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System Dynamics Modeling of Medical Use, Nonmedical Use and Diversion of Prescription Opioid Analgesics

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Abstract: The objective of the study was to develop a system dynamics model of the medical use of pharmaceutical opioids to treat pain, and the associated diversion and nonmedical use of these drugs. The model was used to test the impact of simulated interventions in this complex system. The study relied on secondary data obtained from the literature and from other public sources for the period 1995 to 2008. In addition, an expert panel provided recommendations regarding model parameters and model structure. The behavior of the resulting systems level model compared favorably with reference behavior data ($R^2=.95$). After the base model was tested, logic to simulate the interventions was added and the impact on overdose deaths was evaluated over a seven-year period, 2008-2015. Principal findings were that a prescriber education intervention reduced total overdose deaths, while reducing the number of persons treated with opioid analgesics. A “popularity” intervention sharply reduced nonmedical overdoses. We conclude that the system dynamics modeling approach shows promise for evaluating potential policy interventions to ameliorate the adverse outcomes associated with the complex system surrounding the use of opioid analgesics to treat pain.

A dramatic rise in the nonmedical use of pharmaceutical opioid pain medicine has presented the United States with a substantial public health problem (Compton and Volkow 2006). Despite the increasing prevalence of negative outcomes, such as non-fatal and fatal overdoses, nonmedical use of pharmaceutical opioids remains largely unabated by current policies and regulations (Fishman et al. 2004). Resistance to policy interventions likely stems from the complexity of the medical and nonmedical use of pharmaceutical opioids, as evidenced by the confluence of many factors which play a role in medical treatment, diversion, and abuse of these products in the United States.

Complex social systems are well known to be resistant to policy interventions, often

exhibiting unintended consequences or unanticipated sources of impedance (Sterman 2000). These undesirable outcomes can result from our inability to simultaneously consider a large number of interconnected variables, feedback mechanisms, and complex chains of causation (Hogarth 1987). Prescription opioid use, diversion, and nonmedical use constitute a complex system with many interconnected components, including prescribers, pharmacists, persons obtaining opioids from prescribers for medical or nonmedical use, persons obtaining drugs from illicit sources, and people selling drugs. Interactions among these actors result in chains of causal relationships and feedback loops in the system. For example, prescribing behaviors affect patients' utilization of opioids; adverse consequences of medical and nonmedical use influence physicians' perceptions of the risks associated with prescribing opioids; and physicians' perception of risk affects subsequent prescribing behaviors (Potter et al. 2001; Joranson et al. 2002).

This paper presents a system dynamics model which attempts to represent the system described above¹. The model is designed to provide a more complete understanding of how medical use, trafficking, and nonmedical use are interrelated, and to identify points of high leverage for policy interventions to reduce the adverse consequences associated with the epidemic of nonmedical use. Two potential interventions are simulated, relative costs and benefits are estimated, and possible downstream effects are highlighted. Except as noted, the term “opioids” is used to mean pharmaceutically-manufactured opioid (morphine-like) medicines, most of which are used to treat pain. Heroin or other illicit opioid drug substances are not included.

Background

Between 1999 and 2006, the number of U. S. overdose deaths attributed to opioids tripled—increasing more than fivefold among youth aged 15 to 24 (Warner, Chen, and Makuc 2009)—signaling the onset of a major public health concern. Overdose deaths where opioid analgesics were involved have outnumbered cocaine and heroin overdoses since 2001 (Unintentional Drug Poisonings in the United States 2010), and estimates from the 2009 National Survey on Drug Use and Health (NSDUH) suggest that 5.3 million individuals (2.1% of the US population aged 12 and older) used opioids for nonmedical purposes within the previous month (SAMHSA 2010). Earlier data from NSDUH suggest that the rate of initiation increased drastically from 1994 to 1999 (SAMHSA 2006), and has continued at high rates, with just over 2 million individuals reporting the initiation of nonmedical use of pain relievers in 2009 (SAMHSA 2010). The 2009 results also indicate that friends or relatives are a common source for pain relievers used nonmedically. Recent increases in prescribing opioids stem in part from increases in the diagnosis and recognition of the need to treat chronic noncancer pain.

¹ This paper updates a paper presented at the 2011 International System Dynamics Society Conference (Schmidt et al., 2011). The figures for two of the model sectors described herein look very similar to the diagrams in the previous paper, but the model logic in those sectors was modified somewhat, and the third sector was modified significantly. Additional model testing has been performed and documented, and different interventions were run and are discussed in some detail in this paper.

As of 2009, the Food and Drug Administration (FDA) required Risk Evaluation and Mitigation Strategies to be implemented for all Schedule II long-acting opioid analgesics including interventions, such as medication guides (Leiderman 2009). REMS vary by product depending on the level of risk, but all REMS must include an evaluation of their effectiveness, and many additionally require specific interventions, such as medication guides. Unfortunately, prior research has found little evidence to suggest that REMS interventions are effective in reducing the risk of medication misuse or abuse (see Chou et al. 2009). Tools and interventions that balance both the benefits and risks of opioids are needed. Policymakers striving to ameliorate the adverse outcomes associated with opioids could benefit from a systems-level model that reflects the complexity of the system and that incorporates the full range of available data.

