether the individual becomes addicted, we include these probabilities of addiction, β_i, and use one rate parameter, η, to correspond to the reciprocal of the average prescription length. Note that our model is deterministic and these probabilities are modelled as proportions at the population level.

Individuals in the addicted compartment move into the recovered compartment with recovery rate, ω, and die from an opioid overdose at rate, μ_2. We classify the recovered compartment, R, as those who have entered or completed a treatment program or individuals that have pursued abrupt sobriety. For example, once a person enters into a treatment program for his/her opioid addiction, he/she moves from the addicted compartment to the recovered compartment. If an individual abuses, misuses or becomes dependent on opioids while in the recovered compartment, he/she moves back into the addicted compartment; this is the relapse rate, δ. After successful completion of a treatment program or entrance into the recovered compartment, the individual remains in the recovered compartment and does not move back into the susceptible compartment. They remain in the recovered compartment since those who are recovered addicts are more likely to relapse without a prescription. As a result of limited data on relapse rates and the increased likelihood of drug mixing throughout addiction, we assume the recovery rates and relapse rates are the same for all individuals and all prescription opioids.

We assume the death rate in the recovered compartment is the same as the natural death rate, μ_1. Finally, we assume a constant population and therefore set the birth rate, λ, equal to the sum of the natural and overdose deaths. For each population, we utilize statistics from 2015 to 2016, as this was the most recent comprehensive data we were able to locate.

2.1 *Parameter values*

With the exception of the prescription rates, α_i, and the probabilities of addiction, β_i, which we calculate below, and the recovery rate, ω, which Battista *et al.* (2019) fit from their model, we were able to find values for the other parameters directly from data sources. See Table 1 for the individual values.

2.1.1 *The prescription rates, α_i.* While the CDC reports the yearly total number of written opioid prescriptions, they do not report the exact quantity of prescriptions per individual opioid. The SAMHSA published a data table that breaks down the proportion of individuals in ‘any use’ and ‘any misuse’ by individual opioid. Unfortunately, their data are in terms of percentage of individuals instead of total prescriptions. In order to find the prescription rate for each of the four individual opioids, α_i, we first calculate the percent of people currently using a prescription opioid, a_i.

$$a_i = \frac{\text{any use} - \text{misuse}}{100} \tag{2}$$

The parameter a_i both over- and under-counts the prescription rate. If a person is using and/or misusing two different opioids at the same time, he/she will appear twice in the data, thus overcounting. These a_i values undercount the prescription rates because the average number of yearly prescription opioids

TABLE 1 *Table of parameter values. Shown above are all estimated parameter values organized by parameter name, estimated calculation or formula used, parameter description and reference. See Sections 2.1.1 and 2.1.2 for prescription rate, α_i, and addiction probability, β_i, calculations.*

Parameter	Value	Units	Description	Source
μ_1	0.0127	Year^{-1}	Natural death rate	(Population Reference Bureau, 2018)
μ_2	0.0002017	Year^{-1}	Overdose death rate	(National Institute on Drug Abuse, 2019)
λ	$\mu_1 N + \mu_2 A$	Year^{-1}	Natural birth rate	See explanation in Section 2.
η	$\frac{1}{0.049}$	Year^{-1}	Average prescription length	(Centers of Disease Control and Prevention, 2019)
α_1	0.3237	Year^{-1}	Hydrocodone prescription rate	Estimated in (4)
α_2	0.1529	Year^{-1}	Oxycodone prescription rate	Estimated in (4)
α_3	0.1496	Year^{-1}	Codeine prescription rate	Estimated in (4)
α_4	0.1122	Year^{-1}	Tramadol prescription rate	Estimated in (4)
β_1	0.005734	1	Hydrocodone addiction probability	Estimated in (6)
β_2	0.01779	1	Oxycodone addiction probability	Estimated in (6)
β_3	0.01663	1	Codeine addiction probability	Estimated in (6)
β_4	0.01544	1	Tramadol addiction probability	Estimated in (6)
ω	0.175	Year^{-1}	Entrance into treatment rate	(Battista *et al.*, 2019)
δ	0.7	Year^{-1}	Relapse rate	(Bailey *et al.*, 2013; Smyth *et al.*, 2010)

per individual is 3.4 (Centers of Disease Control and Prevention, 2018a), conditioned on receiving at least one opioid prescription. If a person is prescribed the same type of opioid multiple times, he/she is only counted once. Data show that once prescribed an opioid, the patient is more likely to have his/her prescription refilled or be given another prescription. In order to combat this, we calculate a ratio, ρ, the total number of prescriptions per person given that the person is prescribed at least one opioid. From here, we multiply this ratio by the respective a_i value to account for the overcounting of people and undercounting of prescriptions within our prescription rates.

