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A System Dynamics Model of Pharmaceutical Opioids: Medical Use, Diversion, and Nonmedical Use

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A SYSTEM DYNAMICS MODEL OF PHARMACEUTICAL OPIOIDS: MEDICAL USE, DIVERSION, AND NONMEDICAL USE

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Abstract: A dramatic rise in the nonmedical of pharmaceutical opioids has presented the United States with a substantial public health problem. Nonmedical use of prescription pain relievers has become increasingly prevalent in the US over the last two decades, and diversion of medicines obtained by prescription is assumed to be a major source of supply for nonmedical opioid use. Policymakers striving to protect population health by ameliorating the adverse outcomes of nonmedical use of opioid analgesics could benefit from a systems-level model which reflects the complexity of the system and incorporates the full range of available data. To address this need, the current project describes the conceptualization and development of a System Dynamics model that is used to complement and leverage results from existing research. Additional testing is needed to authenticate preliminary intervention simulation results, which suggest that a reduction in the initiation of nonmedical use may have a more profound impact on the total number of opioid overdose deaths than more tamper-resistant formulations, decreases in opioid prescribing, or decreases in rates of abuse among medical users. Results indicate that System Dynamics can help to identify points of high leverage for policy interventions as well as bring attention to the unanticipated negative consequences of these interventions.

Introduction

A dramatic rise in the nonmedical use of pharmaceutical opioids has presented the United States with a substantial public health problem (Comptom & Volkow, 2006). Results from the National Survey of Drug Use and Health suggest that in 2009, 5.3 million individuals (2.1% of the U.S. population age 12 and up) had used pharmaceutical opioids for nonmedical purposes within the past month (SAMHSA, 2010a). Trend data suggest that nonmedical use is becoming increasingly severe and remains largely unabated by current policies and regulations (e.g., Fishman et al., 2004). Tools and interventions are sorely needed to reduce nonmedical use of opioids, and practitioners are in need of efficacious strategies to detect, prevent, and treat the nonmedical use of opioid medications (Compton & Volkow, 2006). This article describes a system dynamics model which is designed to inform efforts to intervene in the epidemic of nonmedical pharmaceutical opioid use by identifying points of high-leverage in the system of nonmedical pharmaceutical opioid consumption in the United States.

Background

Nonmedical use of prescription pain relievers has become increasingly popular in the United States over the last two decades. Pharmaceutical opioids are now among the most popular drugs for nonmedical use in the United States, second only to marijuana (NCASA, 2005). The rate of initiation has increased drastically from the early 90s through the early 2000s (SAMHSA, 2006), with 2.2 million individuals initiating the nonmedical use of pain relievers in 2008 (SAMHSA, 2009a). The rate of opioid-related overdose has also 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 (Warner et al., 2009). Overdose deaths due to pharmaceutical opioids have outnumbered deaths due to both cocaine and heroin since 2001, and in 2007 outnumbered heroin by more than five times (CDC, 2010).

The diversion of pharmaceutical opioids is assumed to be a major source of supply for nonmedical use. Results from the 2009 National Survey on Drug Use and Health (SAMHSA, 2010) demonstrate that friends or relatives commonly reported as the source of the pain reliever used nonmedically most recently. Fifty-five percent of respondents said they obtained the pain reliever they nonmedically used most recently from a friend or relative for free, and another 14.9% said they either purchased or stole them from a friend or relative. Among survey respondents who received the drugs for free, 80% of them also reported that their friend or relative had originally received the drugs from a doctor, although the survey didn't ask whether the source's relationship with that doctor was a legitimate one. These results suggest that the largest source of pharmaceutical opioids for nonmedical use is the reservoir found in the home medicine cabinet kept by patients and others.

Recent increases in the prescribing of pharmaceutical opioids stems in part from recent surges in the diagnosis of and recognition of the need to treat chronic noncancer pain. A longitudinal analysis of chronic pain prevalence at a primary care facility in Seattle, Washington suggested that 11.2% of primary care patients who were previously free from chronic pain (defined as pain symptoms lasting 6 months or longer) were found to suffer from chronic pain during the year of the study (Gureje et al., 2001). Data from NHANES (Hardt et al., 2008), coupled with data from the U.S. Census Bureau, support an estimated prevalence of 29 million Americans aged 20 or older with chronic pain (defined as pain lasting three months or longer) in the period 1999-2002, indicating that pain is a significant cause of disability (National Center for

Health Statistics, 2006). 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 (Collett, 2001), pharmaceutical opioids have been found to be more effective at ameliorating pain than alternative medications (see Furlan et al., 2006 for a review), and their prescription and medical use has become increasingly common over the last decade (Governale, 2007, 2008a, 2008b).

It is not entirely understood why pharmaceutical opioids have become so popular for nonmedical use, especially relative to other licit and illicit substances. Users may feel a false sense of safety when using these products because, unlike illicit drugs, they are a medication that is endorsed and frequently prescribed by physicians (Compton & Volkow, 2006). In addition, the surge in chronic pain treatment may provide non-patients with access to pharmaceutical opioids through friends or relatives, and may also provide many youth with role models who are taking pain medication in the context of everyday activities (Compton & Volkow, 2006).

As of February 2009, the Food and Drug Administration (FDA) has begun requiring Risk Evaluation and Mitigation Strategies (REMS) for all Schedule II long-acting pharmaceutical opioids as a way to ensure that the benefits of these medications outweigh their risks (Leiderman, 2009). REMS requirements vary for each opioid product, depending on the level of risk, but all REMS must include an evaluation of their effectiveness and may additionally require specific interventions, including: (a) a medication guide, (b) a patient package insert, (c) a communication plan, (d) other "elements to assure safe use," and (e) an implementation system. Unfortunately, prior research has found little evidence to suggest that these types of interventions are effective in reducing the risk of medication misuse or abuse (see Chou et al., 2009 for a systematic review). There remains a need for tools and interventions that effectively reduce the adverse outcomes associated with the misuse of pharmaceutical opioids.

System Dynamics

The system dynamics (SD) modeling approach uses a set of differential equations to simulate system behavior over time. Such 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, such as for cocaine abuse prevention (Homer, 1993), health care reform (Milstein, Homer, & Hirsch, 2010), diabetes population dynamics (Jones et al., 2006), and tobacco policy options (Cavana & Tobias, 2008).

The SD approach can help to identify points of high-leverage for policy interventions as well as unanticipated negative consequences of these interventions, providing policymakers with information that is not available through research that is focused on individual aspects of a system (Sterman, 2006). In the current project, the development of an SD model complements and leverages results from an extensive amount of research based on surveys and statistical analyses, such as Fleming et al. (2007) who identify factors associated with opioid abuse, Butler et al. (2010) who use factor analysis to identify the aspects of opioid product formulations that are related to attractiveness for abuse, and Davis and Johnson (2007) who report on opioid use, abuse & diversion, concluding with a call for models to be developed.

Policymakers striving to protect population health by ameliorating the adverse outcomes of nonmedical opioid use could benefit from a systems-level model of pharmaceutical opioid medical and nonmedical use which reflects the complexity of the system and incorporates the

full range of available data. This article describes a SD model designed to increase understanding of the system of pharmaceutical opioid nonmedical use and to help identify and assess leverage points for reducing the associated adverse outcomes. The following sections describe the conceptual approach and research method employed and outlines how the model represents the fundamental dynamics of pharmaceutical opioids as they are prescribed, diverted, used nonmedically, and involved in overdose morbidity and mortality. Model testing is then discussed briefly, followed by a description of several simulated interventions and their effectiveness in reducing the adverse outcomes and population risk in the model. The discussion section highlights the main contributions of the model findings, future directions for continued research in this area, and the likely implications of the study's preliminary findings.

Model Creation Process

The model creation process began in May, 2009, with a core modeling team and a panel of leading experts in various related fields. The core modeling team included Lewis Lee, M.S., Louis Macovsky, D.V.M., M.S., and Wayne Wakeland, Ph.D., and was joined by Teresa Schmidt, M.A., as of January, 2010. Advisory panel members included leading authorities on the use of pharmaceutical opioids to treat chronic pain, prescription drug diversion and addiction, health policy analysis, and SD modeling (see Table 1). Purdue Pharma L.P., which markets some pharmaceutical opioids, provided the funding and support necessary for the team to independently develop an epidemiological model of pharmaceutical opioid use, diversion, and nonmedical use.