A System Dynamics Simulation Model

The current work features a system dynamics simulation model that represents the fundamental dynamics of opioids as they are prescribed, trafficked, used nonmedically, and involved in overdose mortality. The model was developed over a two-year period through collaborative efforts of a system dynamics (SD) modeling team and a panel of pain care and policy experts. The SD modeling approach uses a set of differential equations to simulate system behavior over time. SD models are well suited to health policy analysis involving complex chains of influence and feedback loops which are beyond the capabilities of statistical models (Sterman 2006), and have been successfully applied to the evaluation of policy alternatives for a variety of public health problems (Cavana and Tobias 2008; Homer 1993; Jones et al. 2006; Homer, Hirsch, and Milstein 2007; Milstein, Homer, and Hirsch 2010). The SD approach can help to identify points of high leverage for interventions as well as unanticipated negative consequences of those interventions. This provides policymakers with information that is not available from research focused on individual aspects of a system (Sterman 2006). In the current research, the development of an SD model complements and leverages results from an extensive amount of research based on surveys and statistical analyses.

Model Creation Process

Model development began with a thorough review of existing literature to locate empirical evidence to support key model parameters. Literature sources included a broad spectrum of data sources, survey results, and scholarly articles covering data collected between 1995 and 2009. An advisory panel provided oversight regarding model logic and the representation of interventions in the model. Panel members discussed areas of particular importance to the pharmaceutical opioid nonmedical use epidemic and shared professional presentations on these areas, including chronic pain treatment, diversion, dependence and abuse, and the FDA Risk Evaluation and Mitigation Strategies.

Multiple data gaps were identified that could not be adequately addressed by existing literature (see Wakeland et al. 2010). In these cases, panel members provided their expert judgment to help fill these data gaps, and rigorous model testing was used to determine whether the model's performance was contingent upon the accuracy of these data. The model was rigorously tested to identify its strengths and weaknesses. A key assumption in early

formulations was that the epidemic of nonmedical use was essentially driven by increases in opioid prescribing. But model testing revealed that increases in prescribing and sharing simply could not account for the full magnitude of the epidemic. Although sharing and other forms of diversion are necessary to fuel the epidemic, test results indicated that the upsurge in nonmedical use must have been primarily driven by increased popularity and demand for opioid products in the nonmedical use sector. This insight led to substantial revision of the model, including additional consultation with the expert panel and revisions to much of the model logic.

Dynamics of the Opioid System

The system model encompasses the dynamics of the medical treatment of pain with opioids, the initiation and prevalence of nonmedical usage, and the diversion of pharmaceutical opioids from medical to nonmedical usage, and adverse outcomes, especially overdose fatalities. Figure 1 shows a high level representation of the model which is divided into three sectors: the nonmedical use sector, the medical use sector and the diversion sector that bridges the two. Discussion of each sector includes a description of empirical support, a narrative of the model's behavior, and a causal loop diagram depicting model structure. Verbal descriptions contain bracketed numbers that correspond to specific points in the diagrams. The model contains 40 parameters, 41 auxiliary variables, and seven state variables, as well as their associated equations and graphical functions.

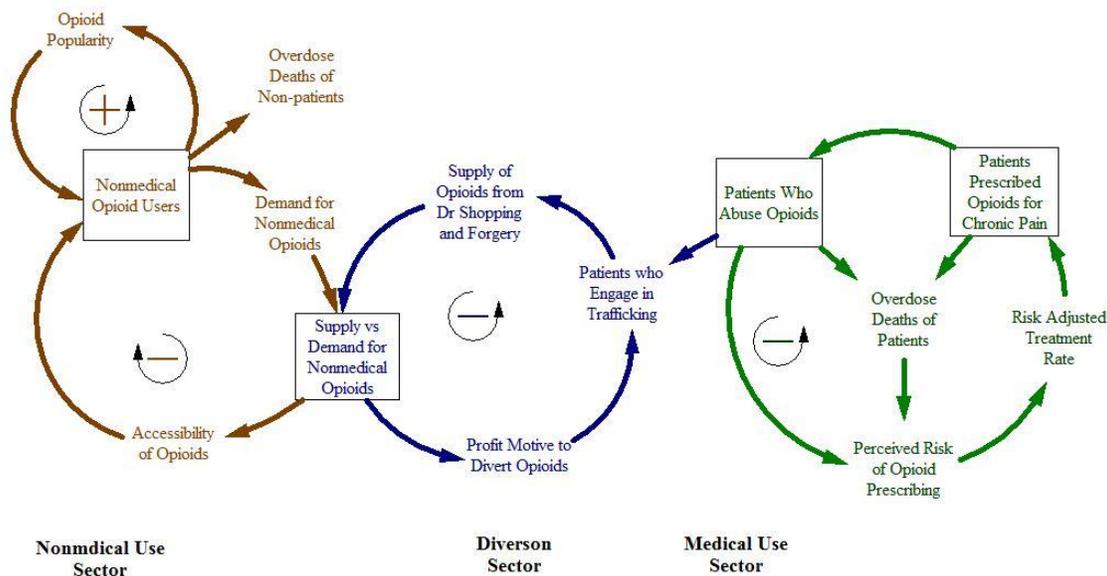


Figure 1: A simple causal loop diagram of the opioid system model shows the relationship among the nonmedical use, diversion and medical use sectors further detailed below.

