Parameter assumptions from calculations done from literature information:
$\beta_A = 0.000273$
$\beta_P = 0.000777$
$\mu = 0.00868$
$\mu_A = 0.00870$
$\mu_H = 0.0507$
$\theta_2 = 3\theta_1$
$\theta_3 = 16\theta_1$
$\nu = 0.0155$
$\zeta = 0.0214$
$\omega = 10^{-10}$
$P_0 = 0.0710$

Used MultiStart to obtain 9 parameter values; these are the results we are settling on as "good enough."
We use the following vectors for the lower and upper bounds for the parameters we are estimating:

parameters estimating:	$[m$	θ_1	ϵ	γ	σ	b	A_0	H_0	$R_0]$
lower bounds:	$[-0.1$	0.00001	0.8	0.0001	0.00001	0.01	0.0001	0.0001	$0.0001]$
upper bounds:	$[\ 0.1$	0.1	8	0.5	0.1	1	0.5	0.5	$0.5].$

We choose these bounds for the following reasons:
-0.1$\leq$m$\leq$ 0.1: we assume that since α will be a value less than 1 based on estimate in [1], so it's slope will not be very large in absolute value
-0.00001$\leq\theta_1\leq$ 0.1: unknown, chosen intuitively that a susceptible individual would have less than a 0.1 probability of transitioning to the heroin class (see below regarding why upper bound is chosen this high)
0.8$\leq\epsilon\leq$ 8: estimate from [1]
0.0001$\leq\gamma\leq$ 0.5: estimate based on value in [1]
0.00001$\leq\sigma\leq$ 0.1: unknown, minimizes objective function value without hitting bounds
0.01$\leq b\leq$ 1: estimated based on value of α in [1]
0.0001$\leq A_0\leq$ 0.5: assume small but no greater than 50% of the population
0.0001$\leq H_0\leq$ 0.5: assume small but no greater than 50% of the population
0.0001$\leq R_0\leq$ 0.5: assume small but no greater than 50% of the population

We use data from Tennessee in the years 2013-2017 and compare it values from our model simulations with the goal of minimizing the difference between the values. We run the model for 6 years total (2013-2018). We denote Data1= [1825910/5517176; 1805325/5559006; 1800613/5602117; 1744766/5651993; 1620955/5708586] as the vector of values that represents the total proportion of the population that enters the P class at some point during the years 2013-2017 and Estim1=y(1:5,2)+y(2:6,6)-y(1:5,6) represents the total proportion that the model simulates as entering the P class at some point during the years 2013-2017. The vector Diff1=Estim1-Data1 represents the difference in these values each of the years. In order to find the relative error we calculate

$$\sqrt{\sum_{i=1}^{5} \text{Diff1(i)}^2} / \sqrt{\sum_{i=1}^{5} \text{Data1(i)}^2}.$$

Similarly, Data2=[43418/5517176; 42928/5559006; 42816/5602117; 37464/5651993; 34805/5708586] and Estim2=y(1:5,3)+y(2:6,7)-y(1:5,7) represent the actual and simulated total proportion of individuals in A at some point during the years 2013-2017. Again, we have Diff2=Estim2-Data being the vector of differences in these values each of the years and the relative error is calculated by

$$\sqrt{\sum_{i=1}^{5} \text{Diff2(i)}^2} / \sqrt{\sum_{i=1}^{5} \text{Data2(i)}^2}.$$

Finally, Data3=[7560/5559006; 7560/5602117; 10260/5651993] and Estim3=y(2:4,4)+y(3:5,8)-y(2:4,8) represent the actual and simulated total proportion of individuals in H at some point during the years 2014-2016, with Diff3=Estim3-Data3 being the vector representing the difference in these values each year. The relative error is calculated as

$$\sqrt{\sum_{i=1}^{3} \text{Diff3(i)}^2} / \sqrt{\sum_{i=1}^{3} \text{Data3(i)}^2}.$$