Table 1. Advisory Panel Members

John Fitzgerald, Ph.D., L.P.C., C.A.S., Associate Director, Risk Management & Epidemiology, Purdue Pharma L. P.
Aaron Gilson, M.S., M.S.S.W., Ph.D., Director of the Pain & Policy Studies Group at the University of Wisconsin Carbone Comprehensive Center.
J. David Haddox, D.D.S., M.D., D.A.B.P.M., Vice President of Health Policy for Purdue Pharma L.P.
Dennis McCarty, M.A., Ph.D., professor and Vice Chair in the Department of Public Health & Preventive Medicine at Oregon Health and Science University
Lynn Webster, M.D., F.A.C.P.M., F.A.S.A.M., cofounder and Chief Medical Director of the Lifetree Clinical Research and Pain Clinic
Jack Homer, M.S., Ph.D., a nationally renowned expert in the application of system dynamics to public health policy evaluation

Model development began with a thorough review of existing literature so that empirical evidence could be found to support key model parameters. Literature sources included a broad spectrum of data sources, survey results, and scholarly articles covering the period from 1995 to 2007. The advisory panel met with the modeling team on several occasions in 2009 (May, July, August, and December) and 2010 (February and June) to oversee the model logic and the representation of parameters and interventions in the model.

In the early meetings, panel members discussed areas of particular importance to the pharmaceutical opioid nonmedical use epidemic and shared professional presentations on these

areas. Key topics included chronic pain treatment, diversion, dependence and abuse, and the FDA REMS. The modeling team drew from panel members' discussions and presentations to shape the initial model structure and to define the boundaries of inclusion. Starting in August, 2009, the modeling team shared drafts of the model with panelists, along with overview presentations that summarized how the model logic had been developed and informed. The panel was invited to critique the model and was presented with dilemmas regarding the most accurate way to represent various aspects of treatment, diversion, and nonmedical use. During these meetings, panel members referred the modeling team to additional resources and drew from their professional knowledge to inform the team's design of the model.

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. In May 2010, the model was reviewed by Homer, who carefully evaluated the model logic and provided a detailed critique to Lee and Wakeland. Model logic and parameters were refined according to Homer's critiques and were then reviewed by the expert panel in June, 2010. Over the subsequent months, the model was subjected to rigorous testing to identify it strengths and weaknesses.

In August, 2010, model testing revealed the need for a fundamental change in model logic. Up until that point, the model had been built under the implicit assumption 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, model testing results indicated that the upsurge in nonmedical use must have been driven at least in part by increased popularity and demand for opioid products in the nonmedical use (NMU) 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 Pharmaceutical Opioid Epidemic

The following sections describe major areas of the system dynamics model. The model encompasses the dynamics of medical treatment with opioid analgesics, the initiation and prevalence of nonmedical usage, drug supply and demand, and opioid-related overdose fatalities. Three major sections of the model are discussed, each of which includes a description of empirical support, a narrative description of the model's behavior, and a causal loop diagram to illustrate the structure and logic. The verbal descriptions contain parenthetical numbers that correspond to specific points along the feedback loops in the diagrams. The model contains 8 state variables and their associated differential equations, 62 auxiliary variables and their associated algebraic equations or graphical functions, and 57 parameters.

Nonmedical Use of Pharmaceutical Opioids

Empirical findings in the literature support key model parameters and help to clarify the model's logic and many of its assumptions. Within the 'Nonmedical Use Sector,' DSM-IV criteria have been used to differentiate persons who engage in problematic substance use according to whether or not they meet diagnostic criteria for "opioid abuse" or "opioid dependence" (American Psychiatric Association, 1994). NSDUH data from the year 2000 to 2004 suggests that around 12-14% of individuals who use pharmaceutical opioids nonmedically meet the criteria for abuse or dependence (Colliver, Kroutil, Dai & Gfroerer, 2006), either of

which is associated with a significantly higher frequency of nonmedical use. Specifically, analyses of NSDUH 2007 data by Lee in 2010 (Lee et al., 2010) indicate that high frequency nonmedical users (who meet the DSM-IV criteria for dependence or abuse) use opioids around 220 days per year, whereas low frequency nonmedical users do so about 30 days per year. Extrapolation from heroin findings indicates that higher frequency of opioid use is associated with a significantly higher all-cause mortality rate (WHO; see Degenhardt et al., 2004; and Hser et al., 2001). This information was interpreted to indicate that low and high frequency users constitute two separate populations in the nonmedical use sector.

The supply of pharmaceutical opioids for nonmedical use often comes from friends or relatives, but can also come from leftover medicine obtained by prescription, prescription forgery, 'doctor shopping' (visiting multiple doctors for the purpose of obtaining the same or similar drugs), theft, or drug dealers (SAMHSA, 2007). Drug trafficking, theft, and forgery among non-patients are not included in the current model, as they would add considerable complexity to model logic and do not relate directly to the dynamics of chronic pain treatment, diversion from patients, and nonmedical use. Extrapolation of results from the 2006 NSDUH survey (SAMHSA, 2007) suggests around 25% of the nonmedical demand for pharmaceutical opioids is 'trafficked,' or bought or stolen from patients with pain conditions who are receiving these products ostensibly for treatment. The empirical evidence described above, as well as other findings (see Appendix A), informs the model logic in the nonmedical sector. This logic and many of its underlying assumptions are described with the following narrative and are illustrated in Figure 1. In the current model, a percentage of the U.S. population {1} is assumed to initiate nonmedical use each year {2}, all of whom start out in a stock (i.e., population) 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 pharmaceutical opioids for nonmedical use {6}. As the popularity of using pharmaceutical opioids for nonmedical use increases, the rate of initiation increases, creating a positive feedback loop that results in exponential increases in the rate of initiation.

Demand for pharmaceutical opioids is calculated from the number of individuals in low- and high-frequency populations {7}. Much of this demand is assumed to be met through illicit channels (e.g., theft, forgery, or interpersonal sharing), but about 25% of it is assumed to depend on diversion from chronic pain patients {8}. When this 25% represents an ample amount compared to demand, the rate of initiation {2} is assumed to be unaffected, as well as the rate of advancement from low frequency to high frequency use {3}. However, when the [trafficking-related] supply is limited, rates of initiation and advancement are assumed to decrease. The number of dosage units diverted from patients divided by the U.S. population, indicates the degree to which opioids are accessible for nonmedical use {9}. As the populations of nonmedical users increase beyond what the patient-diverted supply can support, accessibility becomes limited, decreasing initiation and advancement, and creating a negative feedback loop that eventually equilibrates the otherwise exponential increases in nonmedical use.