Nonmedical Use Sector. Diagnostic criteria from DSM-IV have been used to differentiate persons who engage in problematic substance use according to whether or not they meet the mutually-exclusive specific criteria for either *opioid abuse* or *opioid dependence*—the latter referred to by many as *addiction* (American Psychiatric Association 1994). Around 12-14% of individuals who use opioids nonmedically meet the criteria for one of these (Colliver et al. 2006), either of which is associated with a high frequency of

Table 1. References of Support for Model Parameters in the Nonmedical Use Sector

	Parameter	Value	Support
NONMEDICAL USE SECTOR			
1	Base Level of Abuse Potential of Opioids	1.3	Panel Consensus
2	Fraction of Demand Met from Chronic Pain Trafficking	.25	Extrapolation from NSDUH 2006 results (SAMHSA 2007)
3	Fraction of Low-Freq Users who switch to High-Freq	0.06	Extrapolation from Monitoring the Future data (Johnston et al. 2007) and results (Mack and Frances 2003)
4	High-Frequency User All-Cause Mortality Rate	0.02	Extrapolation from heroin research findings (WHO; see Degenhardt et al. 2004; Hser et al. 2001)
5	High-Frequency User Cessation Rate	0.08	Imputation from NSDUH data (SAMHSA 2009)
6	Low-Frequency User All-Cause Mortality Rate	0.012	Extrapolation from heroin research findings (Rehm et al. 2005)
7	Low-Frequency User Cessation Rate	0.15	Imputation from NSDUH data (SAMHSA 2009)
8	Number of Days of Nonmedical Use Among High-Freq Users	220	Extrapolation from NSDUH 2007 results (Lee et al. 2010)
9	Number of Days of Nonmedical Use Among Low-Freq Users	30	Extrapolation from NSDUH 2007 results (Lee et al. 2010)
10	Number of Dosage Units Taken per Day	2	Modeling Team Judgment, reviewed by Panel
11	Overdose Mortality Rate for High-Freq Nonmedical Users	0.002	Extrapolation from research findings (Fischer et al. 2004; Warner, Chen, and Makuc 2009; Warner-Smith et al. 2000)
12	Overdose Mortality Rate for Low-Freq Nonmedical Users	0.0002	Extrapolation from research findings (Fischer et al. 2004; Warner, Chen, and Makuc 2009; Warner-Smith et al. 2000)
13	Rate of Initiation of Nonmedical Opioid Use	0.006	Imputed from National Drug Use and Health Survey Data (SAMHSA 1996)
14	Table Function for the Impact of Limited Accessibility on Initiation and Increasing Use	[(0,0)-(5,2)]	Modeling Team Judgment, reviewed by Panel
15	Table Function for the Number of Individuals Using Illicit Drugs Excluding Marijuana and Opioids	6.7M in '95 to 8.6M in '09	Calculated from NSDUH 2006 results, (SAMHSA 2007)
16	US Population Ages 12 and Older	211M in '95 to 357M in '07	Imputed from NSDUH data National Survey on Drug Use and Health 1995, 2002 (see SAMHSA 1996, 2002)

¹ A Table Function is a series of XY coordinates representing a relationship (usually nonlinear) between two variables

nonmedical use. Extrapolation from heroin findings indicates that higher-frequency opioid use is associated with a significantly higher all-cause mortality rate (WHO; see Degenhardt et al. 2004; Hser et al. 2001) and supports a distinction between two subpopulations of nonmedical users (low- and high-frequency) in this sector of the model.

As illustrated in Figure 2 and Table 1, a percentage of the US population {1} is assumed to initiate nonmedical use each year {2}, all of whom start out in a stock of ‘low-frequency nonmedical users,’ and a small percentage of whom advance to a stock of ‘high-frequency nonmedical users’ {3} during each subsequent year. The total number of individuals using opioids nonmedically {4} is divided by the current number of individuals in the US who are using other drugs nonmedically {5} to calculate the relative popularity of opioids for nonmedical use {6}. As the popularity of using opioids nonmedically increases, the rate of initiation increases, creating a positive feedback loop that *ceteris paribus* would result in an exponential increase in the rate of initiation. Nonmedically used opioids are obtained through a variety of routes, but of chief interest for the current research is the prevalence of opioid ‘trafficking’ (i.e., buying or selling) via persons who are receiving these products ostensibly for treatment. Extrapolation of results from the 2006 NSDUH survey (SAMHSA 2007) suggests around 25% of the nonmedical demand for opioids is met via trafficking.

In the model, demand for opioids is calculated from the number of individuals in low- and high-frequency populations {7}. As noted above, 25% of demand is assumed to be met by trafficking {8}, with the rest coming from sources not modeled explicitly (mostly interpersonal sharing among friends and relatives, per SAMHSA, 2007). When the trafficking supply is ample relative to demand, the rate of initiation {2} and the rate of advancement from low-frequency to high-frequency use {3} are assumed to be somewhat enhanced. When the trafficking supply is limited, however, rates of initiation and advancement are assumed to decrease dramatically. The ratio of supply to demand {9} indicates the degree to which opioids are accessible for nonmedical use. As the populations of nonmedical users increase beyond what trafficking can support, accessibility becomes limited, decreasing initiation and advancement; which creates a negative feedback loop that eventually equilibrates the otherwise exponential increase in nonmedical use driven by the popularity feedback loop.

