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System Dynamics Modeling as a Potentially Useful Tool in Analyzing Mitigation Strategies to Reduce Overdose Deaths Associated with Pharmaceutical Opioid Treatment of Chronic Pain

Wayne Wakeland, PhD,* Teresa Schmidt, MA,* Aaron M. Gilson, PhD,† J. David Haddox, DDS, MD,‡ and Lynn R. Webster, MD, FACPM, FASAM§

*Portland State University, Systems Science Graduate Program, Portland, Oregon;

†Comprehensive Cancer Center, University of Wisconsin, Madison, Wisconsin;

‡Risk Management & Health Policy, Purdue Pharma L.P., Stamford, Connecticut;

§LifeSource Foundation, Salt Lake City, Utah, USA

Reprint requests to: Wayne Wakeland, PhD, Portland State University, Systems Science Graduate Program, P.O. Box 751, Portland, OR 97207, USA. Tel: 503-725-4975; Fax: 503-725-8489; E-mail: wakeland@pdx.edu.

Abstract

Objective. To illustrate a system-level, simulation-based approach for evaluating mitigation strategies to address the dramatic rise in abuse, addiction, and overdose deaths associated with the use of pharmaceutical opioid analgesics to treat chronic pain.

Simulated Interventions. Making available drug formulations with increased tamper-resistance, prescriber education programs, and programs that reduce rates of medical user-related abuse and addiction.

Simulated Outcome Measure. Number of overdose deaths of medical users of pharmaceutical opioid analgesics, including those who abuse or have become addicted.

Methods. A demonstration system dynamics model is developed, tested, and used to evaluate the impact of candidate mitigation strategies on the outcome measures.

Results. Tamper-resistant drug products will likely reduce overdose death rates but may not reduce overall deaths if there is increased prescribing. Prescriber education would likely reduce deaths through a reduction in patient access to pharmaceutical opioid analgesics.

Conclusions. The system dynamics approach may have potential for opioid-related policy evaluation. However, metrics must be carefully selected, and trade-offs may be involved. For example, it may be difficult to limit negative outcomes associated with pharmaceutical opioids without adversely affecting chronic pain patients' access to pharmaceutical treatment. Ultimately, a combination of metrics and value judgments will be needed to properly evaluate mitigation strategies.

Key Words. Chronic Pain; Outcome Assessment; Opioids; Prescriptions; Mitigation Strategies; System Dynamics

Introduction

Pharmaceutical opioid analgesics are considered by some to be one of the most effective treatments for chronic noncancer pain [1]. Abuse of these medications, however, leads to many adverse outcomes and presents an increasingly severe public health problem in the United States [2]. While only a fraction of patients with pain being treated with opioid analgesics develop abuse or addiction [3,4], the dramatic rise in the use of pharmaceutical opioids to treat pain, and an associated increase abuse and addiction involving these same medicines, has created a substantial public health problem in the United States [5]. Rates of opioid-related overdose have been escalating in the United States, with more than a threefold increase between 1999 and 2006 and more than a fivefold increase among youth aged 15–24 [6]. Abuse and poly-drug use or abuse are frequently involved in opioid overdose deaths [4,7,8], but complications from prescribed opioids can also lead to unintentional deaths, particularly when using methadone to treat pain [9].

Dramatic increases in the prescribing of pharmaceutical opioids stem in part from recent surges in the diagnosis

chronic noncancer pain. A longitudinal analysis of diagnoses in Seattle, Washington suggested that 11.2% of individuals who were previously free from chronic pain were diagnosed with a chronic pain condition during the year of the study [10]. Data from the National Health and Nutrition Examination Survey (NHANES) [11], coupled with data from the U.S. Census Bureau, support an estimated prevalence of 29 million persons aged 20 or older with chronic pain (pain lasting 3 months or longer) in the period 1999–2002, making it a significant national health problem. The increased rate of diagnosis of chronic pain has increased the demand for medical treatment, and while opioid treatment for chronic, noncancer pain is considered by some to be controversial [12], pharmaceutical opioids have been found to be more effective at ameliorating pain than alternative medications (see [1] for a review), and their prescription and medical use has become increasingly common since the late 1980s [13–15].