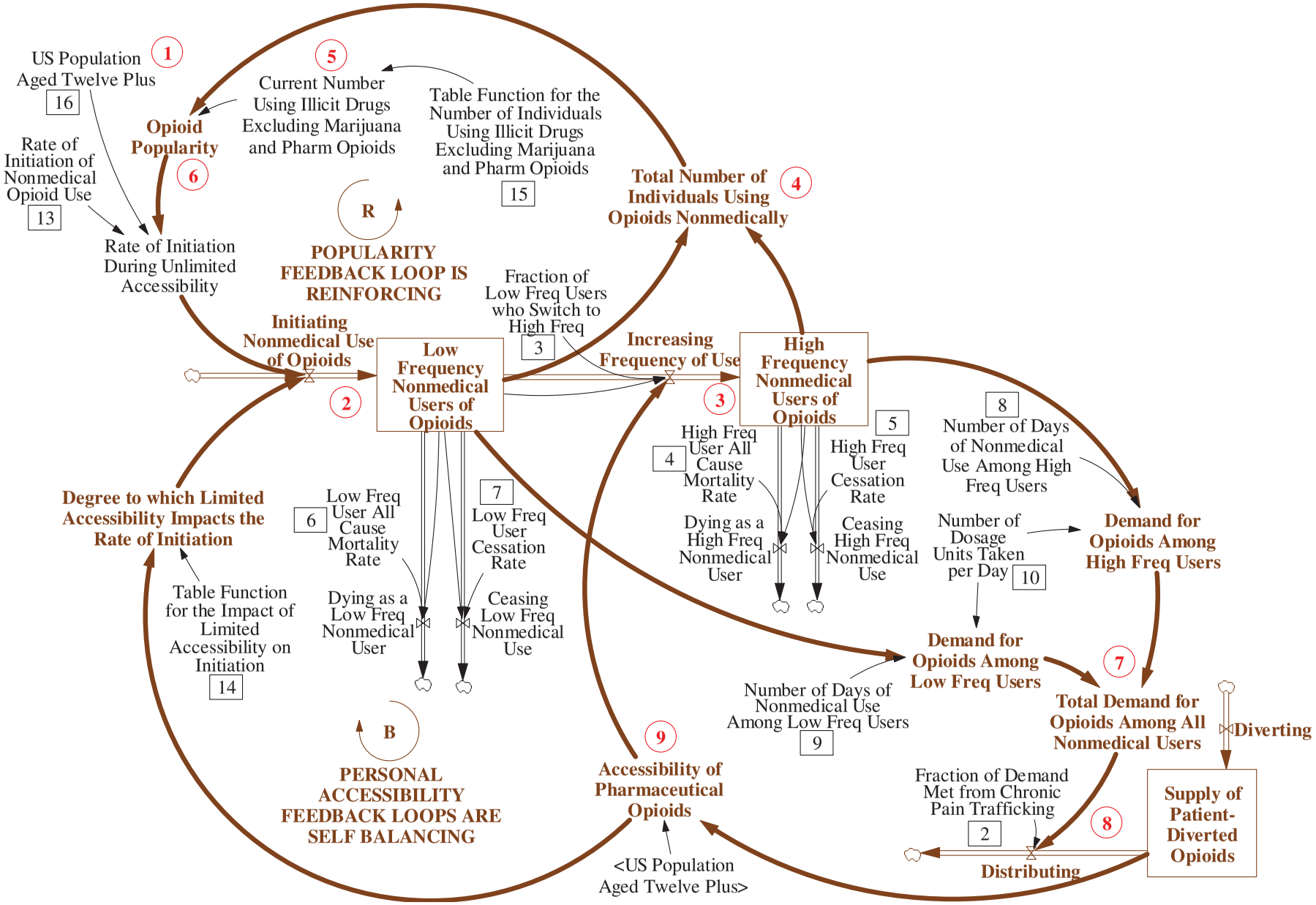


Figure 1. Causal Loop Diagram of the Nonmedical Use of Pharmaceutical Opioids. Circled numbers correspond to parenthetical notations in the text. Numbers in boxes correspond to model parameters in Appendix A.

Medical Use of Pharmaceutical Opioids

An overview of some key empirical findings helps to clarify the logic and assumptions of the 'Medical Use Sector' as well. Historically, increases in opioid *abuse*, defined as the self-administered use of a pharmaceutical opioid medication for a nonmedical purpose (Katz et al., 2010), and increases in *addiction*, which involves uncontrollable compulsions and significant adverse consequences (Compton, Darakjian, & Miotto, 1998), have led to the implementation of regulatory policies for pharmaceutical opioids (FDA, 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, Gilson, Dahl, & Haddox, 2002). 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, limiting 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; Wolfert, Gilson, Dahl, & Cleary, 2010).

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 (Cicero, Surratt, Inciardi, & Munoz, 2007). Another way of evaluating relative risk, 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, since 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 (products that are pharmacologically long-acting, such as methadone, and those which 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 1000 URDD than do the immediate-release opioid analgesics. For example, from 2003 to 2006, 5-8 cases of long-acting opioid abuse were found per 1,000 URDD, compared to <1 case of abuse per 1,000 URDD for short-acting opioids (Cicero et al., 2007). Support materials for a recent FDA meeting, using numbers of prescriptions, as distinct from numbers of URDD, included an analysis of emergency department (ED) data which 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" (FDA, 2010). Physicians have been found to be sensitive to this information regarding relative risk, and exhibit more caution in prescribing long-acting opioids (Potter et al., 2001).

The empirical evidence described above, as well as other findings (see Appendix B) informs the model logic in the medical sector. This logic and its underlying assumptions are described with the following narrative and are illustrated in Figure 2. In the current model, a proportion of the U.S. population is diagnosed with a chronic pain condition each year {1}. Patients are subsequently treated with either short-acting {2} or long-acting {3} opioid formulations, and become members of one of the stocks (populations) of chronic pain patients under treatment. 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 worsen {4}.

Each year a portion of patients in both the short-acting and long-acting populations begin to abuse and/or become addicted to the prescribed opioids, causing their membership to transfer to either the stock of long-acting patients with opioid abuse or addiction {5} or the stock of short-acting patients with opioid abuse or addiction {6}. Note that this stock {6} does not include people who initiate nonmedical use of opioids without having been prescribed opioids, and, therefore, the people in this stock are also considered to be another category of opioid user. The fraction of patients with abuse or addiction{7} influences physicians' perception of the risk involved in prescribing opioids {8}, as does the total number of opioid overdose deaths each year {9}. As physicians perceive higher levels of risk {8} they become increasingly biased toward prescribing short-acting (lower risk) formulations {10}, and their overall rates of opioid prescribing decrease {11}. 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 towards a state of dynamic equilibrium, stabilized by physicians' response to increasing rates of abuse, addiction, and overdose.

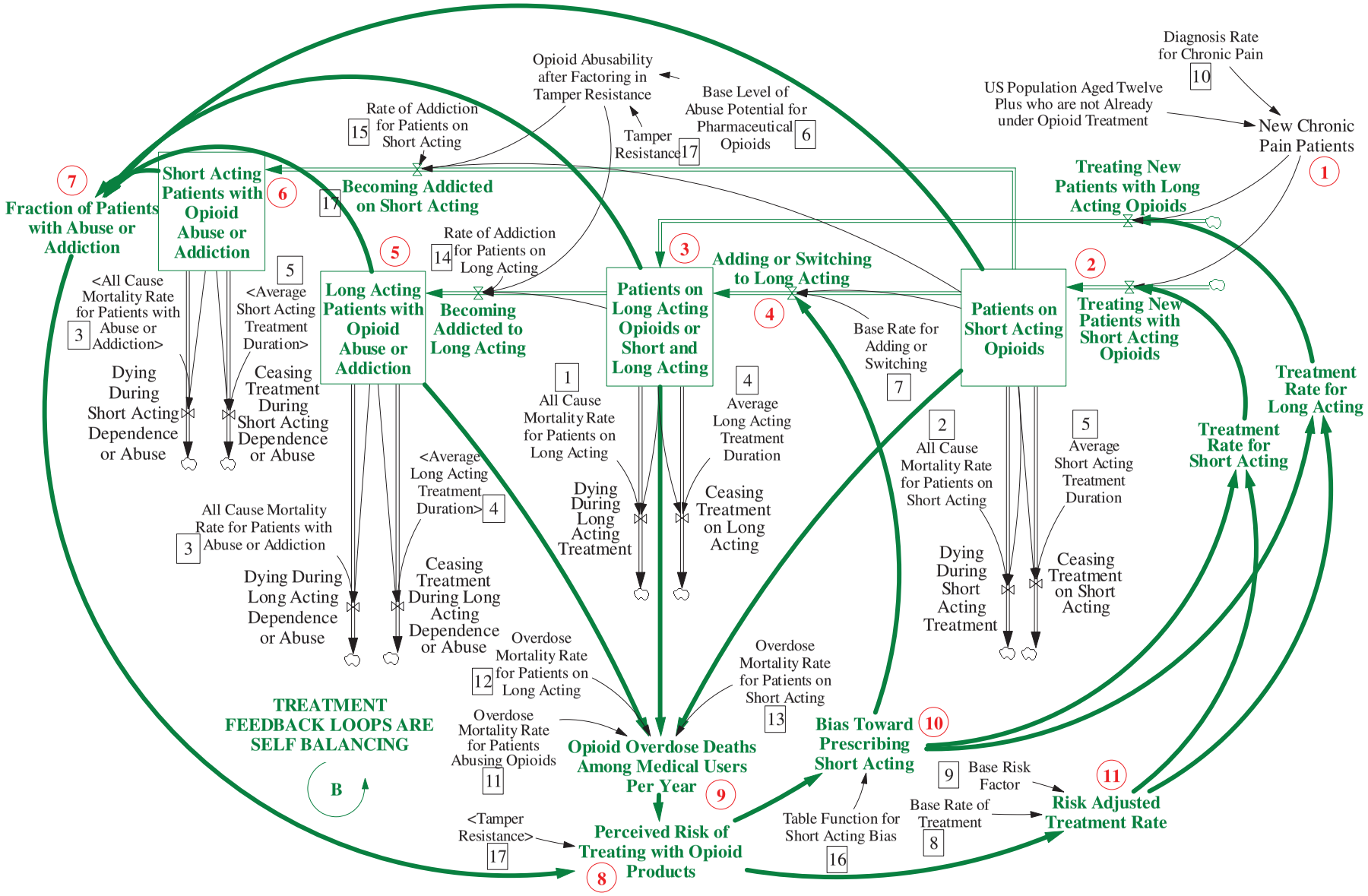


Figure 2. Causal Loop Diagram of the Medical Usage of Pharmaceutical Opioids. Circled numbers correspond to parenthetical notations in the text. Numbers in boxes correspond to model parameters in Appendix B.