To calculate ρ, we first determine the number of susceptible individuals, $S = N - P - A - R$, where N is the total population and P, A and R are the populations defined in Fig. 1. We calculate N to be $247,868,396$, as this was the total population older than 18 years in the USA in 2015–2016 (Kids Count Data Center, 2019). The population P is the sum of the four individual prescription populations, $P = \sum_{i=1}^{4} P_i$; however, calculating P_i is difficult as multiplying a_i by N will miscount P_i. The population A is reported as 11.5 million (Substance Abuse and Mental Health Services Administration, 2017a). We calculate the population R to be the product $A \cdot 0.175$ as 17.5% of people who misuse opioids are estimated to receive treatment (Battista *et al.*, 2019).

As stated above, multiplying a_i by N will miscount P_i. Similarly to how the data miscounts P_i, it also miscounts A. We calculate A_d from the SAMHSA data as $A_d = \text{misuse} \cdot N$. To determine how much the A population is miscounted by the SAMHSA data, we compare A_d to the reported value of A. We equate ψ to represent the miscounted number of individuals misusing opioid prescriptions given by the SAMHSA data, yielding $\psi = \frac{11.5 \cdot 10^6}{A_d}$. We multiply this ratio by P_i as we assume that the data miscounts P_i in a similar way. In addition, we multiply by $\frac{1}{\eta}$ to account for the proportion of a year.

$$P = \sum_{i=1}^{4} \frac{a_i N \psi}{\eta} \tag{3}$$

This yields a susceptible population equal to $230,092,079$ people. These values of S, P_i, A and R are used as initial conditions in the simulations plotted in Fig. 2.

With this calculated value of S, we can now proceed with calculating the prescription rate for each specific opioid, α_i. We denote $W = S \cdot \sum_{i=1}^{4} a_i$, where W is the total number of people prescribed per year. The CDC reports that in 2015–2016, the average number of prescriptions written per 100 people was 68.55 prescriptions. To obtain the total number of prescriptions, we multiply $\frac{68.55}{100} \cdot N$ to yield $169,913,785$ total prescriptions, which we denote as B (Centers of Disease Control and Prevention, 2018c). To find the ratio of the total number of prescriptions per person, we set $\rho = \frac{B}{W}$, yielding $\rho = 2.54$. Finally, the product of a_i and ρ yields the prescription rates, α_i, as shown below.

$$\alpha_i = a_i \rho \tag{4}$$

See Table 1 for the calculated α_i values.

2.1.2 *Addiction probabilities, β_i.* The probability of misusing individually prescribed opioids is not documented in the literature. Similarly to how we calculate our prescription rates, the SAMHSA published data detailing the total percentage of people who have misused individual opioids as well as the percent of people who have misused opioids given that they used opioids in any context the previous year (Substance Abuse and Mental Health Services Administration, 2017b). From these, we calculate the addiction probabilities of each prescription opioid.