Effective tools and interventions are needed to reduce opioid overdose deaths, and a necessary first step is to increase understanding about the factors that interact to influence opioid-related deaths. System dynamics (SD) is a method whereby modelers identify the key elements of a system, define those elements formally as variables, and simulate the interactions between them by solving a set of interwoven differential equations [16,17]. The aim of the method is to create a model that replicates system behavior "on its own" through the integration of these mathematical equations and without using external time series data to "force" model behavior over time. Often, the creation of an SD model leads to the identification of self-reinforcing or self-balancing feedback loops that drive the behavior of individual components in the system. The SD methodology is particularly well-suited for studying health care systems [18]. It has been successfully applied to the study of public health problems, such as the prevalence of cocaine abuse [19], and the evaluation of public policy alternatives, such as for cocaine abuse prevention [20], health care reform [21], diabetes population dynamics [22], and tobacco policy options [23].

Policy-makers striving to protect population health by reducing the risk of accidental opioid overdose could benefit from a systems-level model of pharmaceutical opioid use and abuse that reflects the complexity of the system and incorporates the full range of available data. This article describes an SD model designed to increase understanding and to help identify and assess policy interventions for reducing the prevalence of adverse outcomes attributed to the medical use of pharmaceutical opioids. The following section describes the conceptual approach and research methods employed and also outlines how the model represents the fundamental dynamics of the medical use of pharmaceutical opioids and associated abuse, addiction, and overdose mortalities. Model testing is then discussed briefly, followed by a description of several simulated interventions to reduce adverse outcomes and population risk. Results of these simulations are followed by a discussion section.

Approach and Methods

The research team included a core modeling team and a panel of experts in several areas, including SD modeling, chronic pain treatment, drug diversion, and drug addiction. Initially, a thorough review of existing literature was conducted by core team members so that empirical evidence could be found to support key model parameters. Literature sources included a broad spectrum of databases, survey results, and scholarly articles covering the period from 1995 to 2010. The modeling team met with the expert panel to establish consensus about key components to include in the model and to review the model structure, logic, parameter values, and results.

Empirical Support

Key empirical findings from the literature support and help to clarify the model's logic and assumptions. Increases in opioid abuse, defined as the self-administered use of a pharmaceutical opioid medication for a nonmedical purpose [24], and increases in addiction, which involves uncontrollable compulsions and significant adverse consequences [25], have led to the implementation of regulatory policies for pharmaceutical opioids [26]. These regulatory policies have been shown to lead many physicians to avoid prescribing opioids out of fear of overzealous regulatory scrutiny [27]. In addition, prescribers who are fearful of regulatory scrutiny of their opioid analgesic prescribing practices have been found to decrease the *amount* of opioids they prescribe, limit quantities and refills, and to 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) [28].

Regarding the relative risks of different opioid products, immediate-release, short-acting formulations (single-entity and opioid + non-opioid combination analgesics) are prescribed much more frequently and are therefore implicated in a larger number of overdose deaths [29]. Another way of analyzing data, however, is to use the number of persons exposed via prescription as opposed to the population, as a whole. The latter denominator estimates the general overall health burden of a particular drug-associated problem, while the former provides a metric whereby the harm is normalized on the basis of exposure as not all persons in a given location will be exposed to a pharmaceutical opioid analgesic and exposure rates can vary by geographic location and over time. When abuse rates are normalized for the number of individuals exposed via out-patient, retail dispensing of these drugs, a metric referred to as Unique Recipients of Dispensed Drug (URDD), long-acting opioids (i.e., those products that are pharmacologically long-acting, such as methadone, and those that are pharmaceutically designed to be long-acting, such as transdermal delivery systems and modified-release oral opioid analgesic formulations) have a higher rate of abuse per 1,000 URDD than do the immediate-release opioid analgesics. For example, from 2003 to 2006, five to eight cases of long-acting opioid