Diversion of Pharmaceutical Opioids

An overview of some key empirical findings helps clarify the model's logic and assumptions regarding the diversion of pharmaceutical opioids to nonmedical use via chronic pain patients. Within the 'Diversion Sector,' results from the 2009 National Survey on Drug Use and Health (SAMHSA, 2010) indicate that among individuals who reported using pain relievers nonmedically in the past year, 17.6% of them stated that they acquired their most recent supply through a prescription from a doctor, indicating that they may have been a patient (medical user). Among non-patient, nonmedical users who have not received a prescription, about 6% acquired their most recent supply through theft or forgery, and 69% received opioids for free from friends or family members, the majority of whom *did* receive prescriptions directly from a doctor, although the survey does not gather information on the nature of the relationship between the source and the doctor (legitimate therapeutic relationship, doctor being deceived, doctor cooperating with source). Based on this information, the current model assumes that the remaining 25% of the demand generated by low and high frequency users is met through buying or stealing it from chronic pain patients (trafficking, as opposed to sharing).

Research suggests that around 5% of chronic pain patients engage in doctor shopping and around 4% engage in forgery (Manchikanti et al., 2006). In the current model, forgery and doctor shopping are assumed to be exhibited entirely by patients with abuse or addiction. Stocks of patients with abuse or addiction constitute around 10% of the total population of chronic pain patients, so 40% of these patients are assumed to exhibit forgery, and 50% of these patients are assumed to exhibit doctor shopping. The proportion of additional prescriptions that are successfully acquired through these methods remains unknown, but is assumed in the model to be 12% and 14% for doctor shopping and forgery, respectively.

The empirical evidence described above, as well as other findings (see Appendix C) informs the model logic in the diversion sector. This logic and its underlying assumptions are described with the following narrative and are illustrated in Figure 3. A fixed proportion of the patients 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 average number of prescriptions given to patients with abuse or addiction, (b) the number of patients who engaging in trafficking, and (c) the fraction of excess prescriptions acquired through forgery and doctor shopping. Some proportion of these excess prescriptions is assumed to be used by the patients themselves, rather than diverted to non-patient users {4}. This number is calculated as a product of (a) the number of patients with abuse or addiction and (b) the average number of extra prescriptions used per year by each patient with abuse or addiction. The number of prescriptions that are used "in excess" by pain patients is subtracted from the number of extra prescriptions acquired, and the rest is converted to dosage units {5} and assumed to be diverted to nonmedical users through trafficking channels {6}.

Diverted pharmaceutical opioids accumulate in a stock of dosage units {7} that are consumed according to the demand in the Nonmedical Use Sector not met by sharing, forgery, or stealing. Supply can also be expressed as 'months of supply available' {8}, which indicates the extent to which the diverted supply is able to meet the demand at any given time. When the supply of opioids becomes limited, a profit motive emerges {9} and patients' motivation for prescription forgery and doctor shopping increases. As this motivation fluctuates, the fraction of

prescriptions acquired through forgery and doctor shopping follows {10}, effectively stabilizing the amount of diversion through a balancing feedback loop.

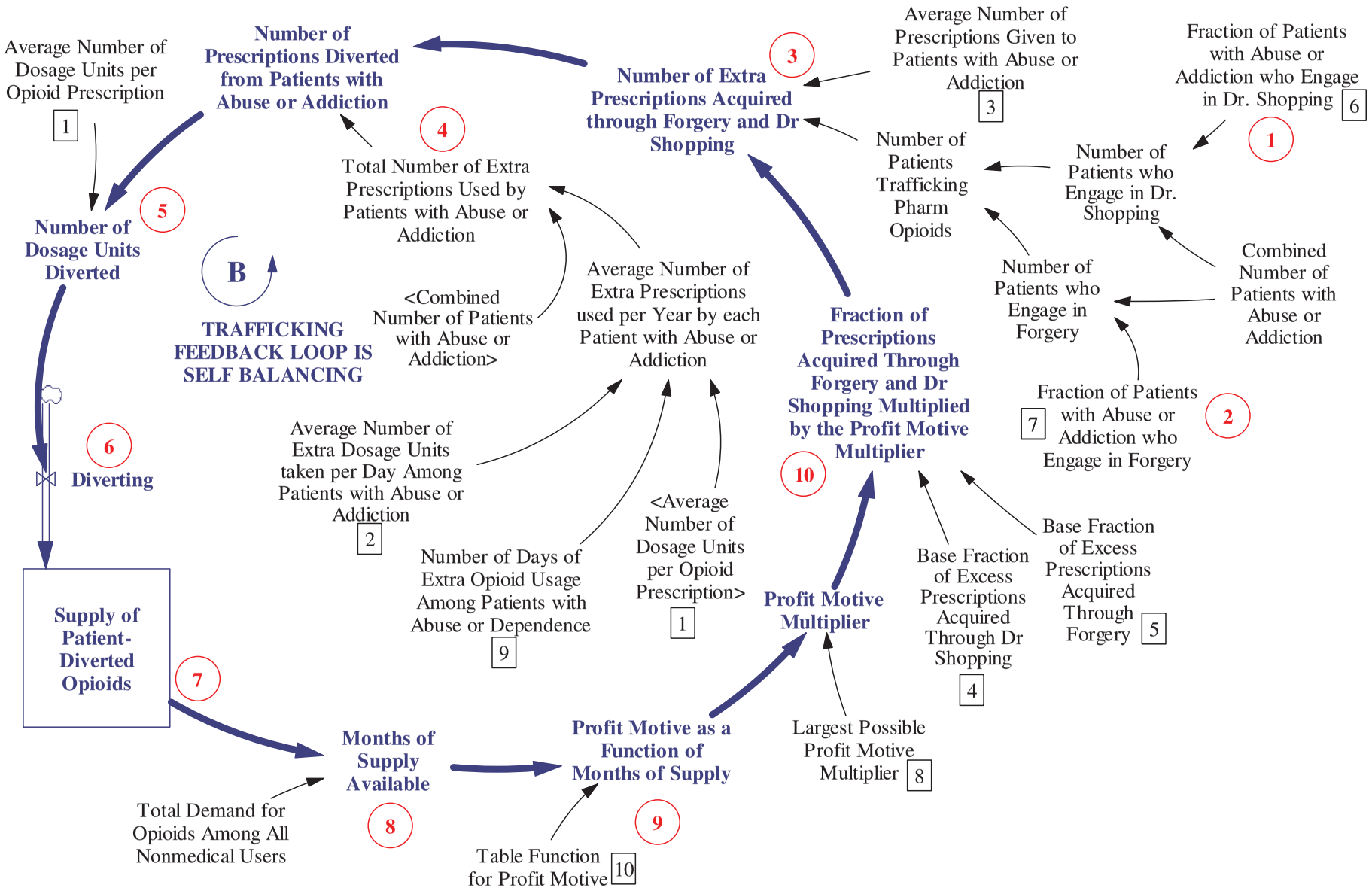


Figure 3. Causal Loop Diagram of the Diversion of Pharmaceutical Opioids. Circled numbers correspond to parenthetical notations in the text. Numbers in boxes correspond to model parameters in Appendix C.

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. (See Appendices for key support references.) System Dynamics models are generally more credible when their behavior is not highly 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.

