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Reducing Overdose Deaths Associated with Pharmaceutical Opioid Treatment of Chronic Pain: Analyzing Interventions with a System Dynamics Model

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***REDUCING OVERDOSE DEATHS ASSOCIATED WITH
PHARMACEUTICAL OPIOID TREATMENT OF
CHRONIC PAIN: ANALYZING INTERVENTIONS WITH
A SYSTEM DYNAMICS MODEL***

Wayne Wakeland
Systems Science Seminar
October 8, 2010

Research Team

Core Team

- Lewis Lee, M.S.
- Teresa Schmidt, M.S.
- Louis Macovsky, DVM, M.S.
- Wayne Wakeland, Ph.D.

**Support provided by
Purdue Pharma, L.P.**

Sponsors & Expert Panelists

- Dave Haddox, DDS
 - Sponsor
- John Fitzgerald, Ph.D.
 - Sponsor
- Dennis McCarty, OHSU
 - Drug abuse expert
- Lynn Webster, MD
 - Pain treatment expert
- Aaron Gilson, Ph.D.
 - Drug abuse policy expert
- Jack Homer, Ph.D.
 - System dynamics expert

Major Health Problem

- Dramatic rise in rates of pharmaceutical opioid (PO) abuse and addiction
- Many people suffer from chronic pain (CP)
- POs used increasingly to treat CP

Prevalence and Incidence of Chronic Pain: WHO Study

Persistent pain in primary care: World Health Organization (WHO) Study

- 5438 patients from 15 sites in 14 countries were assessed by interview and questionnaires
- 22% of primary care patients had persistent pain (>6 months + care or disability)
 - More likely to have anxiety or depressive disorder (OR*=4.14)
- Pain-distress relationships were more consistent across cultures than pain-disability

Gureje et al, *JAMA* 1998;280:147-151

11.2% for Seattle

Persistent pain in primary care: WHO Study

- 3197 patients from 15 sites in 14 countries were assessed at baseline and 12 months
- 50% with persistent pain at baseline still had pain at 12 months
 - Predicted by number of pain sites at baseline
- 8.8% had new-onset persistent pain
 - Predicted by psychiatric disorder, perceived poor health, and occupational role disability