Since we wish to minimize the difference in all three of these data sets with the values that our model simulates, we add together their relative norms and set this as our objective function value to minimize. Thus our

$$\text{objective function value} =$$

$$\sqrt{\sum_{i=1}^{5} \text{Diff1(i)}^2} / \sqrt{\sum_{i=1}^{5} \text{Data1(i)}^2} + \sqrt{\sum_{i=1}^{5} \text{Diff2(i)}^2} / \sqrt{\sum_{i=1}^{5} \text{Data2(i)}^2} + \sqrt{\sum_{i=1}^{3} \text{Diff3(i)}^2} / \sqrt{\sum_{i=1}^{3} \text{Data3(i)}^2}.$$

Note that we take the relative error in each of these due to the differences in magnitude of the data. This results in an objective function value of 0.1821 for the following set of parameters.

parameters: $[m \quad \theta_1 \quad \epsilon \quad \gamma \quad \sigma \quad b \quad A_0 \quad H_0 \quad R_0]$
estimates: $[-0.0123 \quad \mathbf{0.0999} \quad 3.09 \quad \mathbf{0.000103} \quad 0.000684 \quad 0.291 \quad 0.00760 \quad 0.00121 \quad 0.000443]$
with each of these rounded to three significant figures, and where $\alpha = mt + b$, $\theta_2 = 3\theta_1$ (assumed), $\theta_3 = 16\theta_1$ (assumed), and $S_0 = 1 - P_0 - A_0 - H_0 - R_0$. Thus, a total of 11 parameter values relied on MultiStart least squares parameter estimation.

Although we have two parameters (θ_1 and γ) in **bold** hitting their bounds (upper and lower, respectively) for each run performed, this was the lowest objective value function we could obtain while keeping in mind realistic values for each of the parameters and initial conditions based on their biological interpretation, and using realistic bounds as described above. We note that increasing the upper bound for θ_1 is not only unrealistic but also raises the objective function value. Although decreasing the bound for γ slightly reduces the objective function value, based on the value being 0.00744 in [1], we do not believe it to be much lower than 0.0001 and thus stopped there for a lower bound. Performing both of these changes simultaneously leads to a seemingly unrealistically high θ_1 value and R_0 to a very unrealistic value. We did our best in striking a balance between minimizing the objective function value, reducing the number of parameters that were hitting bounds, and having biologically reasonable estimated values.

Thus, we have the following parameter estimates overall (red values most concerning):
$\alpha = [0.291\ 0.279\ 0.266\ 0.254\ 0.242\ 0.229]$
$\beta_A = 0.000273$
$\beta_P = 0.000777$
$\theta_1 = 0.0999$ (seems too high)
$\epsilon = 3.09$
$\gamma = 0.000103$ (seems too low)
$\sigma = 0.000684$
$\mu = 0.00868$
$\mu_A = 0.00870$
$\mu_H = 0.0507$
$\theta_2 = 0.300$ (seems too high)
$\zeta = 0.0214$
$\theta_3 = 1.60$ (seems too high)
$\nu = 0.0155$
$\omega = 10^{-10}$
$P_0 = 0.0710$
$A_0 = 0.00760$
$H_0 = 0.00121$
$R_0 = 0.000443$
$S_0 = 0.9197$

May 6, 2019 meeting (2 options):

Not using 2016 heroin data point (36 data points, estimating 15 values)

fval=0.0925

Used calculations:

$\mu = 0.00868$

$\mu_A = 0.00870$

$\mu_H = 0.0507$

$\beta_A = 0.000273$

$\beta_P = 0.000777$

$\omega = 10^{-10}$

Estimated:

$m = -0.0149$

$b = 0.290$

$\alpha = [0.290\ 0.276\ 0.261\ 0.246\ 0.231\ 0.216\ 0.201]$

$\theta_1 = 0.000518$

$\epsilon = 2.66$

$\gamma = 0.000802$

$\sigma = 0.00394$

$\theta_2 = 0.754$

$\theta_3 = 3.756$

$P_0 = 0.0801$

$A_0 = 0.007967$

$H_0 = 0.00124$

$R_0 = 0.00280$

$S_0 = 0.9079$

$\zeta = 0.0617$

$\nu = 0.0421$

Using all data points but estimating 2 extra parameters than the first (37 data points, estimating 17 values)

fval=0.1613

Used calculations:

$\mu = 0.00868$

$\mu_A = 0.00870$

$\mu_H = 0.0507$

$\omega = 10^{-10}$

Estimated:

$m = -0.0159$

$b = 0.309$

$\alpha = [0.309\ 0.293\ 0.277\ 0.261\ 0.245\ 0.230\ 0.214]$

$\theta_1 = 0.000507$

$\epsilon = 2.48$

$\gamma = 0.00117$

$\sigma = 0.0243$

$P_0 = 0.0805$

$A_0 = 0.00669$

$H_0 = 0.000875$

$R_0 = 0.0613$

$S_0 = 0.850635$

$\theta_2 = 0.0477$

$\theta_3 = 2.476$

$\zeta = 0.270$

$\nu = 0.00733$

$\beta_A = 0.000468$

$\beta_P = 0.000136$

May 15, 2019 meeting (final results): Using all data points (37 data points, estimating 17 values)

fval=0.1609
Used calculations:
$\mu = 0.00868$
$\mu_A = 0.00870$
$\mu_H = 0.0507$
$\omega = 10^{-10}$

Estimated with 200 starting points (187 converged):
$m = -.0156$
$b = 0.303$
$\alpha = [0.303\ 0.287\ 0.272\ 0.256\ 0.240\ 0.225\ 0.209]$
$\beta_A = 0.00235$
$\beta_P = 0.000141$
$\theta_1 = 0.0005074$
$\epsilon = 2.54$
$\gamma = 0.00115$
$\theta_2 = 0.0370$
$\sigma = 0.0284$
$\zeta = 0.265$
$\theta_3 = 3.51$
$\nu = 0.00657$
$\omega = 0.0000000001$
$P_0 = 0.0835$
$A_0 = 0.00671$
$H_0 = 0.000874$
$R_0 = 0.0509$
$S_0 = 0.858016$

parameters estimating:	[m	β_A	β_P	θ_1	ϵ	γ	θ_2	σ]
lower bounds:	[−0.1	0.00001	0.000001	0.00001	0.8	0.001	0.0001	0.0001]
upper bounds:	[0.1	0.01	0.01	0.001	8	0.1	2	1],

parameters estimating:	[ζ	θ_3	ν	b	P_0	A_0	H_0	R_0]
lower bounds:	[0.0001	0.001	0.0001	0.1	0.0001	0.00001	0.00001	0.00001]
upper bounds:	[0.5	4	0.1	0.8	0.5	0.1	0.1	0.1].

We choose these bounds for the following reasons:
-0.1≤m≤ 0.1: we assume that since α will be a value less than 1 based on estimate in [1], so it's slope will not be very large in absolute value
$0.00001 \leq \beta_A \leq 0.01$: based on preliminary calculations in Appendix A
$0.000001 \leq \beta_P \leq 0.01$: based on preliminary calculations in Appendix A

$0.00001 \leq \theta_1 \leq 0.001$: chosen intuitively that a susceptible individual interacting with a heroin user would have less than a 0.1 probability of transitioning to the heroin class
$0.8 \leq \epsilon \leq 8$: estimate from [1]
$0.001 \leq \gamma \leq 0.1$: estimate based on value in [1]
$0.0001 \leq \theta_2 \leq 2$: chosen intuitively that a prescription opioid user interacting with a heroin user would have a larger probability of transitioning to the heroin class than that of a susceptible individual (see *) [**?**]
$0.0001 \leq \sigma \leq 1$: unknown, chosen intuitively for relapses that could occur from a stably recovered state
$0.0001 \leq \zeta \leq 0.5$: based on preliminary calculations in Appendix A
$0.001 \leq \theta_3 \leq 4$: chosen intuitively that an opioid addict interacting with a heroin user would have a much larger probability of transitioning to the heroin class than that of a susceptible individual (see *) [**?**]
$0.0001 \leq \nu \leq 0.1$: based on preliminary calculations in Appendix A
$0.01 \leq b \leq 0.8$: estimated based on value of α in [1]
$0.0001 \leq P_0 \leq 0.5$: assume small but no greater than 50% of the population
$0.00001 \leq A_0 \leq 0.1$: assume small but no greater than 10% of the population
$0.00001 \leq H_0 \leq 0.1$: assume small but no greater than 10% of the population
$0.00001 \leq R_0 \leq 0.1$: assume small but no greater than 10% of the population