Parameters that were both sensitive and empirically limited included the impact of perceived risk on prescribing behavior, the percentage of diagnosed chronic pain patients who are treated with opioids, the average number of dosage units taken per day of nonmedical usage, the impact of a limited nonmedical supply on forgery and doctor shopping behavior, and the impact of three intervention alternatives (discussed in more detail below), including (a) increased perceived risk on the part of physicians, (b) increased tamper resistance of opioid formulations, and (c) decreased popularity of pharmaceutical opioids for nonmedical use. (See Wakeland et al., 2010 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, the average number of prescriptions given to chronic pain patients, the average number of dosage units per prescription, 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 were compared to historical reference data, where available. The results of these tests were generally favorable, which indicated to us at least a preliminary degree of model validity.

Simulated Interventions

To illustrate the potential for evaluating interventions, several areas in the model were identified as likely to exhibit high-leverage. Several possible interventions were added to the simulation to explore their potential effects on the number of opioid overdose deaths in the U.S. population. All interventions were represented as simple toggles that would double beneficial parameters or halve harmful parameters in the model. While somewhat unrealistic, these dramatic interventions help to illustrate the dynamics of the model and the system's response to interventions at each point of leverage.

Tamper resistance intervention. This intervention 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 in the medical sector: a) the rate at which opioid-treated chronic pain patients become

abusers or addicts was reduced by 50%, and b) 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. Tamper resistance also reduced the rate of nonmedical use initiation by 50% in the nonmedical sector.

Prescriber intervention. This intervention 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 developing abuse or addiction is decreased by 50%.

Patient intervention. This intervention simulated a reduction in the rate at which patients develop abuse or addiction but maintained the baseline level of physician risk perception. The fraction of patients developing abuse/addiction was decreased by 50%, similar to the prescriber intervention. However, this third intervention isolated the effects of patient behavior from the behavior of prescribers, so the results could be interpreted separately.

Popularity intervention. This intervention simulated a reduction in the popularity of pharmaceutical opioids for nonmedical use, which is calculated as the total number of individuals using pharmaceutical opioids divided by the total number of individuals using other illicit substances in the U.S. When this ratio is halved, it effectively reduces the rate of initiation by 50%.

Results

Figure 4 shows a baseline model run for the historical period from 1995 to 2008, plus a policy evaluation period from 2008 to 2015. Reference data is scant, but total opioid-related deaths, resulting from all types of medical and nonmedical use, was reported to be 13, 755 in 2006, and historical data suggests the pattern of increase has been almost exponential, increasing more gradually in the late 90s and more rapidly throughout the early 2000s (Warner, Chen & Makuc, 2009).

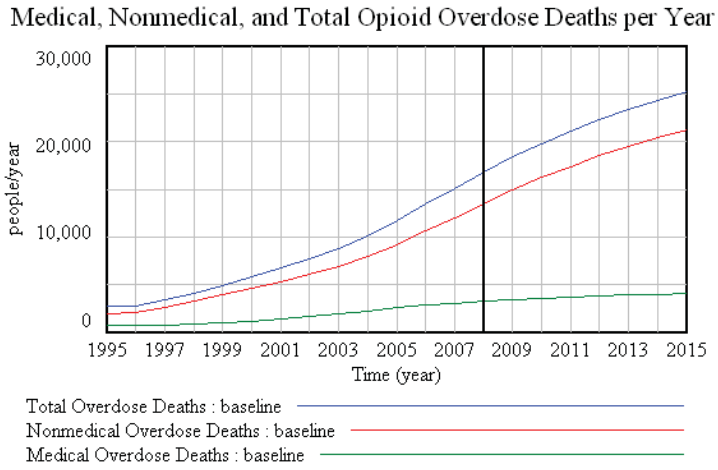


Figure 4. Baseline calculated opioid-related deaths

As shown in Figure 4, the model's baseline behavior exhibits a nearly exponential shape between the late 90s and early 2000s, and calculates a total number of opioid overdose deaths to be around 13,400 in 2006, with 2,823 overdose deaths among medical users and 10,580 overdose deaths among nonmedical users. So these baseline results can be considered plausible, but additional support is needed to know how accurately the model reproduces the proportion of overdose deaths suffered by medical and nonmedical users. The fraction of deaths associated with *only* medical or nonmedical use is not known, and must be estimated. One study of opioid overdose deaths found that less than half of the decedents had ever been prescribed opioids (Hall et al., 2008), suggesting that medical users probably account for much less than half of the overdose deaths. This rough estimate is captured by the model's baseline behavior, but additional validation of the proportion of opioid overdose deaths attributable to medical users is needed.

Even with limited reference data, the current model illustrates the potential usefulness of SD model for policy analysis. The model was configured to show the response to the four interventions described in the methods section. All four interventions were modeled as having a very high degree of effectiveness in order to exaggerate their impacts; and for each case, the simulated intervention began in 2008 and persisted until the end of the simulation, 2015.

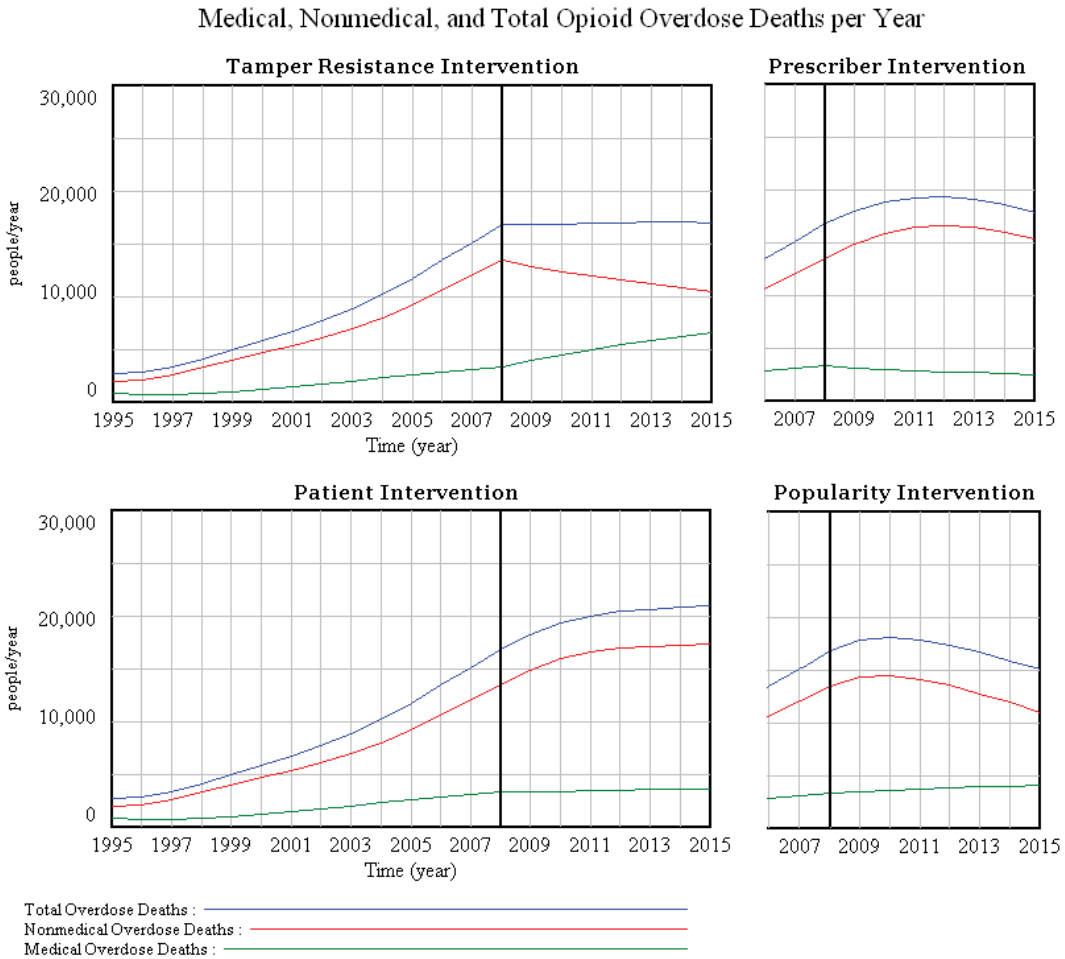
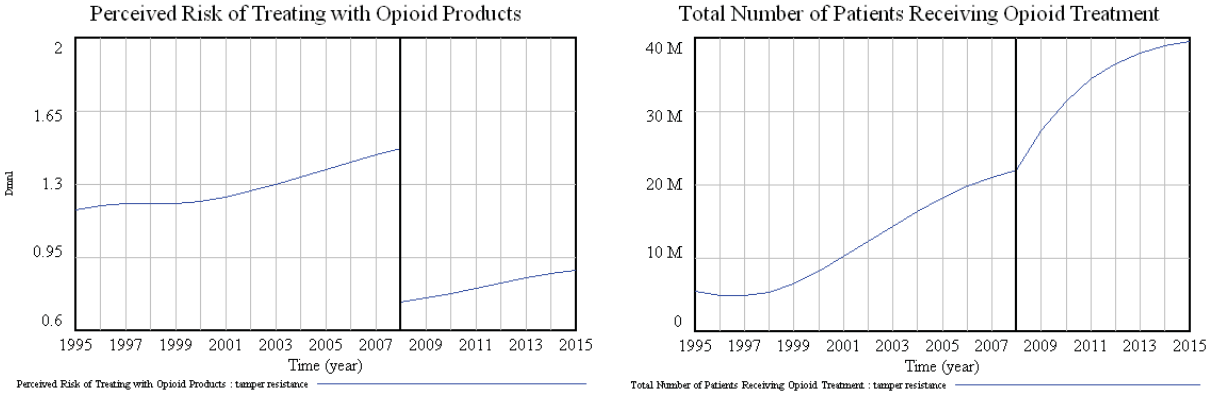