Gureje et al, *JAMA* 1998;280:147-151

PO Treatment Rate in CP Patients: *Incidence*

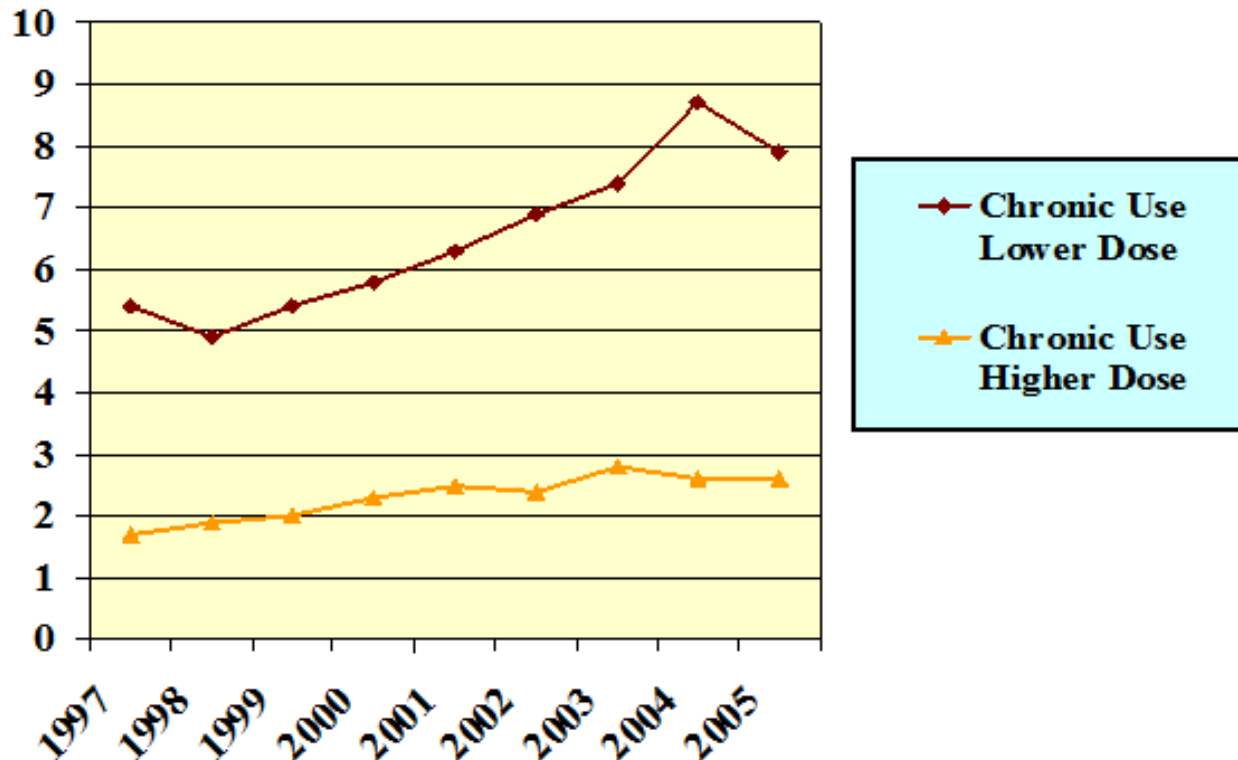
Provisional Results

Incidence of Opioid Use Episodes per 1,000 Adults:
Chronic Non-Cancer Pain at Group Health Cooperative*
*population of approximately 300,000 adults



Suggests in 2005 that
(10.5/1000)*250M or
~3M new patients
received opioid
treatment for chronic
non-cancer pain

⇒ OpA initiation rate of
(3/75) = 4% for chronic
non-cancer pain



Supported by NIDA grant DA-022557 (PIs: Michael Von Korff and Connie Weisner)

From: Sullivan M, Epidemiology of Pain
Source: National Health Interview Survey

PO Treatment Rate in CP Patients: *Prevalence*

Provisional Results

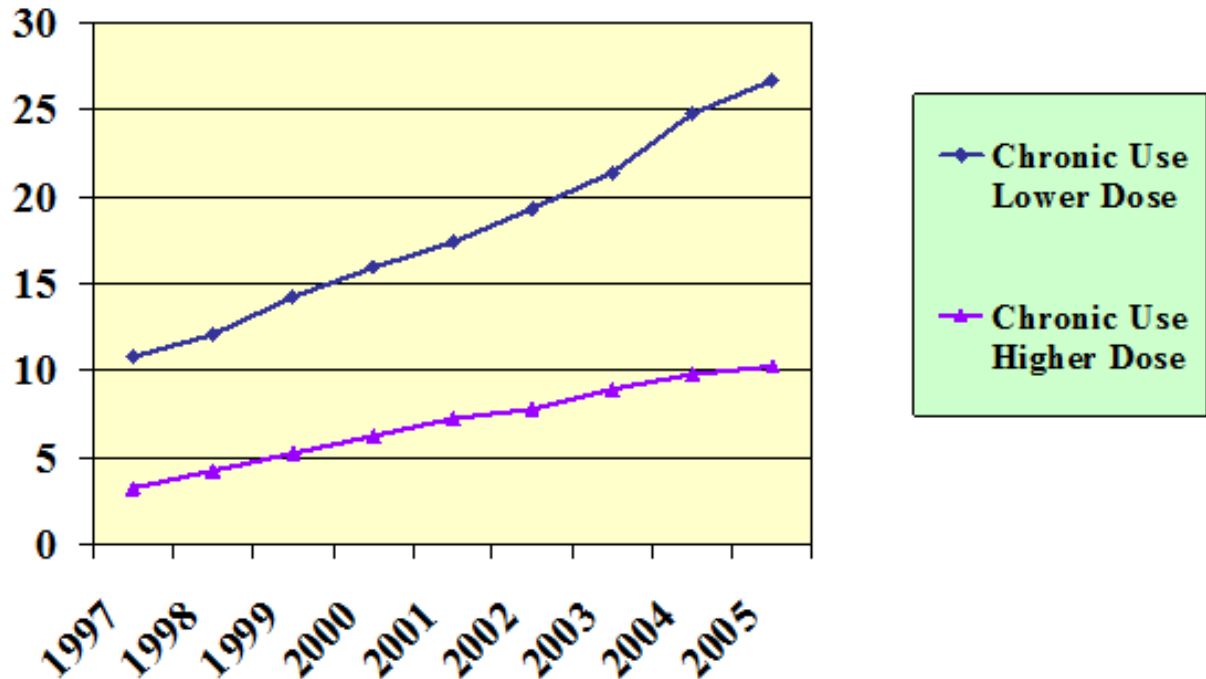
Prevalence of opioid use episodes per 1,000 adults:
chronic non-cancer pain at Group Health Cooperative*

* population of approximately 300,000 adults



Suggests in 2005 that
(35/1000)*250M or
~9M under opioid
treatment for chronic
non-cancer pain

⇒ OpA treatment rate
of (9/75) = 12%
for chronic non-cancer
pain



Supported by NIDA grant DA-022557 (PIs: Michael Von Korff and Connie Weisner)

From: Sullivan M, Epidemiology of Pain
Source: National Health Interview Survey

Opioid Prescriptions and Patients (Verispan's Total Patient Tracker)

Reflects total product uses for chronic and acute pain, includes patients on both.