Medical Use Sector. Historically, increases in opioid *abuse*, defined as the self-administered use of an opioid medication for a nonmedical purpose (Katz et al. 2010), and increases in *addiction*, which involves uncontrollable compulsions and significant adverse consequences (Compton, Darakjian, and Miotto 1998), have led to the implementation of regulatory policies for opioids (Food and Drug Administration 2008). These regulatory policies have been shown to lead many physicians to avoid prescribing opioids to patients out of fear of overzealous regulatory scrutiny (Joranson et al. 2002). In addition, prescribers, fearful of regulatory scrutiny of their opioid analgesic prescribing practices, may decrease the amount of opioids they prescribe, limit quantities and refills, and shift prescribing to opioid products with a presumably lower risk of abuse, addiction, or overdose (i.e., products in less-restrictive schedules under the federal Controlled Substances Act; (Wolfert et al. 2010).

Long-acting opioids have been shown to have a higher rate of abuse than immediate-release opioid analgesics when abuse rates are normalized for the number of individuals exposed

Table 2. References of Support for Model Parameters in the Medical Sector

	Parameter	Value	Support
MEDICAL USE SECTOR			
1	All-Cause Mortality Rate for those receiving Long-acting Opioids	0.012	US Population mortality data, adjusted by panel consensus
2	All-Cause Mortality Rate for those receiving Short-acting Opioids	0.01	US Population mortality data, adjusted by panel consensus
3	All-Cause Mortality Rate for those with Abuse/Addiction	0.015	US Population mortality data, adjusted by panel consensus
4	Average Long-acting Treatment Duration (in years)	7	Panel Consensus
5	Average Short-acting Treatment Duration (in years)	5	Panel Consensus
6	Base Level of Abuse Potential for Opioids	1.3	Modeling Team Judgment, reviewed by Panel
7	Base Rate for Adding or Switching (to Long-acting)	0.03	Extrapolation from outcome data: Verispan, LLC, SDI Vector One®: National VONA see (Governale 2008)
8	Base Rate of Treatment	.05 in '95 to .23 in '05	Panel Consensus, informed by (Potter et al. 2001)
9	Base Risk Factor (degree Tx reduced in 1995 due to perceived risk)	1.3	Modeling Team Judgment, reviewed by panel
10	Diagnosis Rate for Chronic Pain	.05 in '95 to .15 in '05	Panel Consensus, informed by the World Health Organization (Gureje, Simon, and VonKorff 2001)
11	Overdose Mortality Rate for those Abusing Opioids	0.0015	Extrapolation from Heroin Research see (Sullivan 2007)
12	Overdose Mortality Rate for those on Long-acting	0.0025	Consortium to Study Opioid Risks and Trends (CONSORT) study see (Potter et al. 2001)
13	Overdose Mortality Rate for those on Short-acting	0.00005	CONSORT study see(Potter et al., 2001)
14	Rate of Addiction for those on Long-acting	0.05	Meta-Analyses see (Dunn et al. 2010; Hojsted and Sjogren 2007)
15	Rate of Addiction for those on Short-acting	0.02	VISN16 data from South Central Veterans Affairs Health Care Network (Fishbain et al. 2008))
16	Table Function ¹ for Short-acting Bias (as function of perceived risk)	[(1,0)-(4,1)]	Modeling Team Judgment, reviewed by panel
17	Tamper Resistance (baseline value)	1	Policy variable (1=status quo)

¹ A Table Function is a series of XY coordinates representing a relationship (usually nonlinear) between two variables.

(Cicero et al. 2007). Sensitive to information regarding relative risk, physicians have been found to exhibit more caution in prescribing long-acting opioids (Potter et al. 2001).

As illustrated in Figure 3, the system model assumes that a proportion of the US population is diagnosed with a chronic pain condition each year {1}. A fraction of these people are subsequently treated with either short-acting {2} or long-acting {3} opioid formulations, and become members of one of the stocks (populations) of patients under opioid treatment ostensibly for chronic pain. Patients who begin treatment with short-acting formulations may cease treatment if their condition improves, or they may switch to long-acting formulations if their pain conditions appear to worsen {4}. Each year some individuals move from the stocks of 'individuals receiving opioids' {2-3} to the stocks of 'individuals receiving opioids with abuse or addiction' {5-6}. The fraction of opioid-prescribed individuals with abuse or addiction {7} influences physicians' perception of the risk involved in opioid prescribing {8}, as does the total number of overdose deaths among medical users each year {9}. As physicians perceive higher levels of risk {8} they become increasingly biased toward prescribing short-acting formulations {10}, and their overall rates of opioid prescribing decrease {11}. Because of these balancing feedback loops, the increase in the amount of abuse and addiction {7} is slowed. Physicians' responses to increasing rates of abuse, addiction, and overdose effectively move the model towards a state of dynamic equilibrium.

Trafficking Sector. Findings from Manchikanti et al. (2006) indicate that 5% of chronic pain patients engage in doctor shopping and around 4% engage in forgery. In the system model, forgery and doctor shopping by persons interacting with prescribers are assumed to be exhibited entirely by those with abuse or addiction, which constitute around 7% of individuals receiving opioid prescriptions for chronic pain. This would imply that about 70% of persons with abuse or addiction (5 out of 7) engage in doctor shopping and over half (4 out of 7) engage in forgery. More research is needed to support these parameters and the associated logic.