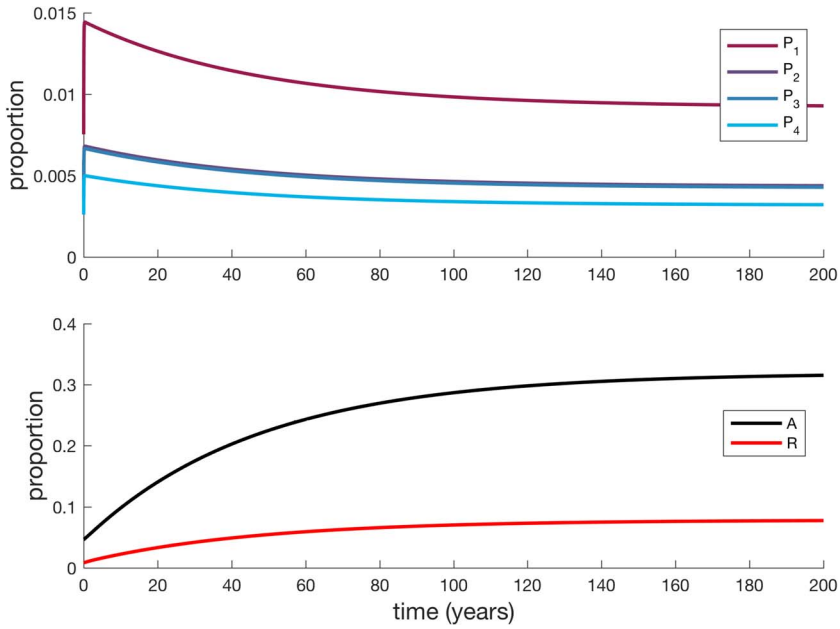

FIG. 2. These graphs are simulations of (1). The top graph displays the proportion of the total population that is in each of the four individual prescription opioids and the bottom graph displays the proportion in the addicted and recovered compartments. Notice the scale on the horizontal axis and how slowly the system approaches the stable equilibrium. Parameter values can be found in Table 1, and the calculations of initial conditions are described in Section 2.1.1 and are $S(0) = 0.928$, $P_1(0) = 0.00754$, $P_2(0) = 0.00356$, $P_3(0) = 0.00348$, $P_4(0) = 0.00261 A(0) = 0.0464$ and $R(0) = 0.00812$. The small spike of the prescription populations in the first few months and then subsequent slow decline likely results from some combination of an underestimate of the initial number of addicted individuals, imprecision in the available data on prescription rates and one or more of our assumptions.

To match the above-described conditional probability, we define x_i as the number of people who are currently misusing a specific prescription opioid divided by the total number of people that used opioids in the previous year; see (5). We use our model framework to calculate the numerator of x_i, the number of individuals currently misusing an opioid. We do this by summing the individuals entering A from a specific prescription compartment in the past year, P_i, the number of individuals who relapse from R into A in the past year and the number of people who start in and remain in A. The denominator, denoted as T_{P+A}, is taken from the CDC data. This yields the following equation for x_i:

$$x_i = \frac{\beta_i \eta P_i + \frac{\delta R}{4} + (1-\omega) A_i \psi}{T_{P+A}}. \tag{5}$$

Rearranging the equation to solve for β_i,

$$\beta_i = \frac{(T_{P+A}) x_i - \frac{\delta R}{4} - (1-\omega) A_i \psi}{\eta P_i}. \tag{6}$$

The parameter values used in (6) are displayed in Table 1. We had previously approximated P_i using (3) as we had yet to calculate α_i. Now that we have α_i, we estimate the prescription population in a more intuitive and presumably more accurate way as the product of the number of susceptible individuals and the prescription rate, $P_i = S \cdot \alpha_i$. Since $A = \sum_{i=1}^{4} A_i$ is miscounted by the SAMHSA data, we assume that the individual A_i are also miscounted. To control for this, we multiply A_i by ψ, yielding $A_i = \text{misuse} \cdot N\psi$, where misuse is obtained from the SAMSHA data. The population R is the product of $A \cdot 0.175$, as stated above. Since there are limited data on relapse rates, we divide $\frac{R}{4}$ as we assume that the relapse rate is the same for each of the four opioids.

The total number of people who used an opioid in the previous year is denoted by T_{P+A}. We calculate T_{P+A} by summing the total number of individuals who misused an opioid and the number of individuals prescribed. To obtain the total number of individuals prescribed an opioid, we divide the number of prescriptions by ρ to account for the miscounting of the prescription use by the SAMHSA data as explained above. We calculate T_{P+A} by using the following equation:

$$T_{P+A} = \text{total number of misuse} + \frac{\text{Total number of prescriptions}}{\rho}. \tag{7}$$

The calculated values for β_i are listed in Table 1. Notice that the probability of addiction for hydrocodone, β_1, falls near the range of values Caldwell *et al.* (2019) found in their modelling paper for Vicodin, a hydrocodone-based opioid.

3. Results

3.1 *Equilibrium*

Using (1), we calculate the equilibrium for each variable and find that the system has a unique equilibrium:

$$\begin{aligned}
S^* &= \frac{\mu_1 N + \mu_2 A^*}{\mu_1 + \sum_{i=1}^{4} \alpha_i - \frac{\eta}{\eta+\mu_1} \sum_{i=1}^{4} \alpha_i(1-\beta_i)} \\
P_i^* &= \frac{\alpha_i A^*}{\eta + \mu_1} \\
A^* &= \frac{\frac{\mu_1 N\left(\frac{\eta}{\eta+\mu_1}\right) \sum_{i=1}^{4} \alpha_i \beta_i}{\mu_1 + \sum_{i=1}^{4} \alpha_i - \frac{\eta}{\eta+\mu_1} \sum_{i=1}^{4} \alpha_i(1-\beta_i)}}{\omega + \mu_1 + \mu_2 - \frac{\delta\omega}{\delta+\mu_1} - \frac{\mu_2\left(\frac{\eta}{\eta+\mu_1}\right) \sum_{i=1}^{4} \alpha_i \beta_i}{\mu_1 + \sum_{i=1}^{4} \alpha_i - \frac{\eta}{\eta+\mu_1} \sum_{i=1}^{4} \alpha_i(1-\beta_i)}} \\
R^* &= \frac{\omega A^*}{\delta + \mu_1}.
\end{aligned} \tag{8}$$