Table 1 Model parameters and supporting references

	Parameter	Value	Support
1	All cause mortality rate for patients on long-acting opioids	0.012	U.S. population mortality data, adjusted by panel consensus
2	All cause mortality rate for patients on short-acting opioids	0.01	U.S. population mortality data, adjusted by panel consensus
3	All cause mortality rate for patients with dependence or abuse	0.015	U.S. 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)	2	Panel consensus
6	Base rate for adding or switching (to long-acting)	0.03	Extrapolation from outcome data: Verispan, LLC, SDI Vector One®: National (see [14])
7	Base rate of treatment	0.25	Panel consensus, informed by [32]
8	Base risk factor (degree Tx reduced in 1995 due to perceived risk)	1.3	Modeling Team Judgment, reviewed by panel
9	New chronic pain diagnosis rate	0.112	World Health Organization (see [10])
10	Overdose mortality rate for patients abusing opioids	0.0015	Extrapolation from heroin research (see [33])
11	Overdose mortality rate for patients on long-acting	0.0025	Consortium to Study Opioid Risks and Trends (CONSORT) study (see [34])
12	Overdose mortality rate for patients on short-acting	0.00005	CONSORT study (see [34])
13	Rate of addiction for patients on long-acting	0.05	Meta-analyses (see [3,4])
14	Rate of addiction for patients on short-acting	0.02	VISN16 data (South Central Veterans Affairs Health Care Network; see [35])
15	Table function* for short-acting bias (as function of perceived risk)	([1,0]–[4,1])	Modeling team judgment, reviewed by panel ([1,0] indicates a bias of 0 when perceived risk is 1, and [4,1] indicates a bias of 1 when perceived risk is 4)
16	Tamper resistance (baseline value)	1	Policy variable (1 = status quo)

* A table function is a series of XY coordinates representing a relationship (usually nonlinear) between two variables.

abuse were found per 1,000 URDD compared with <1 case of abuse per 1,000 URDD for short-acting opioids [30]. Support materials for a recent Food and Drug Administration (FDA) meeting, using numbers of prescriptions, as distinct from numbers of URDD, included an analysis of emergency department (ED) data that showed that "the rate of ED visits per 10,000 prescriptions was about five times higher for OxyContin [a long-acting formulation] compared to oxycodone [a short-acting formulation] over a recent three-year period" [26]. Physicians have been found to be sensitive to relative risk, exhibiting more caution in prescribing long-acting opioids [31].

Based on this and other information sources (see Table 1), the model was built on the assumption that higher rates of opioid abuse, addiction, and overdose deaths lead to increased regulation and increased perceived risk on the part of physicians for prescribing pharmaceutical opioids. Physicians are assumed to respond to increased perceived risk by prescribing opioids to fewer patients overall and especially by prescribing less long-acting opioids. In the model, this physician response is thought to effectively stabilize the system of pharmaceutical opioid prescribing: when rates of abuse, addiction, and overdose get too high, physicians prescribe less, but when rates of abuse, addiction, and overdose are low, physicians are more comfortable prescribing pharmaceutical opioids. A more thorough description of the model's logic can be seen in Figure 1 and is narrated in the following paragraphs.

Model Narrative

The following paragraphs narrate the logic and assumptions that are included in the SD model, and the numbers in ellipses refer to specific points marked on Figure 1. The story begins with a variable that represents the annual number of new chronic pain sufferers [1]. Many patients are diagnosed with chronic pain and subsequently treated with either long-acting [2] or short-acting [3] opioid formulations, becoming members of one of the "stocks" (populations) of chronic pain patients treated with opioids [4,5]. Patients who begin treatment with short-acting formulations may cease treatment if their condition improves, or they may switch to or add long-acting formulations if their pain conditions worsen [6].

Each year, a small fraction of patients in both the short-acting and the long-acting populations begin to abuse and/or become addicted to the prescribed opioids, causing their membership to transfer to the stock of