As shown in Figure 4, a fixed proportion of the persons with abuse or addiction are assumed to engage in trafficking each year, including doctor shopping {1} and forgery {2}. The number of extra prescriptions acquired {3} is calculated as a product of (a) the total number of individuals engaging in trafficking and (b) the number of extra prescriptions obtained per trafficker {11}. Some proportion of these excess prescriptions is assumed to be used by the traffickers themselves, rather than diverted to other nonmedical users {4}. This number is calculated as a product of (a) the number of individuals with abuse or addiction and (b) the average number of extra prescriptions used per year by such individuals. The number of prescriptions that are used "in excess" by medical users is subtracted from the number of extra prescriptions acquired. The remainder is converted to dosage units {5} and assumed to be diverted to nonmedical users {6}.

Trafficked opioids accumulate in a stock of dosage units {7} that are consumed according to demand from the nonmedical use sector. Supply can also be expressed as 'months of supply available' {8}, which indicates the extent to which the trafficked supply is able to meet the demand at any given time. When the supply of opioids becomes limited, a profit motive emerges {9} and motivation to forge and doctor shop increases. When supply is large compared

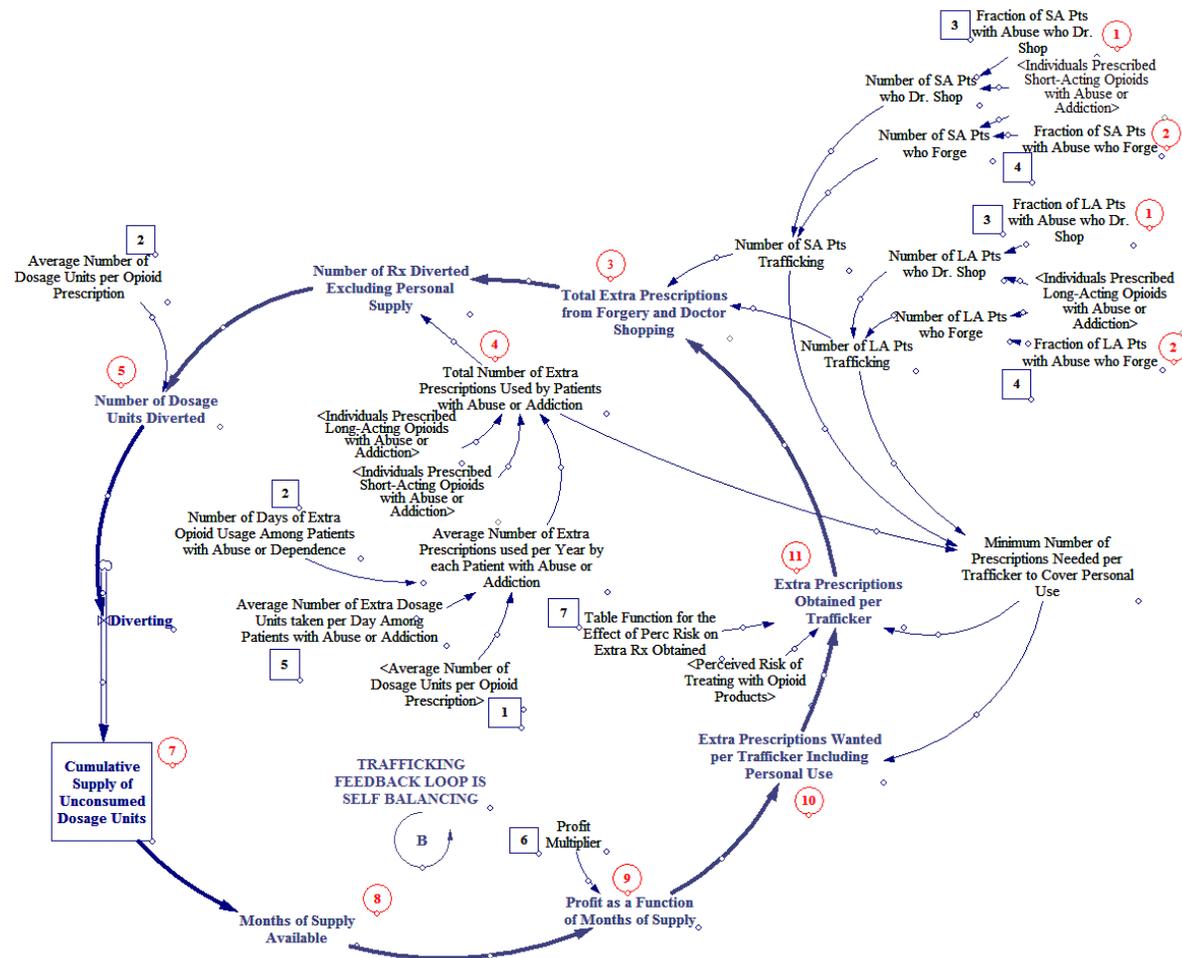


Figure 4. Causal Loop Diagram of the Trafficking Sector. Circled numbers correspond to bracketed notations in the text. Numbers in boxes correspond to model parameters in Table 3.