Figure 5. Effect of simulated interventions (tamper resistance, prescriber, patient, and popularity)

in 2008 on opioid-related overdose deaths

Tamper Resistance Intervention

Figure 5 shows the number of opioid overdose deaths per year among chronic pain patients, including the historical period from 1995 to 2008, plus the policy evaluation period from 2008 to 2012. As might be expected, doubling the degree to which tamper resistance prevents abuse has an impact on the number of nonmedical users who suffer overdose deaths. Interestingly, increased tamper resistance also leads to an *increase* in the number of patients who die of overdose. This is because, as shown in Figure 6, the prescribers' perception of the risk of these medicines drops sharply, which significantly increases the total number of patients who received opioid therapy. So although tamper resistance leads to a smaller percentage of patients dying, its implementation causes the percentage of individuals receiving opioids to increase by an even greater percentage.



Prescriber and Patient Interventions

The tamper resistance intervention influences both the perception of risk and the death fraction, and these effects are somewhat confounding. To isolate perceived risk from the total number of opioid overdose deaths, two additional simulations were implemented in the medical sector. The prescriber intervention, as shown in Figure 5, leads to an immediate increase in perceived risk that reduced rates of opioid treatment and leads to an immediate reduction in the annual number of medical overdose deaths. The reduction in total patients eventually leads to a reduced supply of diverted opioids and reduces the number of nonmedical users who die of overdose. Unfortunately, this delay takes several decades to effectively reduce nonmedical overdose deaths, and much of the nonmedical supply is acquired outside of diversion from chronic pain patients, so the number of nonmedical overdose deaths stabilizes at around 14,000 by the year 2025.

The patient intervention simply reduces the abuse/addiction rate of chronic pain patients by 50% without directly influencing prescriber risk. As shown in Figure 5, this reduces the steepness of the slope of medical overdose deaths, but they still increase gradually through 2015 (and stabilize at around 3850 deaths per year by 2030). The effect of this patient intervention on the number of overdose deaths in the nonmedical sector is negligible.

Popularity Intervention

Lastly, the popularity intervention decreases the popularity of pharmaceutical opioids for nonmedical use (and subsequently the initiation rate) by 50%. As might be expected, this does not have an impact on the number of chronic pain patients who suffer from overdose deaths, but it has a dramatic effect on the number of nonmedical users who do. By the year 2025, nonmedical overdose deaths are calculated to reach the level of medical overdose deaths, at around 4,200 deaths per year. Because a larger proportion of the overdose deaths are attributed to nonmedical users, these results indicate that the rate of initiation is a more powerful leverage point for reducing the total number of opioid overdose deaths than the rate of abuse/addiction among chronic pain patients.

Discussion

The preliminary results from the model indicate that system dynamic modeling has promise as a tool for understanding the epidemic of nonmedical use of pharmaceutical opioids. It holds promise for contributing to the evaluation of policy options and could be used to address opioid-related mortality and morbidity. More specifically, the results of the prescriber and patient interventions suggest that changes in the number of patients who are prescribed opioids have a greater impact on the total number of medical overdose deaths than changes in the fraction of patients who develop abuse or addiction. 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, tamper-resistant formulations may have other public health benefits, such as reduced transmission of infectious diseases by injection drug use (eg, HIV/AIDS, hepatitis B and C), thromboembolic events from injection of tablet particulates, abscesses, and septicemia. This model did not attempt to estimate such other public health benefits.

In addition, previous research has indicated that over half of opioid overdose deaths are suffered by individuals who have never been prescribed pharmaceutical opioids directly (Hall et al., 2008). The preliminary results of the model indicate that reducing the initiation of nonmedical use is indeed a more powerful point of leverage than reducing the number of chronic pain patients who develop addiction or abuse. Furthermore, results from NSDUH 2006 data (SAMHSA, 2007) indicate that a substantial fraction of the opioids that are used among nonmedical populations are acquired through sources outside of diversion from patients. Results from the simulated prescriber intervention suggest that the impact of efforts to reduce overdose deaths among non-patient populations may take a long time to manifest.

A key strength of this study is its system-level perspective and deliberate recognition of the complex interconnections and feedback loops associated with pharmaceutical opioid consumption and the adverse outcomes that are associated with it. Although the current model has not yet been sufficiently calibrated to predict the absolute impact of the four simulated interventions, 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, diversion, and adverse outcomes such as overdose 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 may be less likely that the total number of overdose deaths among

medical users would be reduced. And while prescriber and patient interventions have the potential for reducing the number of medical overdose deaths, they are likely to be less effective in reducing the *total* number of opioid-related overdose deaths when compared to interventions that reduce the rate of initiation of nonmedical use among non-patient populations.

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 have been excluded, often because support remains elusive. For example, the model is limited in that it focuses exclusively on prescribing and diversion of pharmaceutical opioids for the treatment of *chronic* pain, without representing acute pain patients and their treatment with pharmaceutical opioids. The nonmedical use sector is designed to capture the overall demand for and nonmedical use of all types of pharmaceutical opioids and the associated adverse consequences. The prescribing of opioids to treat acute pain accounts for a significant 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. A closely related limitation in the medical sector 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 (see Weaver & Schnoll, 2007).

Beyond the limited representation of variations in opioid treatment, the model also does not account for either poly-drug use or poly-drug abuse, either of which may involve other opioids or non-opioids with additive effects in the central nervous system (eg, benzodiazepines, cocaine, heroin), both of which dramatically increase the risk of unintentional overdose, nor does the model account for the tendency for drug abusers to switch between or to 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 non-pharmacologic alternatives to using opioids for chronic pain treatment, such as cognitive behavioral therapy (Morley, Williams, & Hussain, 2008). 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 poly-drug 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 many of the above limitations. Still, it is hoped that the insights achieved by applying a system dynamics approach to this important public health concern can inform policy makers about the value of system dynamics for analyzing alternative points of intervention. It is believed that system dynamics has much to offer in evaluating interventions and policy alternatives that are intended to ameliorate the adverse outcomes associated with pharmaceutical opioids.

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References

American Psychiatric Association. (1994). Diagnostic and Statistical Manual of Mental Disorders: DSM-IV. Washington D.C.: American Psychiatric Association, 181-183.

Butler, S. F. et al. (2010). Measuring attractiveness for abuse of prescription opioids. *Pain Medicine, 11*(1), 67-80.

Cabana, R. Y., & Tobias, M. (2008). Integrative system dynamics: Analysis of policy options for tobacco control in New Zealand. *Systems Research & Behavioral Science, 25,* 675-694.