Using the parameter values from Table 1, we compute the equilibrium values for each variable. Table 2 displays these equilibrium values as percentages of the total population.

To classify the stability of the equilibrium, we simulate our model, see Fig. 2, for the time series results. Visual inspection suggests that the equilibrium is stable. We see that hydrocodone has the largest equilibrium prescription population while tramadol has the smallest. We also note that the addicted

TABLE 2 *Equilibrium values for the population in each compartment.*

Compartment	Equilibrium value (%)
S^*	58.146
P_1^*	0.922
P_2^*	0.435
P_3^*	0.426
P_4^*	0.320
A^*	31.871
R^*	7.826

TABLE 3 *Percent of the population within individual compartments based upon the calculated equilibrium values above. The rows display the equilibrium values recalculated without one of the four types of opioid prescriptions to demonstrate the effect of the complete removal of each prescription. We focus on the differences in the addicted populations, which are bolded in the Table.*

	S(%)	P_1(%)	P_2(%)	P_3(%)	P_4(%)	**A**(%)	R(%)
Original	58.146	0.922	0.435	0.426	0.320.	**31.871**	7.826
No hydrocodone	64.113	0	0.480	0.470	0.352	**27.694**	6.800
No oxycodone	66.623	1.056	0	0.488	0.366	**25.221**	6.193
No codeine	65.831	1.043	0.493	0	0.362	**25.864**	6.351
No tramadol	63.305	1.003	0.474	0.464	0	**27.855**	6.840

population remains much larger than the recovered population over time. We performed additional simulations for a variety of parameter values and initial conditions and always observe similar qualitative dynamics of one non-trivial stable equilibrium.

3.2 *Reallocation of prescriptions*

In order to evaluate the relative role of each of the four most commonly prescribed opioids, we first reduce the prescription rate to zero for each opioid one at a time. We then recompute the respective equilibrium values for the addicted population, A^*; see Table 3. This reduction of an individual prescription naturally leads to fewer total prescriptions written. To more accurately represent the effect of the choice a physician makes in which opioid to prescribe, when we reduce the prescription rate of a given opioid to zero, we redistribute the eliminated prescriptions equally among the other three opioids. This keeps the number of prescriptions constant as the adjusted prescription rates for each of the opioids that were not eliminated become $\frac{1}{3} \cdot \alpha_{\text{eliminated}} + \alpha_i$. Table 4 displays the results after this reallocation.

Tables 3 and 4 both indicate that prescriptions for oxycodone and codeine have the largest effect on the total addicted population. In the case of prescription removal, eliminating one of these two prescriptions decreases A^* by approximately 20.865% and 18.848%, respectively, and by 5.622% and 3.828% if the removed prescriptions are reallocated. Despite oxycodone and codeine having similar prescription rates, $\alpha_2 \approx \alpha_3$, oxycodone has a larger probability of addiction, β_2, which explains why there is a slightly greater decline in the total addicted population after eliminating all oxycodone prescriptions. Reallocating the hydrocodone prescriptions to the other three opioids increases the addicted population by 20.781%. That reallocating the hydrocodone prescriptions increases A^* is not

TABLE 4 *Percent of the population within individual compartments based upon the calculated equilibrium values above. The rows display the equilibrium values recalculated without one of the four types of opioid prescriptions to demonstrate the effect of the complete removal of each prescription. When a prescription opioid is removed, the total number of prescriptions written for that opioid are equally redistributed to the three remaining prescription opioids so that the total number of prescriptions remains constant. We focus on the differences in the addicted populations, which are bolded in the Table.*

	S(%)	P_1 (%)	P_2 (%)	P_3 (%)	P_4 (%)	**A**(%)	R (%)
Original	58.146	0.922	0.435	0.426	0.320.	**31.871**	7.826
No hydrocodone and redistribute among others	50.158	0	0.641	0.633	0.541	**38.494**	9.452
No oxycodone and redistribute among others	60.306	1.106	0	0.592	0.482	**30.079**	7.386
No codeine and redistribute among others	59.616	1.091	0.592	0	0.473	**30.651**	7.526
No tramadol and redistribute among others	58.758	1.039	0.548	0.538	0	**31.363**	7.701

surprising given that it has a high prescription rate but a relatively low probability of addiction. We cannot conclude that there is a 'safe' opioid, but rather our results indicate decreasing the prescriptions to the more addictive opioids, oxycodone and codeine, could help limit the opioid addiction crisis. These results are illustrated graphically in Fig. B3; see Appendix B.