Table 3. References of Support for Model Parameters in the Trafficking Sector

Parameter	Value	Support	
TRAFFICKING SECTOR			
1	Average Number of Dosage Units Per Opioid Prescription	86	Extrapolation from dispensing data: Verispan, LLC, SDI Vector One®: National (VONA) (Governale 2008; Governale 2008)
2	Average Number of Extra Dosage Units taken per Day Among those with Abuse or Addiction	1.5	Panel Consensus
3	Fraction of those with Abuse/Addict who Engage in Dr Shopping	.5	Extrapolation from study results (Manchikanti et al. 2006)
4	Fraction of those with Abuse/Addict who Engage in Forgery	.4	Extrapolation from study results (Manchikanti et al. 2006)
5	Number of Days of Extra Opioid Usage Among those with Abuse/Addiction	50	Generalized from NSDUH data (National Survey on Drug Use and Health 2002, 2003, & 2004; see Table 2.18B in Colliver et al., 2006)
6	Profit Multiplier	15	Modeling team judgment
7	Table Function for the Effect of Rec Risk on Extra Rx Obtained	[(0,0) – (2,1)]	Modeling team judgment

¹ A Table Function is a series of XY coordinates representing a relationship (usually nonlinear) between two variables

to demand, motivation to commit fraud for the purpose of sale is small. As this motivation fluctuates, the number of extra prescriptions each trafficker would like to obtain {10} also changes. But the number of prescriptions that can be successfully trafficked is attenuated by cautious dispensing when perceived risk is high among physicians and pharmacies {11}, which creates a balancing feedback loop that stabilizes the amount of trafficking.

Model Testing

The model was tested in detail to determine its robustness and to gain an overall sense of its validity. As is often the case with system dynamics models, the empirical support for some of the parameters was limited, as indicated in Tables 1-3. System Dynamics models are generally more credible when their behavior is not overly sensitive to changes in the parameters that have limited empirical support. Therefore, to determine sensitivity of primary outcomes to changes in parameter values, each parameter in turn was increased by 30% and then decreased by 30%, and the outcome was recorded in terms of cumulative overdose deaths. Though smaller percentages are often employed, we wanted to be sure to push the potential nonlinearities further while remaining well within the model's design limits. One parameter with limited empirical support *did* have a substantial influence on model behavior, meaning that a 30% change in the parameter value resulted in a greater than 30% change in the cumulative number of overdose deaths

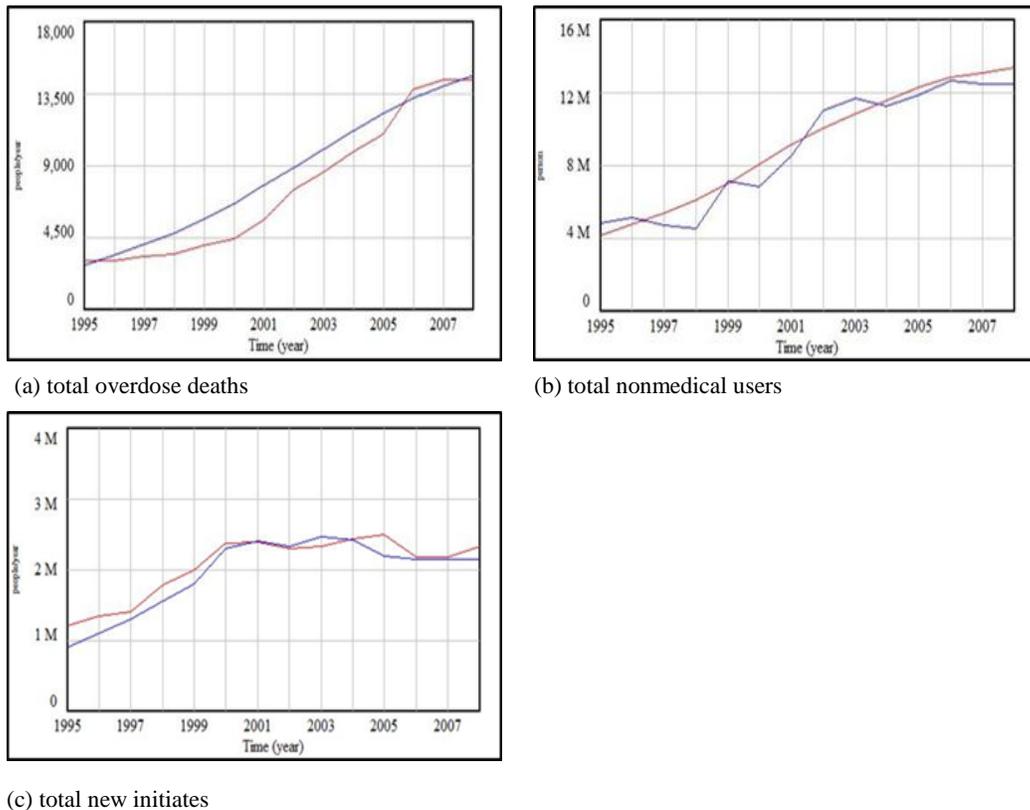


Figure 5: Model output versus reference behavior. From top left, clockwise, (a) total prescription opioid overdose deaths per year ($R^2 = .96$), (b) total nonmedical users of prescription opioids ($R^2 = .95$), (c) total number of individuals initiating nonmedical opioid use per year ($R^2 = .95$).

of the number of patients treated for pain with long-acting opioids. This parameter was the impact of limited accessibility on initiation and increasing use. Refer to Wakeland et al. (2010) for a more detailed discussion of data gaps. Another parameter strongly influenced model behavior and *did* have sufficient empirical support: the rate of initiation of nonmedical use. Because model testing revealed a high degree of sensitivity to a single parameter for which empirical support is limited, study results should be considered exploratory and viewed with caution.