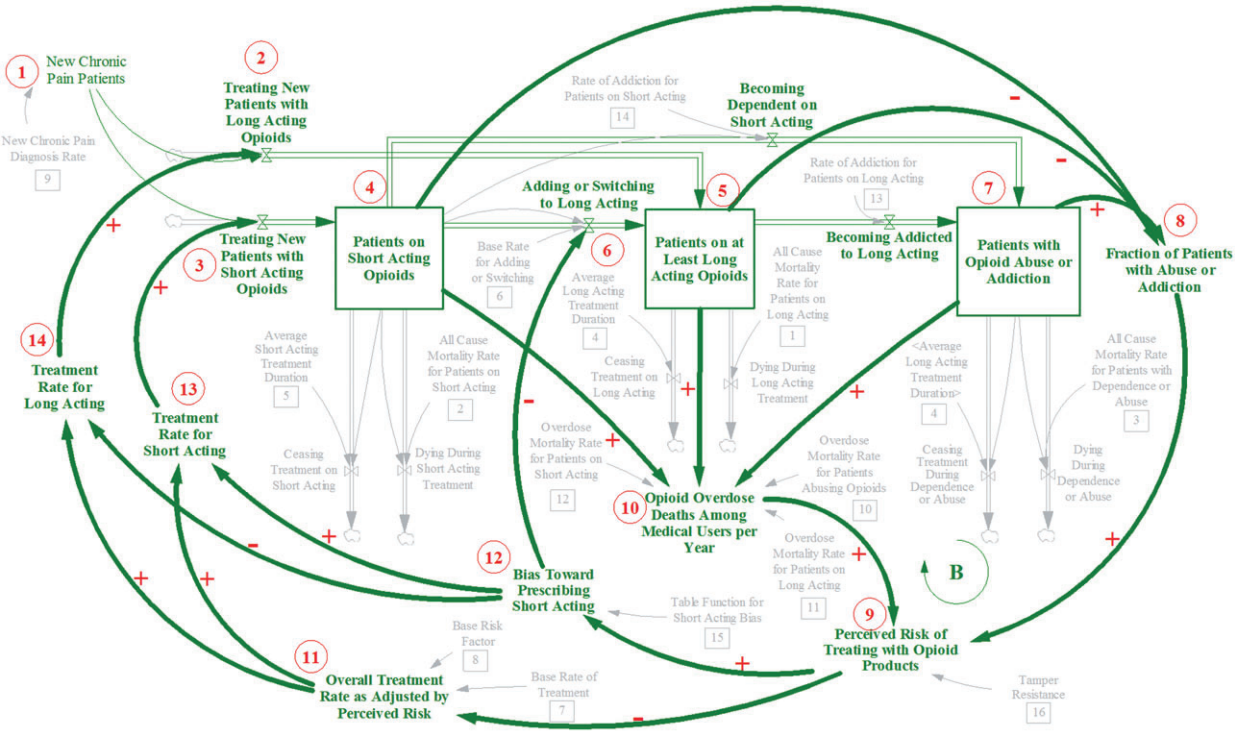

Figure 1 Causal loop diagram of medical usage of prescription opioids. Circled numbers correspond to parenthetical notations in the text. Numbers in boxes correspond to model parameters in Table 1.

people with opioid abuse or addiction [7]. Note that this stock [7] does not include people who initiate nonmedical use of opioids without having been prescribed opioids, and therefore, the people in this stock are considered to be a category of patients. The fraction of patients with abuse or addiction [8] influences physicians' perception of the risk involved in prescribing opioids [9] as does the total number of opioid overdose deaths each year [10]. As physicians perceive higher levels of risk [9], their overall rates of opioid prescribing decrease [11], and they become increasingly biased toward prescribing short-acting (lower risk) formulations [12]. Because of these balancing feedback loops, increases in the amount of abuse and addiction [7] is slowed when physicians begin to perceive higher levels of risk. Thus, the model variables move toward a state of dynamic equilibrium.

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 SD models, the empirical support for some of the parameters was limited (see Table 1 for key support references). SD models are generally more credible when their behavior is not 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. Several parameters with limited empirical support *did* have a substantial influence on model behavior, meaning a 30% change in the parameter resulted in a greater than 30% change in the cumulative number of overdose deaths of the number of patients treated for pain with long-acting opioids. The parameters that were both sensitive and empirically limited included the impact of perceived risk on prescriber behavior, the percentage of chronic pain patients treated with opioids, and the impact of two intervention alternatives, the development of tamper-resistant formulations of opioid analgesics that would provide a meaningful barrier to some methods of abuse and prescriber education programs, which will be discussed in more detail later (see [36] for more information regarding data gaps). Some of the parameters that strongly influenced model behavior *did* have sufficient empirical support, such as baseline rates of opioid abuse/addiction and overdose mortality rates. However, because model testing revealed a high degree of sensitivity to parameters for which empirical support is limited, study results must be considered preliminary and exploratory.

In addition to sensitivity analyses, the model was also tested to ensure that its behavior remained plausible when subjected to tests involving extreme conditions (i.e., abnormal parameter values), and model results compared favorably with historical reference data, where available,

suggesting at least a preliminary degree of model validity. "Goodness of fit" indices were not calculated as the current model serves primarily as a proof-of-concept prototype.

Simulated Interventions

Several possible interventions for policy-makers and pharmaceutical companies were explored with the current model. *Intervention One* tested the introduction of new, highly effective tamper-resistant formulations for long-acting pharmaceutical opioids. In the model, this was simulated by increasing the tamper resistance by a factor of two, which caused two proximal effects: the rate at which opioid-treated chronic pain patients become abusers or addicts was reduced by 50% and physicians perceived there to be much less risk of abuse and therefore prescribed opioid therapy for a higher fraction of their patients, including more prescribing of tamper-resistant long-acting formulations.