3.3 *Sensitivity analysis*

We perform a sensitivity analysis to measure the effect of each prescription opioid on the size of the addiction epidemic. In order to evaluate the effect of small changes in a prescription rate on the size of the epidemic, we compute the normalized forward sensitivity index of A^* with respect to each α_i. We denote the normalized forward sensitivity index with respect to prescription i as $A^*_{\alpha_i}$. Each $A^*_{\alpha_i}$ measures the ratio of the relative change in the size of the addicted population to a small relative change in the prescription rate.

$$A^*_{\alpha_i} = \frac{\frac{\partial A^*}{A^*}}{\frac{\partial \alpha_i}{\alpha_i}} \tag{9}$$

The normalized forward sensitivity indices are displayed in Table 5 and Appendix B. Notice the inverse relationship between the sensitivity of each prescription rate and the effect of reallocating those prescriptions. See Appendix A for details on the calculation of this partial derivative.

Larger sensitivity indices indicate a greater increase in the number of addicted individuals due to a small increase in that prescription rate. Therefore, removing prescriptions corresponding to the largest sensitivity indices will lead to the greatest reduction in the number of addicted individuals. Similarly to the reallocation of prescriptions performed above, oxycodone appears to contribute the most to the addicted population since it has the largest value. For every increase in the prescription rate for oxycodone, α_2, of 1%, the addicted population increases by 0.181%, or 142, 987 individuals. Likewise, for every 1% increase in the prescription rate for codeine, α_3, the addicted population increases by

TABLE 5 *Table values for normalized forward sensitivity index. This table displays the normalized forward sensitivity index of the addicted population, A^*, with respect to each prescription rate α_i and is calculated by $A^*_{\alpha_i} = \frac{\frac{\partial A^*}{A^*}}{\frac{\partial \alpha_i}{\alpha_i}}$. This measures the ratio of the relative change in the size of the addicted population to a small relative change in the prescription rate. For example, if the prescription rate for hydrocodone (α_1) is increased by 1%, then the equilibrium value for the number of addicted individuals would increase by 0.117%. Because these values are calculated from partial derivatives, we would only expect them to be meaningful for small changes in each prescription rate.*

	Normalized forward sensitivity index
$A^*_{\alpha_1}$	0.117
$A^*_{\alpha_2}$	0.181
$A^*_{\alpha_3}$	0.165
$A^*_{\alpha_4}$	0.115

0.165%, or 130, 347 individuals. This supports our earlier conclusion that decreasing prescriptions of oxycodone and codeine will have the greatest impact in decreasing the total addicted population.

4. Conclusion

Of the 67, 000 people that died from drug overdoses in 2018 in the USA, 70% involved a prescription or illicit opioid (Centers of Disease Control and Prevention, 2019). In comparison in 2018, 40, 000 people died from a motor vehicle accident (Occupational Health and Safety, 2019) and 48, 344 people died from suicide (USA Today, 2020). Even though the CDC reports a 4% decrease from 2017 in the number of drug overdose deaths, drug overdose is still a leading cause of injury related deaths in the USA. Additionally, the combination of over-prescribing opioids and prescribing more addictive opioids has led to extreme misuse, often resulting in heroin and other illicit opioid use, and even overdose deaths (National Institute on Drug Abuse, 2019).