In addition to sensitivity analyses, the model was also carefully checked for dimensional consistency and appropriate integration step-size, subjected to a rigorous model walk through to uncover logical flaws, and subjected to a variety of hypothesis tests. The model walkthrough revealed logical flaws that required substantial model revision. Several parameters with a high degree of sensitivity and limited empirical support were replaced, and all tests were rerun. The results of these tests were generally favorable, indicating at least a preliminary degree of model validity.

When empirical support was available, model outputs were validated against reference data for the historical period. While this reference period is relatively short, the model does fit the data reasonably well, as shown in Figure 5.

Figure 5a shows the number of prescription opioid overdose deaths from a baseline model run for the historical period overlaid on a plot of the reported number of overdose deaths obtained from the CDC multiple cause of death database. Reference data are not entirely consistent, but it appears that total opioid-related deaths resulting from all types of medical and nonmedical use has been reported to be 13,755 in 2006 and approximately 14,000 in 2007. The data suggest that the pattern has been an S-shaped curve, with modest growth in the late 90s and more rapid growth throughout the early 2000s before leveling between 2006 and 2007 (Warner, Chen, and Makuc 2009). Also shown in Figure 5a, the model's baseline behavior exhibits a similar S-shaped growth curve, with the number of opioid overdose deaths calculated to be approximately 13,200 in 2006 and 14,300 in 2007 ($R^2 = .96$). While additional data are needed to more fully validate these results, the model behavior does exhibit a preliminary level of credibility for this metric.

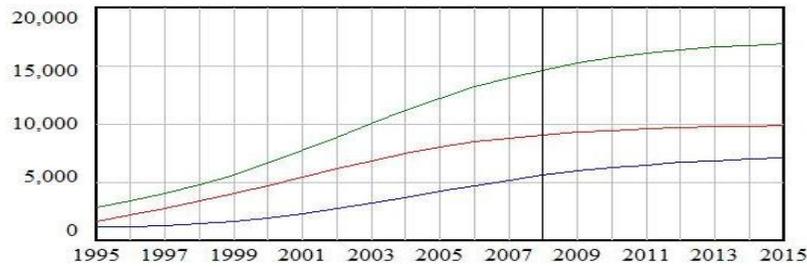
Figure 5b shows the total number of individuals using prescription opioids non-medically overlaid on reference data for the historical time period. The graph of historical data is not smooth, but again, the general pattern of growth is S-shaped. The graphical output from a baseline model run is a smooth S-shaped curve that is a good fit for the limited time series data available ($R^2 = .95$).

Figure 5c overlays model output and reference data for the number of individuals initiating nonmedical use of prescription opioids. The reference behavior pattern here is highly non-linear with the number of initiates more than doubling from 1995 to 2000, then approximately no change between 2000 and 2004, followed by a decrease and leveling from 2004 to 2007. The baseline model run matches the reference behavior pattern very closely ($R^2=.95$).

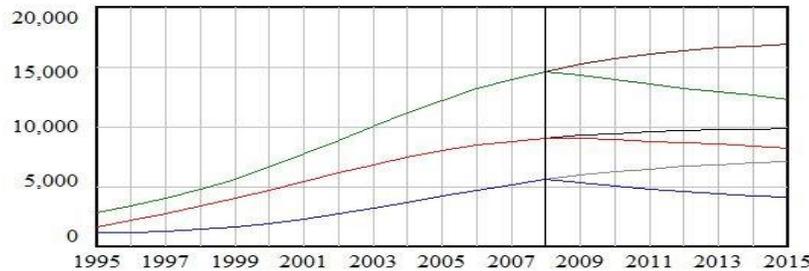
Overall, model results closely track the graphs of empirical data despite the complex patterns exhibited. Thus, although the reference data is somewhat limited, baseline results are deemed sufficiently plausible to proceed with analyzing potential interventions.

Results

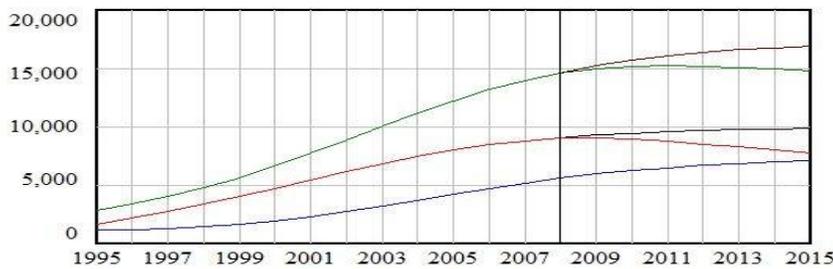
A baseline model run is shown in Figure 6a that includes opioid-related medical sector deaths, opioid-related nonmedical sector deaths, and total opioid-related deaths. To illustrate the use of the model to evaluate interventions, logic representing two possible interventions was added to the model. The two interventions presented here impact different parts of the system. The first intervention, a prescriber education initiative, directly impacts the medical sector, while the second, an intervention to reduce the popularity of nonmedical use of opioids, affects only the nonmedical sector. The model was run over a time period of twenty years, which was divided into an historical period from 1995 to 2008, and an evaluation period from 2008 to 2015. Both interventions were represented as simple toggle switches that double beneficial parameters or halve harmful parameters. While the scale of their impact is exaggerated, these interventions help to illustrate the dynamics of the model and the how the system responds to interventions applied at two different points of leverage. The response of the model to these interventions is described below.