Intervention Two simulated the possible outcome of a highly effective prescriber education program by doubling physicians' perception of risk and therefore reducing rates of treatment with opioids. This intervention reduced the percentage of patients who develop abuse or addiction because the interventions assumed that educated prescribers would be much more selective in the use of opioid treatment and would monitor treatment more effectively. In the model, when physicians' perception of risk doubles, the fraction of patients treated is decreased by 50%, and the fraction of patients becoming dependent is decreased by 50%. By contrast, *Intervention Three* simulated a reduction in the rate at which patients develop abuse or addiction but maintained the baseline level of physician risk perception. Essentially, this third intervention isolated the effects of patient behavior from the behavior of prescribers so the results could be interpreted separately.

Results

Figure 2 shows a baseline model run for the historical period from 1995 to 2007 plus a policy evaluation period from 2008 to 2012. Reference data are scant, but total opioid-related deaths resulting from all types of medical and nonmedical use was reported to be 13,755 in 2006 [6]. From these data, the fraction of deaths associated with *only* medical use must be estimated. To guide this estimation, one study of opioid overdose deaths found that less than half of the decedents had ever been prescribed opioids [7], suggesting that medical users probably account for much less than half of the overdose deaths.

As shown in Figure 2, the model's baseline behavior suggests that the number of opioid deaths among medical users was 3,700 in 2007. This number is 27% of the total opioid deaths reported in that year [6] so these baseline results can be considered plausible, but additional support is needed to know how accurate they are. Furthermore, the shape of the curve in Figure 2 is not validated as reference data are not available on the pattern of opioid deaths among medical users from 1995 on. Historical data on the *total* number of opioid-related deaths (for both medical and nonmedical users) suggest the pattern of increase has been almost exponential, increasing more gradually in the late 1990s and more rapidly throughout the early 2000s [6]. By contrast, the current model shows a rapid initial increase that evens out over time as increases in prescriber risk and decreases in opioid prescribing bring the system to a stable equilibrium. This suggests strongly that additional validation of the model is warranted. Still, to illustrate the use of the SD model for policy analysis, the model was configured to show its response to the three interventions described in the methods section. All three interventions were modeled as having a very high degree of effectiveness in order to exaggerate their impacts, and for all three cases, interventions began in 2008 and persisted until the end of the simulation, 2012.

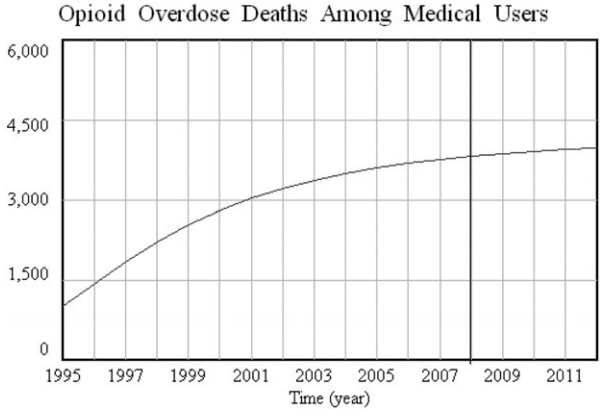

Figure 2 Baseline calculated opioid-related deaths among medical users.

Figure 3 shows the number of opioid overdose deaths per year among chronic pain patients, including the historical period from 1995 to 2007 plus the policy evaluation period from 2008 to 2012. Figure 3 seems puzzling because *Intervention One* (increased tamper resistance) lead to an *increase* in the number of deaths. This is because, as shown in Figure 4, the prescribers' perception of the risk of these medicines dropped sharply, which significantly increased the total number of patients who received opioid therapy. So although tamper resistance leads to a smaller percentage of patients dying, its implementation caused the percentage of individuals receiving opioids to increase by an even greater percentage.