The purpose of this manuscript was to understand how individual opioid prescriptions impact the severity of this crisis by determining the prescription rate and probability of addiction of the four most commonly prescribed opioids: hydrocodone, oxycodone, codeine and tramadol. In general, the total number of opioid prescriptions and their addictive properties have been recently well studied. However, at the individual level, these properties are less clear. The total number of opioid prescriptions is reported by the Centers of Disease Control and Prevention (2017) and there has been some investigation into the addictive properties for opioids in general (Battista *et al.*, 2019; Caldwell *et al.*, 2019; White & Comiskey, 2007); however, we were unable to find any research or studies that look at individual opioids and these properties. By combining data from the SAMHSA, which tracked the proportion who used or misused the four individual opioids and the CDC, which tracked the total numbers of prescriptions, we derived formulas for the individual prescription rates and probabilities of addiction. Our results indicate that oxycodone has the largest probability of addiction per prescription at 1.8% and is 3.1 times larger than hydrocodone, which has the smallest probability of addiction per prescription at 0.57%. Because there is little clinical evidence supporting a systematic choice of one opioid over another, physicians should strongly consider our results and results similar to ours when looking to prescribe an opioid.

In order to evaluate each opioid's effect on the number of addicted individuals, we perform a local sensitivity analysis on each prescription rate and we reallocate the prescriptions of the four individual opioids. Both types of analyses show that hydrocodone use has the smallest effect on the addiction population, while oxycodone has the largest effect, with codeine close behind. Our initial results indicate that lowering the number of oxycodone prescriptions would prevent the largest number of people prescribed an opioid from becoming addicted. These results are of course preliminary as there are many other addiction risk factors and more work needs to be done before these modelling results should inform physician prescription choices. A recent paper by Alpert *et al.* (2019) analysed state-by-state data and found that state prescription regulations as well as marketing dollars spent on OxyContin by Purdue Pharma had a statistically significant increase on prescription rates and overdose deaths. This provides another piece of evidence suggesting that prescription habits can play an important role in driving the opioid epidemic.

There are a number of additional directions that could be done to better understand the relative role of these four opioids in driving the opioid epidemic. While misusing prescriptions is the leading cause of addiction, some individuals become addicted through social interaction with other addicts. Our model assumes the only pathway to opioid addiction is through prescription. Adding a direct pathway between the susceptible compartment, S, and the addicted compartment, A, as was done in Battista *et al.* (2019), which did not distinguish between different types of opioids, could improve our understanding of the addiction process. However, without data breaking down this process by individual opioid, adding this direct route to our model would not change the ranking of the four opioids. Another future direction could be changing the functional form of our relapse rate to depend on the populations of individuals that are currently addicted and currently taking prescriptions, similarly to Battista *et al.* (2019), with the recovered compartment to the addicted compartment pathway represented as δRA rather than δR. Furthermore, looking at contact networks through the use of agent-based modelling could better help understand the social effect of opioid addiction.

We assume that each individual is equally likely to be prescribed an opioid and to abuse an opioid prescription. Allowing for the probability of addiction to be a function of prescription length and the number of repeat prescriptions would be an interesting addition to this model and could improve our external validity. There are a variety of risk factors that can greatly increase an individual's probability of addiction. Dilokthornsakul *et al.* (2016) found that there is a threefold greater risk of overdose occurring in individuals that have a history of alcohol or drug abuse; this implies that history of alcohol and/or drug abuse is a high risk factor. Similarly, these risk factors and which opioid or combination of opioids a person specifically misuses can influence a later relapse. For example, the relapse rate for heroin is estimated to be 78.2% (Lautieri *et al.*, 2020). As stated above, Bailey *et al.* (2013) and Smyth *et al.* (2010) estimated the relapse rate for opioids in general to be 70%. Therefore, it is probable that the relapse rates are different with respect to each opioid; however, more research is necessary to determine these specific relapse rates. The CDC reports that 80% of people who used heroin in 2013 first misused a prescription opioid (National Institute on Drug Abuse, 2019). Incorporating heroin use into our model would demonstrate how quickly the crisis escalates, as opioids are often a gateway for heroin addiction. Incorporating these more detailed properties of prescriptions backed by appropriate data could provide a better understanding of addiction risk and be helpful guidance for physicians making prescription decisions. Finally, combining this model framework with prescription, misuse and overdose data that are refined by a specific opioid would be vital in better understanding the relative impacts of individual opioids.

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References

Addiction Center (2019) Tramadol addiction and abuse. https://www.addictioncenter.com/opiates/tramadol/.

Alpert, A., Evans, W., Lieber, E. & Powell, D. (2019) Origins of the opioid crisis and its enduring impacts. NBER Working Paper Series 26500.

Bailey, G. L., Herman, D. S. & Stein, M. D. (2013) Perceived relapse risk and desire for medication assisted treatment among persons seeking inpatient opiate detoxification. *J. Subst. Abuse Treat.*, **45**, 302–305.

Battista, N. A., Pearcy, L. B. & Strickland, W. C. (2019) Modeling the prescription opioid epidemic. *Bull. Math. Biol.*, **81**, 2258–2289.