(a) Baseline



(b) With prescriber education



(c) With nonmedical use suppression

Figure 6: (a) Baseline model run, and (b), (c) with the effect of simulated interventions as of 2008—prescriber education program and popularity suppression—on opioid overdose deaths.

Prescriber Intervention

The implementation of a highly impactful prescriber education program was simulated through two mechanisms: (a) the number of patients per year who become addicted to opioids was halved (see Figure 3 {5} and {6}), based on the assumption that educated prescribers would be more selective in the use of opioid treatment and would monitor treatment more effectively, and (b) the prescribers' perception of risk was doubled (see Figure 3 {8}), which reduced by 50% the fraction of opioid recipients among new persons presenting to physicians with complaints of chronic pain, and also reduced by 50% physicians' willingness to prescribe long-acting formulations.

This intervention caused a marked decrease in the number of overdose deaths among medical users (see Figure 6b) because wary prescribers offered opioid therapy to far fewer individuals, possibly resulting in denial of therapeutic treatment to those with legitimate chronic pain complaints. Nonmedical overdose deaths also decreased following this intervention due to the presence of fewer individuals with abuse or addiction (who could engage in trafficking), and their increased difficulty in obtaining fraudulent prescriptions due to heightened prescriber risk perception. The constrained trafficked supply reduced the number of nonmedical users, which reduced nonmedical overdose deaths.

Popularity Intervention

The popularity intervention simulated a reduction in the (perceived) popularity of opioids for nonmedical use by 50%, which effectively reduced the rate of initiation by half (see Figure 2 {6} and {2} respectively). This sharply reduced initiation and nonmedical user populations, which reduced overdose deaths substantially (see Figure 6c). Once the user populations begin to decline, positive feedback again results in a virtuous cycle of decreased use and decreased popularity, which further reduces use and associated deaths. Medical usage-related deaths were not impacted.

Discussion

Results from the model indicate that SD modeling holds promise as a tool both for understanding the complex challenges inherent in the epidemic of nonmedical use of opioids and for evaluating the potential impact on overdose deaths of interventions to minimize the risks of opioid analgesics. By deliberately exaggerating the direct effects of two potential options that affect different populations, downstream effects are accentuated to make as obvious as possible any unintended consequences or counterintuitive results.

Results of the physician intervention suggest that careful screening of patients who receive opioid therapy may be an effective way to reduce overdose deaths involving opioids. Since previous research has indicated that over half of opioid overdose deaths are suffered by individuals who have never been prescribed opioids directly (Hall et al. 2008), it is important to consider the distal effects of the medical sector interventions on nonmedical use and overdose deaths. Here as well, the principal cause of change in overdose deaths was the change in the

number of persons receiving opioids via prescription ostensibly for pain. Decreasing this population tended to reduce the supply available to nonmedical users.

Limitations

Despite great efforts to find empirical support for all model parameters, parameter validity remains a primary limitation in the study (see Wakeland, et al. 2010). Several parameters have weak empirical support, as mentioned previously, and a number of potentially important factors have been excluded, often because support remains elusive. For example, the model is limited because it focuses exclusively on prescribing and trafficking of opioids for the treatment of *chronic* pain, without representing the vastly-larger number of persons who receive them for acute pain. The prescribing of opioids to treat acute pain accounts for a larger fraction of the opioids dispensed annually, so it is likely to contribute the supply of opioids for the nonmedical use sector, as well as to physician's perception of risk in the medical use sector. For both of these reasons, the exclusion of acute pain treatment may threaten the validity of the model.

In the trafficking sector, by focusing primarily on trafficking versus interpersonal sharing, the model may be exaggerating the notion of profit as a motive for diversion. Since the fraction of demand met by interpersonal sharing is large, it may be necessary to model this mechanism in a more detailed fashion. Further, not all who traffic abuse. Some individuals are merely engaged in a criminal enterprise and have no interest in abusing the drugs they buy and sell. There are no reliable data on how many of these individuals masquerade as patients with complaints of pain (acute or chronic) merely to obtain prescriptions with which to acquire medicine for illicit resale.

Additionally, poly-drug use and abuse, opioid treatment programs, alternative treatments, and institutional factors that impact opioid use, such as payer policies and formularies, can all influence rates of medical and nonmedical use of opioids and the outcomes associated with such use. The exclusion of these many factors imposes limitations on the model's ability to provide conclusive inferences.

Work is underway to expand the scope of the model to address many of the above limitations, including the use of Monte Carlo simulation to assess the impact of parameter uncertainty on outcome variables. Still, it is hoped that the insights achieved by this preliminary application of the system dynamics method to this important public health concern may help to inform policy makers of the value of applying a system dynamics approach to analyze alternative points of intervention and evaluate policy alternatives.

Conclusion

The principal strength of this study is its system-level perspective and deliberate recognition of the complex interconnections and feedback loops associated with the use of opioids to treat pain and associated adverse outcomes. From a systems perspective it is clear that interventions focused on prescribing and dispensing behavior can have implications beyond the medical aspects of the system, and that a multifaceted approach that addresses licit as well as illicit use is warranted. The present study serves well to demonstrate how a systems-level model

may help to evaluate the relative potential efficacy of interventions to reduce opioid-related overdose deaths.

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