Because changes in the perception of risk and the death fraction confounded one another during *Intervention One,* two additional simulations were conducted to isolate the main effects of both of these parameters. As shown in Figure 3, *Intervention Two* (a physician education program

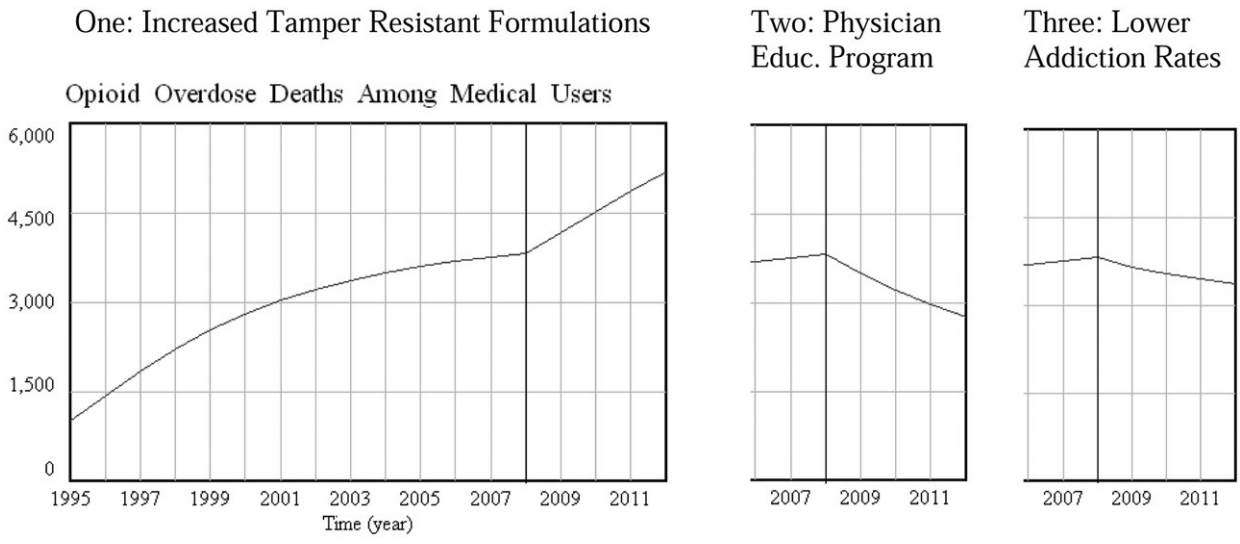

Figure 3 Effect of simulated interventions (A, Intervention One, increased tamper-resistant formulations; B, Intervention Two, physician educational program; and C, Intervention Three, lower addiction rates) starting in 2008 on opioid-related overdose deaths.

to increase perceived risk) leads to a reduction in the number of deaths as would be expected as perception of risk was increased and the amount of opioid prescribing was reduced. *Intervention Three* (reduction in abuse and addiction rates) also reduced deaths but to a lesser degree than *Intervention Two* as the number of patients receiving opioid therapy remained close to the baseline value.

The results of *Interventions Two* and *Three* reiterate that in the current model, changes in the number of patients prescribed have a greater impact than changes in the fraction of patients who suffer overdose deaths. So long as tamper-resistant formulations cannot offer perfect protection against overdose deaths, this may be a valid concern for the implementation of tamper-resistant formulations into the pharmaceutical market.

However, results from the model can also be viewed from an alternate perspective. The number of deaths per 10,000 chronic pain patients (shown in Figure 5) is a metric that reflects both costs and benefits from intervention alternatives. According to the model, this metric increased dramatically during the late 1990s and then began to stabilize at around 3.5 deaths per 10,000 patients. The three interventions look quite different when using this alternative metric.

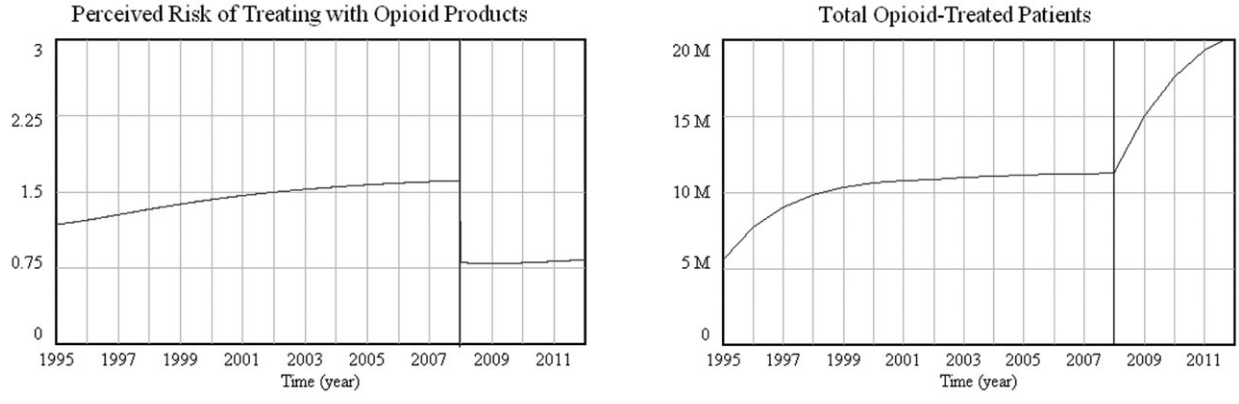

Figure 4 Effect of Intervention One (increased tamper-resistant formulations) on perceived risk and the total number of patients treated with opioid products. (A) Perceived risk of treating with opioid products; (B) total opioid-treated patients.