Caldwell, W. K., Freedman, B., Settles, L., Thomas, M. M., Camacho, E. T. & Wirkus, S. (2019) The Vicodin abuse problem: a mathematical approach. *J. Theor. Biol.*, **483**, 110003.

Centers of Disease Control and Prevention (2017) U.S. state prescribing rates, 2017. https://www.cdc.gov/drugoverdose/maps/rxstate2017.html .

Centers of Disease Control and Prevention (2018a) 2018 annual surveillance report of drug-related risks and outcomes. https://www.cdc.gov/drugoverdose/pdf/pubs/2018-cdc-drug-surveillance-report.pdf.

Centers of Disease Control and Prevention (2019) Annual Surveillance Report of Drug-Related Risks and Outcomes – United States. Surveillance Special Report 2. https://www.cdc.gov/drugoverdose/pdf/pubs/2018-cdc-drug-surveillance-report.pdf.

Centers of Disease Control and Prevention (2018c) U.S. opioid prescribing rate maps. https://www.cdc.gov/drugoverdose/maps/rxrate-maps.html.

Centers of Disease Control and Prevention (2019) Understanding the Epidemic. https://www.cdc.gov/drugoverdose/epidemic/index.html.

Dilokthornsakul, P., Moore, G., Campbell, J. D., Lodge, R., Traugott, C., Zerzan, J., Allen, R. & Page II, R. L. (2016) Risk factors of prescription opioid overdose among Colorado medicaid beneficiaries. *J. Pain*, **17**, 436–443.

Kids Count Data Center (2019) Total population by child and adult populations in the United States. https://datacenter.kidscount.org/data/tables/99-total-population-by-child-and-adult-populations#detailed/1/any/false/37,871,870,573,869,36,868,867,133,38/39,40,41/416,417.

Lautieri, A., Thomas, S., Kelley, R., Stein, S., Osbourne, N. & Ackermann, K. (2020) What does it mean to relapse? https://lagunatreatment.com/relapse/.

Mushanyu, J. & Nyabadza, F. (2018) A risk-structured model for understanding the spread of drug abuse. *Int. J. Appl. Comput. Math.*, **4**, 1–19.

National Institute on Drug Abuse (2018) Prescription opioids and heroin research report. https://www.drugabuse.gov/publications/research-reports/prescription-opioids-heroin/prescription-opioid-use-risk-factor-heroin-use.

National Institute on Drug Abuse (2018) Opioid overdose crisis. https://www.drugabuse.gov/drugs-abuse/opioids/opioid-overdose-crisis.

National Institute on Drug Abuse (2019) Overdose death rates. https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates .

Occupational Health and Safety (2019) 2018 third consecutive year of at least 40,000 motor vehicle deaths. https://ohsonline.com/articles/2019/02/18/nsc-motor-vehicle-deaths.aspx?m=1.

Orwa, T. O. & Nyabadza, F. (2019) Mathematical modelling and analysis of alcohol-methamphetamine co-abuse in the Western Cape province of South Africa. *Cogent Math. Stat.*, **6**, 1641175.

Population Reference Bureau (2018) Average life expectancy in North America for those born in 2018, by gender and region (in years). https://www.statista.com/statistics/274513/life-expectancy-in-north-america/.

Smyth, B. P., Barry, J., Keenan, E. & Ducray, K. (2010) Lapse and relapse following inpatient treatment of opiate dependence. *Ir. Med. J.*, **103**, 176–179.

Substance Abuse and Mental Health Services Administration (2017a) 2016 national survey on drug use and health. https://www.samhsa.gov/data/sites/default/files/nsduh-ppt-09-2017.pdf.

Substance Abuse and Mental Health Services Administration (2017b) Results from the 2016 national survey on drug use and health: detailed tables. https://www.samhsa.gov/data/sites/default/files/NSDUH-DetTabs-2016/NSDUH-DetTabs-2016.pdf.

USA Today (2020) More and more Americans are dying by suicide. What are we missing? https://www.usatoday.com/story/news/nation/2020/01/30/u-s-suicide-rate-rose-again-2018-how-can-suicide-prevention-save-lives/4616479002/.

White, E. & Comiskey, C. (2007) Heroin epidemics, treatment and ODE modelling. *Math. Biosci.*, **208**, 312–324.