*We consider a national study of individuals 12 and older to establish a general relationship among these three rates. For a national study consisting of 609,000 participants, "the recent heroin incidence rate was 19 times higher among those who reported prior non-medical pain reliever (NMPR) use (0.39%) than among those who did not report NMPR use (0.02%) [**?**]. NMPR use can occur within the prescription class (i.e. from misuse that's not considered addiction), or in the addiction class. Thus, we will extrapolate this information to say that the rate that prescription opioid users and opioid addicts move to heroin use is at least 19 times greater than the rate at which susceptibles move to heroin use (i.e. $\theta_2 + \theta_3 > 19\theta_1$), where both θ_2 and θ_3 are greater than θ_1.

Parameter	Description	Units
μ	natural mortality rate	$\frac{1}{\text{year}}$
μ_A	opioid addict overdose death rate	$\frac{1}{\text{year}}$
μ_H	heroin addict overdose death rate	$\frac{1}{\text{year}}$
α	prescription rate	$\frac{1}{\text{year}}$
β_A	illicit addiction rate from the black market	$\frac{1}{\text{year}}$
β_P	illicit addiction rate from availability of excess pills	$\frac{1}{\text{year}}$
θ_1	heroin addiction rate for susceptible individuals	$\frac{1}{\text{year}}$
ϵ	rate of finishing prescription addiction-free	$\frac{1}{\text{year}}$
γ	opioid addiction rate from prescription	$\frac{1}{\text{year}}$
θ_2	heroin addiction rate for prescription opioids users	$\frac{1}{\text{year}}$
σ	relapse to addiction	$\frac{1}{\text{year}}$
ζ	rate of stable recovery for opioid addict	$\frac{1}{\text{year}}$
θ_3	heroin addiction rate for opioid addicts	$\frac{1}{\text{year}}$
ν	rate of stable recovery for heroin addict	$\frac{1}{\text{year}}$
ω	perturbation term	dimensionless
S	proportion of susceptible individuals	dimensionless
P	proportion of susceptible individuals	dimensionless
A	proportion of susceptible individuals	dimensionless
H	proportion of susceptible individuals	dimensionless
R	proportion of susceptible individuals	dimensionless

Table 1: Number of individuals in each category, 2013-2018

	2013	2014	2015	2016	2017	2018
Total population	6,493,432	6,540,826	6,590,808	6,645,011	6,708,794	6,770,010
Population 12 and older	*5,519,417*	*5,559,702*	*5,602,187*	*5,648,259*	*5,702,475*	**5,754,509**
Heroin users	-	14,000	14,000	19,000	-	-
Heroin addicts	-	**7,560**	**7,560**	**10,260**	-	-
Prescription opioid addicts (includes heroin addicts)	-	-	48,000	42,000	-	-
Prescription opioid addicts (excludes heroin)	*43,418*	*42,928*	**42,816**	**37,464**	*34,816*	-
Prescribed opioid users (includes those addicted)	1,845,144	1,824,342	1,819,581	1,761,363	1,636,374	-
Prescribed opioid users (excludes those addicted)	*1,825,910*	*1,805,325*	**1,800,613**	**1,744,766**	*1,620,951*	-
Prescription opioid overdose deaths	-	-	679	-	-	-
Heroin/fentanyl overdose deaths	-	-	374	-	-	-
Prescription opioid treatment admissions	4,485	4,530	4,326	-	-	-
Heroin treatment admissions	555	743	1,083	-	-	-

italicized values are numbers that we estimated by extrapolating from a different year
bolded values are numbers that we estimated by information within the same year
the rest of the numbers are actual data
the numbers in blue are data used for parameter estimation

References

[1] Battista, N., Pearcy, L., and Strickland, W. C. (2018). Modeling the prescription opioid epidemic. *NEED TO UPDATE.*