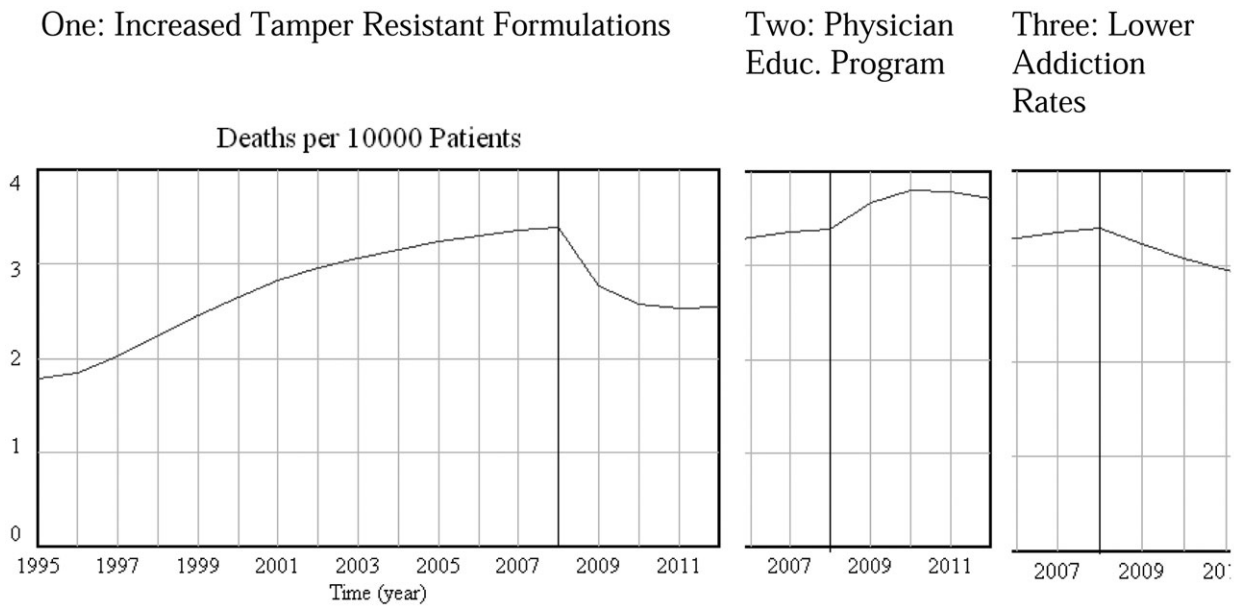

Figure 5 Effect of simulated interventions (A, Intervention One, increased tamper-resistant formulations; B, Intervention Two, physician educational program; and C, Intervention Three, lower addiction rates) starting in 2008 on opioid-related overdose deaths per 10,000 patients treated with opioid products.

Although the increased tamper resistance (which leads to increased prescribing in this model) in *Intervention One* was found earlier to *increase* the total number of opioid overdose deaths, it has a dramatically *favorable* impact on the number of deaths per 10,000 patients, and although the initial impact of reducing abuse potential without increasing prescribing (*Intervention Three*) is less dramatic, its impact over time is appreciable. By contrast, physician education to increase risk perception (*Intervention Two*) has the opposite effect in terms of the deaths per 10,000 patients metric because the model logic for this intervention causes the total number of patients receiving opioids to become significantly smaller. Even though less opioid prescribing leads to a smaller number of overdose deaths overall, it also prevents many chronic pain patients from accessing pharmaceutical treatment and therefore does not decrease the *fraction* of patients who suffer overdose deaths.

Discussion

Preliminary results indicate that system dynamics modeling has promise as a tool for understanding the public health problem of opioid abuse and addiction and for evaluating policy options that could be used to address opioid-related mortality. In addition, these findings suggest that it may be difficult to minimize the total number of overdose deaths without adversely affecting the degree to which chronic pain patients can access pharmaceutical treatment, and the findings also indicate the importance of the specific metric(s) chosen for evaluating effectiveness.