A. Appendix. Partial derivatives

We calculate the normalized forward sensitivity index by taking the partial derivative of equilibrium value with respect to each prescription rate. Using (8), we find

$$\frac{\partial A^*}{\partial \alpha_i} = \frac{\frac{\partial F}{\partial \alpha_i} G - F \frac{\partial G}{\partial \alpha_i}}{F^2} \tag{A.1}$$

$$F = \frac{\mu_1 N \frac{\eta}{\eta+\mu_1} \sum_{i=1}^{4} \alpha_i \beta_i}{\mu_1 + \sum_{i=1}^{4} \alpha_i - \frac{\eta}{\eta+\mu_1} \sum_{i=1}^{4} \alpha_i (1-\beta_i)}$$

$$G = \omega + \mu_1 + \mu_2 - \frac{\delta\omega}{\delta+\mu_1} - \frac{\mu_2 \sum_{i=1}^{4} \alpha_i \beta_i}{\mu_1 + \sum_{i=1}^{4} \alpha_i - \frac{\eta}{\eta+\mu_1} \sum_{i=1}^{4} \alpha_i (1-\beta_i)}$$

$$\frac{\partial F}{\partial \alpha_i} = \frac{\left[\mu_1 N \frac{\eta}{\eta+\mu_1} \beta_i \cdot \left(\mu_1 + \sum_{i=1}^{4} \alpha_i - \frac{\eta}{\eta+\mu_1} \sum_{i=1}^{4} \alpha_i (1-\beta_i)\right)\right] - \left((1 - \frac{\eta}{\eta+\mu_1}(1-\beta_i)) \mu_1 N \frac{\eta}{\eta+\mu_1} \sum_{i=1}^{4} \alpha_i \beta_i\right)}{\left(\mu_1 + \sum_{i=1}^{4} \alpha_i - \frac{\eta}{\eta+\mu_1} \sum_{i=1}^{4} \alpha_i (1-\beta_i)\right)^2}$$

$$\frac{\partial G}{\partial \alpha_i} = -\frac{\left[\mu_2 \frac{\eta}{\eta+\mu_1} \beta_i \cdot \left(\mu_1 + \sum_{i=1}^{4} \alpha_i - \frac{\eta}{\eta+\mu_1} \sum_{i=1}^{4} \alpha_i (1-\beta_i)\right)\right] - \left(\mu_2 \frac{\eta}{\eta+\mu_1} \sum_{i=1}^{4} \alpha_i \beta_i (1 - \frac{\eta}{\eta+\mu_1}(1-\beta_i))\right)}{\left(\mu_1 + \sum_{i=1}^{4} \alpha_i - \frac{\eta}{\eta+\mu_1} \sum_{i=1}^{4} \alpha_i (1-\beta_i)\right)^2}$$

B. Appendix. Visual representation of sensitivity analysis

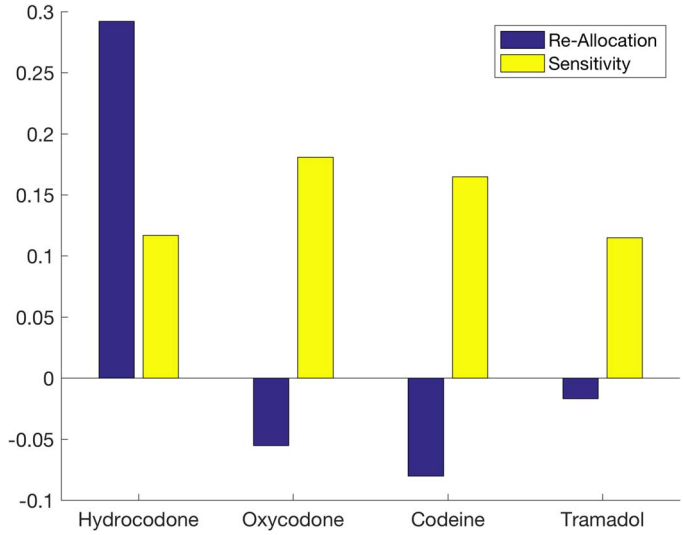

FIG. B3. This figure is a graphical representation of the reallocation of prescriptions, Table 4, and the sensitivity analysis, Table 5. The blue bars represent the proportional increase (or decrease when negative) to A^* when a prescription, P_i, is removed and those individual prescriptions are divided up into the other prescription opioids. The yellow bars are calculated as $\frac{\alpha_i}{A^*}\frac{\partial A^*}{\partial \alpha_i}$ and measure the sensitivity of the equilibrium value, A^*, to small changes in each prescription rates α_i.