Centers for Disease Control and Prevention (2010). *Unintentional drug poisonings in the United States.* CDC Issue Brief. Retrieved on September 14, 2010 from http://www.cdc.gov/HomeandRecreationalSafety/pdf/poison-issue-brief.pdf

Chou, R., Ballantyne, J. C., Fanciullo, G. J., Fine, P. G., Miaskowski, C. (2009). Research gaps on the use of opioids for chronic noncancer pain: Findings from a review of the evidence for an American Pain Society and American Academy of Pain Medicine clinical practice guideline. *Journal of Pain, 10*(2), 147-159.

Cicero, T. J., Surratt, H., Inciardi, J. A., Munoz, A. (2007). Relationship between therapeutic use and abuse of opioid analgesics in rural, suburban, and urban locations in the United States. *Pharmacoepidemiol Drug Safety, 16*(8), 827-840.

Collett, B. J. (2001). Chronic opioid therapy for non-cancer pain. *British Journal of Anaesthesia, 87,* 133-143.

Colliver, J. D., Kroutil, L. A., Dai, L., & Gfroerer, J. C. (2006). Misuse of prescription drugs: Data from the 2002, 2003, and 2004 National Surveys on Drug Use and Health (DHHS Publication No. SMA 06-4192, Analytic Series A-28). Rockville, MD: Substance Abuse and Mental Health Services Administration, Office of Applied Studies.

Compton, P., Darakjian, J., & Miotto, K. (1998). Screening for addiction in patients with chronic pain and "problematic" substance use: Evaluation of a pilot assessment tool. *Journal of Pain and Symptom Management, 16*(6), 355-363.

Compton, W. M. & Volkow, N. D. (2006). Major increases in opioid analgesic abuse in the United States: Concerns and strategies. *Drug and Alcohol Dependence, 81*(2), 103-107.

Davis, W. R., & Johnson, B. D. (2007). Prescription opioid use, misuse, and diversion among street drug users in New York City. *Drug and Alcohol Dependence, 92*(1-3), 267-276.

Degenhardt, L., Hall, W., Warner-Smith, M., & Lynskey, M. (2004). In M. Ezzati, A. D. Lopez, A. Rodgers, & C. J. L. Murray (Eds.), *Comparative quantification of health risks: Global and regional burden of disease attributable to selected major risk factors, Vol 1.* Geneva: Switzerland, p. 1109-1175.

Dunn et al. (2010). Opioid prescriptions for chronic pain and overdose. *Annals of Internal Medicine, 152*(2), 85-92.

Drug Use and Research Management (2001). *Opioid utilization analysis.* Oregon State University College of Pharmacy. Retrieved on August 20, 2010 from http://pharmacy.oregonstate.edu/drug_policy/pages/dur_board/evaluations/articles/opioid.html

Fishbain et al., (2008). What percentage of chronic nonmalignant pain patients exposed to chronic opioid analgesic therapy develop abuse/addiction and or aberrant drug-related behaviors? A structured, evidence-based review. *Pain Medicine, 9*(4), 444-459.

Fisher, B., et al., (2004). Determinants of overdose incidents among illicit opioid users in 5 Canadian cities. *Canadian Medical Association Journal, 171*(3), 235-239.

Fishman, S. M., et al. (2004). Regulating opioid prescribing through prescription monitoring programs : Balancing drug diversion and treatment of pain. *Pain Medicine, 5*(3), 309-324.

Fleming, M. F. et al. (2007). Substance use disorders in a primary care sample receiving daily opioid therapy. *Journal of Pain, 8*(7), 573-82.

Food and Drug Administration. (2008). Federal register: Identification of drugs deemed to have REMS. *Federal Register, 73*(60). 16313-16314.

Furlan, A. D., Sandoval, J. A., Mailis-Gagnon, A., & Tunks, E. (2006). Opioids for chronic noncancer pain: A meta-analysis of effectiveness and side effects. *Canadian Medical Association Journal, 174*(11), 1589-1594.

Governale, L. (2007). Methadone utilization in the U.S., 2002-2006. *PowerPoint Presentation.* Retrieved on June 8, 2010 from http://www.dpt.samhsa.gov/ppt/FINAL%20Methadone%20Governale%20SAMHSA%20207-20-07.ppt

Governale, L. (2008a). Outpatient drug utilization trends for extended release morphine products. *PowerPoint Presentation.* Retrieved on June 8, 2010 from http://www.fda.gov/ohrms/DOCKETS/ac/08/slides/2008-4395s2-04-FDA-Governale.ppt

Governale, L. (2008b). Outpatient drug utilization trends for Oxycodone products. *PowerPoint Presentation.* Retrieved on June 8, 2010 from http://www.fda.gov/ohrms/dockets/ac/08/slides/2008-4395s1-04-FDA-Governale.ppt

Gureje, O., Simon, G. E., & Von Korff, M. (2001). A cross-national study of the course of persistent pain in primary care. Pain, 92, 195-200.

Hall, A. J., et al. (2008). Patterns of abuse among unintentional pharmaceutical overdose fatalities. *Journal of the American Medical Association, 300*(22), 2613-2620.

Hardt, J., Jacobsen, C., Goldberg, J., Nickel, R., Buchwald, D. (2008). Prevalence of chronic pain in a representative sample in the United States. *Pain Medicine, 9*(7), 803-812.

Højsted, J., & Sjøgren, P. (2007). Addiction to opioids in chronic pain patients: A literature review. *European Journal of Pain, 11*, 490–518.

Homer. J. B. (1993). Projecting the impact of law enforcement on cocaine prevalence: A system dynamics approach. *Journal of Drug Issues, 23*(2), 281-295.

Hser, Y., Hoffman, V., Grella, C. E., & Anglis, M. D. (2001). A 33-year follow-up of narcotics addicts. *Archives of General Psychiatry, 58*, 503-508.

Johnston, L. D., O'Malley, P. M., Bachman, J. G., & Schulenberg, J. E. (December 11, 2007). *Overall illicit drug use by American teens continues gradual decline in 2007.* University of Michigan News Service: Ann Arbor, MI. Retrieved on August 20, 2010 from www.monitoringthefuture.org.

Jones, A., Homer, J., Murphy, D., Essein, J., Milstein, B., Seville, D. (2006). Understanding diabetes population dynamics through simulation modeling and experimentation. *American Journal of Public Health, 96*, 488-494.

Joranson, D. E., Gilson, A. M., Dahl, J. L., Haddox, J. D. (2002). Pain management, controlled substances, and state medical board policy: A decade of change. *Journal of Pain Symptom Management, 23,* 138-147.

Lee, L. et al. (2010). *Non-prescribed use of Vicodin® and OxyContin® among U.S. youth.* College on Problems of Drug Dependence. 72nd Annual Scientific Meeting. Scottsdale, AZ.Leiderman, D. B. (2009). Risk management of drug products and the U.S. Food and Drug Administration: Evolution and context. *Drug and Alcohol Dependence, 105*, S9-S13.

Leiderman, D. B. (2009). Risk management of drug products and the U.S. Food and Drug Administration: Evolution and context. *Drug and Alcohol Dependence, 1055,* S9-S13.

Mack, A. H. & Frances, R. J. (2003). Substance-related disorders. *FOCUS, 1,* 125-146.

Manchikanti, L., Cash, K., Damron, K. S., Manchukonda, R., Pampati, V., & McManus, C. D. (2006). Controlled substance abuse and illicit drug use in chronic pain patients: An evaluation of multiple variables. *Pain Physician, 9,* 215-226.

Milstein, B., Homer, J., & Hirsch, G. (2010). Analyzing national health reform strategies with a dynamic simulation model. *American Journal of Public Health, 100*(5), 811-819.

Morley, S., Williams, A., Hussain, S. (2008). Estimating the clinical effectiveness of cognitive behavioural therapy in the clinic: Evaluation of a CBT informed pain management programme. *Pain, 137,* 670-680.

NCASA (2005). Under the counter: The diversion and abuse of controlled prescription drugs in the United States. New York: National Center on Addiction and Substance Abuse.

National Center for Health Statistics. (2006). *Health, United States, 2006 with chartbook on trends in the health of Americans.* Hyattsville, MD: Dept of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics.

Potter, M., et al. (2001). Croughan-Minihane, M. Opioids for chronic nonmalignant pain. Attitudes and practices of primary care physicians in the UCSF/Stanford Collaborative Research Network. *Journal of Family Practice, 50*(2),145-51.