Although the current model has not yet been sufficiently calibrated to predict the absolute impact of the three interventions under focus, the present study serves well to demonstrate how a systems-level model may help to evaluate the potential efficacy of interventions to reduce opioid-related overdose deaths. The model demonstrates a comparison of the relative impacts of three alternative interventions and illuminates the complex interactions associated with pharmaceutical treatment of chronic pain, the risk of abuse and addiction, prescriber perceptions, and adverse outcomes, such as mortality. From a systems perspective, it is likely that highly effective tamper-resistant opioid formulations could significantly reduce the fraction of medical users who die from accidental overdose, but it is less likely that this would reduce the total number of overdose deaths among medical users. By contrast, physician education programs do have the potential for reducing the total number of accidental overdose deaths but as with Intervention One, probably not without dramatically reducing the number of patients who have access to opioid therapy for chronic pain.

A key strength of this study is its system-level perspective and deliberate recognition of the complex interconnections and feedback loops associated with opioid treatment for chronic pain and the adverse outcomes that are associated with it. Results from these preliminary analyses already highlight the importance of metric selection and consideration of multiple metrics in evaluating intervention alternatives. The total number of accidental deaths is an

important metric and illustrates the severity of the public health problem of opioid abuse and addiction. The number of deaths per 10,000 patients is another valuable metric, which may better reflect the benefits and costs of opioid therapy. Taken by themselves, these two metrics would lead to different conclusions about the efficacy and secondary consequences for these types of interventions for opioid-related overdose. It is clear that value judgments are needed regarding the relative importance of the negative outcomes associated with opioid therapy and the undertreatment of chronic pain as a public health problem.

Limitations

Despite great efforts to find empirical support for all model parameters, validity remains a primary limitation in the current study. Several parameters have weak empirical support, as mentioned previously, and a number of potentially important factors, such as payor policies and formulary coverage of certain products, have been excluded in part because empirical support remains elusive. A key indication of the model's limited validity is the comparison of the shape of the curve in Figure 2 with reference behavior data. As mentioned earlier, reference behavior data for the pattern of total opioid overdose deaths suggest an almost exponential increase from the late 1990s until the early 2000s [6]. By contrast, the model demonstrates a markedly rapid increase during the late 1990s, which then flattens out through the early 2000s. This suggests that the model may not be calibrated to accurately represent the dynamics of pharmaceutical opioid use. However, it is worth noting that autopsy diagnoses of opioid overdose deaths for a long time were listed as "narcotic unspecified" [37], which could have created a lag in the number of opioid-related overdose deaths that were recorded and might explain some of the discrepancy between the model results and historical reference data.

Regarding the exclusion of important factors, the model is limited in that it exclusively focuses on opioid treatment of *chronic* pain without representing acute pain treatment or patients. This may be appropriate as the scope of the present research and model was restricted to medical opioid user populations, and nonmedical user segments were excluded. However, the prescribing of opioids to treat acute pain accounts for a significant fraction of the opioids dispensed annually, and it is likely that opioid misuse by acute pain patients contributes to physicians' perception of risk. Therefore, the exclusion of acute pain treatment may threaten the validity of the model. A closely related limitation is that all "new" chronic pain patients in the model are considered to have legitimate medical need for analgesics, when in reality, some of the people presenting with purported pain are motivated by illicit intent [38].

Beyond the limited representation of variations in opioid treatment, the model also does not account for either polydrug use or polydrug abuse, which dramatically increases the risk of accidental overdose, or the tendency for drug abusers to switch between or combine pharmaceutical opioids and other drugs, both pharmaceutical and illicit, due to supply, cost, and other factors. The model excludes the influence of opioid addiction treatment programs and common nonpharmacologic alternatives to using opioids for chronic pain treatment, such as cognitive behavioral therapy [39] and institutional factors that impact opioid use, such as payor policies and formularies, as well as cost constraints, are also excluded from the model at this time. Because polydrug use and abuse, opioid treatment programs, alternative treatments, and institutional factors can all influence rates of both the medical and nonmedical use of opioids and the negative 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 the aforementioned limitations and to incorporate, among other things, nonmedical users of pharmaceutical opioids. Still, it is hoped that the insights achieved by applying a SD approach to this important public health concern can inform policy-makers about the importance of using multiple metrics and deliberate value judgments to determine the potential effectiveness of interventions intended to ameliorate the adverse outcomes of pharmaceutical opioids.

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