Rehm, J., Frick, U., Hartwig, C., Gutzwiller, F., Gschwend, P., & Uchtenhagen, A. (2005). Mortality in heroin-assisted treatment in Switzerland 1994-2000. *Drug and Alcohol Dependence, 79*(2), 137-143.

SAMHSA (1996). National household survey on drug abuse advance report #18. *Office of Applied Studies, Substance Abuse and Mental Health Services Administration.* Retrieved on June 12, 2010 from http://www.oas.samhsa.gov/nhsda/ar18ttoc.htm

SAMHSA (2002). *National Survey on Drug Use and Health, 2002.* United States Department of Human Services, Substance Abuse and Mental Health Services Administration. Office of Applied Studies. Ann Arbor, MI: Inter-university consortium for Political and Social Research. doi:10.3886/ICPSR03903.

SAMHSA (2006). Overview of findings from the 2005 National Survey on Drug Use and Health. Office of Applied Studies, NSDUH Series H-30, DHSS Publication No. SMA 06-4194). Rockville, MD.

SAMHSA (2007). Results from the 2006 national survey on drug use and health: National findings. *Retrieved on June 12, 2010 from* http://www.oas.samhsa.gov/nsduh/2k6nsduh/2k6results.pdf

SAMHSA (2009a). *Results from the 2008 National Survey on Drug Use and Health: National Findings.* (Office of Applied Studies, NSDUH Series H-36, HHS Publication No. SMA 09-4434). Rockville, MD.

SAMHSA (2009b). *National Survey on Drug Use and Health, 2007.* United States Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Office of Applied Studies. Ann Arbor, MI: Inter-university consortium for Political and Social Research. Doi:10.3886/ICPSR23782.

SAMHSA (2010). *Results from the 2009 National Survey on Drug Use and Health: Volume I. Summary of National Findings* (Office of Applied Studies, NSDUH Series H-38A, HHS Publication No. SMA 10-4586Findings). Rockville, MD.

Sterman, J. D. (2000). *Business dynamics: Systems thinking and modeling for a complex world.* Boston: McGraw-Hill.

Sterman, J. D. (2006). Learning from evidence in a complex world. *American Journal of Public Health, 96*, 505-514.

Sullivan, M. (April, 2007). Epidemiology of chronic non-cancer pain and its treatment with opioids. Retrieved on October 10, 2010 from http://drugabuse.gov/whatsnew/meetings/painopioides/powerpoint/sullivan.ppt

Warner, M., Chen, L. H., & Makuc, D. M. (2009). Increase in fatal poisonings involving opioid analgesics in the United States, 1999-2006. NCHS Data Brief, No. 22. Retrieved on August 20, 2010 from http://www.cdc.gov/nchs/data/databriefs/db22.pdf

Warner-Smith, M., Lynskey, M., Darke, S., & Hall, W. (2000). *Heroin overdose: Prevalence, correlates, consequences, and interventions.* National Drug and Alcohol Research Centre, University of South Wales. Monograph No. 46. Retrieved on August 20, 2010 from http://www.med.unsw.edu.au/NDARCWeb.nsf/resources/Mono_6/$file/Mono.46.PDF

Wakeland, W. et al. (2010, June). *Key data gaps for understanding trends in prescription opioid analgesic abuse and diversion among chronic pain patients and nonmedical users.* College on Problems of Drug Dependence, 72nd Annual Scientific Meeting, Scottsdale, AZ.

Weaver, J. & Schnoll, S. (2007). Addiction issues in prescribing opioids for chronic nonmalignant pain. *J. Addict Med, 1*(1), 2-10.

White, A. G. , Birnbaum, H. G., Mareva, M. N., Daher, M., Vallow, S., Schen, J., and Katz, N. (2005). Direct costs of opioid abuse in an insured population in the United States. *Journal of Managed Care Pharmaceuticals 11*(6), 469-479.

Wolfert, M. Z., Gilson, A. M., Dahl, J. L., & Cleary, J. F. (2010). Opioid analgesics for pain control: Wisconsin physicians' knowledge, beliefs, attitudes, and prescribing practices. *Pain Medicine, 11*(3), 425-34.

Appendix A. References of Support for Model Parameters in the Nonmedical Use Sector

	Parameter	Value	Support
	NONMEDICAL USE SECTOR		
1	Base Level of Abuse Potential of Pharmaceutical 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	0.01	Extrapolation from MTF data (Monitoring the Future; see Johnston et al., 2007) and results (Mack et al., 2003)
4	High Frequency User All-Cause Mortality Rate	0.02	Extrapolation from heroin research findings (WHO; see Degenhard et al., 2004; and Hser et al., 2001)
5	High Frequency User Cessation Rate	0.2	Imputation from NSDUH data (National Survey on Drug Use and Health, 2007; see SAMHSA 2009b)
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	0.06	Imputation from NSDUH data (National Survey on Drug Use and Health, 2007; see SAMHSA 2009b)
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 (Fisher et al., 2004; Warner et al., 2009; Warner-Smith et al., 2000)
12	Overdose Mortality Rate for Low Freq Nonmedical Users	0.0002	Extrapolation from research findings (Fisher et al., 2004; Warner et al., 2009; Warner-Smith et al., 2000)
13	Rate of Initiation of Nonmedical Opioid Use	0.005	Imputed from National Drug Use and Health Survey Data (NDUHS, 1995; see SAMHSA, 1996)
14	Table Function for the Impact of Limited Accessibility on Initiation	[(0,0)-(4,1)]	Modeling Team Judgment, reviewed by Panel
15	Table Function for the Number of Individuals Using Illicit Drugs Excluding Marijuana and Pharmaceutical Opioids	6.7M in ‘95 to 8.6M in ‘10	Calculated from NSDUH 2006 results, see 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

Appendix B. References of Support for Model Parameters in the Medical Sector

	Parameter	Value	Support
	MEDICAL USE SECTOR		
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 Abuse/Addiction	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)	5	Panel Consensus
6	Base Level of Abuse Potential for Pharmaceutical 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, 2008a)
8	Base Rate of Treatment	.06 in '95 to .21 in '00	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 WHO (World Health Organization; see Gureje et al., 2001)
11	Overdose Mortality Rate for Patients Abusing Opioids	0.0015	Extrapolation from Heroin Research (see Sullivan, 2007)
12	Overdose Mortality Rate for Patients on Long-acting	0.0025	CONSORT study (Consortium to Study Opioid Risks and Trends; see Potter et al., 2001)
13	Overdose Mortality Rate for Patients on Short-acting	0.00005	CONSORT study (Consortium to Study Opioid Risks and Trends; see Potter et al., 2001)
14	Rate of Addiction for Patients on Long-acting	0.05	Meta-Analyses (see Dunn et al., 2010; Højsted & Sjøgren, 2007)
15	Rate of Addiction for Patients on Short-acting	0.02	VISN16 data (South Central Veterans Affairs Health Care Network; see 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

Appendix C. References of Support for Model Parameters in the Diversion Sector

	Parameter	Value	Support
	DIVERSION SECTOR		
1	Average Number of Dosage Units Per Opioid Prescription	86	Extrapolation from dispensing data: Verispan, LLC, SDI Vector One®: National (VONA; see Governale, 2008a, 2008b)
2	Average Number of Extra Dosage Units taken per Day Among Patients with Abuse or Addiction	1.5	Panel Consensus
3	Average Number of Prescriptions Prescribed to Patients with Abuse or Addiction	10	Extrapolation from DURM data (Drug Use and Research Management, 2001) and dispensing data: Verispan, LLC, SDI Vector One®: National (VONA; see Governale, 2008a, 2008b)
4	Base Fraction of Excess Prescriptions Acquired Through Dr Shopping	0.13	Modeling Team Judgment, reviewed by Panel
5	Base Fraction of Excess Prescriptions Acquired Through Forgery	0.13	Modeling Team Judgment, reviewed by Panel
6	Fraction of Patients with Abuse/Addict who Engage in Dr Shopping	.5	Extrapolation from study results (Manchikanti et al., 2006)
7	Fraction of Patients with Abuse/Addict who Engage in Forgery	.4	Extrapolation from study results (Manchikanti et al., 2006)
8	Largest Possible Motive Multiplier	5	Panel Consensus
9	Number of Days of Extra Opioid Usage Among Patients 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)
10	Table Function for Profit Motive	[(0,0) – (20,1)]	Modeling Team Judgment, reviewed by Panel

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