Prescriptions (TRX, millions)										
	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
Long-acting										
oxycodone ER	1.80	3.10	5.40	6.50	6.30	6.50	6.30	6.40	7.00	7.50
methadone	0.45	0.60	0.80	1.10	1.60	2.20	2.80	3.40	3.90	4.10
fentanyl	1.00	1.20	1.60	2.20	3.10	4.00	4.50	4.60	5.00	5.50
morphine ER	1.00	1.20	1.30	1.50	1.80	2.20	2.70	3.20	3.70	4.20
Short-acting										
hydrocodone	60.00	68.00	76.00	80.00	85.00	90.00	95.00	105.00	110.00	120.00
oxycodone IR	14.00	15.90	16.60	18.50	20.50	23.50	25.00	27.50	31.00	34.70
hydromorphone	0.50	0.50	0.50	0.60	0.70	0.80	1.00	1.20	1.40	1.60
morphine IR	0.60	0.60	0.70	0.80	0.90	1.00	1.20	1.10	1.20	1.40

Patients (Millions)										
	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
Long-acting										
oxycodone ER	0.36	0.62	1.08	1.30	1.26	1.30	1.26	1.28	1.40	1.50
methadone	0.09	0.12	0.16	0.22	0.36	0.48	0.55	0.65	0.72	0.82
fentanyl	0.20	0.24	0.32	0.44	0.62	0.80	0.90	0.92	1.00	1.10
morphine ER	0.21	0.25	0.27	0.31	0.37	0.45	0.56	0.66	0.76	0.87
Short-acting										
hydrocodone	22.82	25.87	28.91	30.43	32.33	34.24	36.14	39.94	41.84	45.65
oxycodone IR	5.33	6.05	6.31	7.04	7.80	8.94	9.51	10.46	11.79	13.20
hydromorphone	0.10	0.10	0.10	0.12	0.14	0.16	0.20	0.24	0.28	0.32
morphine IR	0.19	0.19	0.23	0.26	0.29	0.32	0.39	0.36	0.39	0.45

From: Governale L, FDA, CDER, Outpatient Drug Utilization Trends for Oxycodone Products, November, 2008
 Governale L, FDA, CDER, Outpatient Drug Utilization Trends for Extended-Release Morphine Products, Nov., 2008
 Governale L, Methadone Utilization in the U.S., 2002 – 2006, July, 2007
 Source: Verispan, LLC, SDI Vector One®: National (VONA) and SDI Total Patient Tracker

Adverse Outcomes

- Overdose incidents
- Emergency room visits
- Fatalities

Rate of Drug Overdose and Mortality among CP Patients

- Overdose rate for individuals receiving 3 or more PO prescriptions within 90 days is 148 per 100,000 person-years.
- Among those prescribed the highest dosage level (100mg/day or more), the annual OD rate was 1791 per 100,000 person-years, representing an “*8.9-fold increase in overdose risk*” (p. 85) compared to those prescribed lower doses.
- Rate of overdose *Mortality* for these individuals is 17 per 100,000 person-years.

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

Opioid Analgesic Poisoning Deaths NCHS/ NVSS

Appendix table. Number of deaths and death rates for poisoning involving opioid analgesics, by demographic characteristics: United States, 1999–2006.

Includes
pain patients
and
nonmedical
users

									Ratio	
	1999	2000	2001	2002	2003	2004	2005	2006	2006 to 1999 ¹	2006 to 2001
Number of deaths										
Total	4,041	4,419	5,538	7,475	8,535	9,876	10,947	13,755	3.4	1
Deaths per 100,000 population										
Total ²	1.4	1.6	1.9	2.6	2.9	3.4	3.7	4.6	3.3	1
Age										
Under 15 years	*	0.0	0.0	0.1	0.1	0.1	0.1	0.1	*	1
15–24 years	0.7	0.8	1.3	1.7	2.2	2.7	2.8	3.8	5.4	1
25–34 years	1.9	1.9	2.3	3.3	3.7	4.4	5.2	6.7	3.5	1
35–44 years	3.5	3.7	4.5	5.7	6.2	6.8	6.9	8.3	2.4	1
45–54 years	2.9	3.3	4.0	5.5	6.2	7.1	8.0	9.7	3.3	1
55–64 years	1.0	1.1	1.4	1.8	2.2	2.6	3.1	4.0	4.0	1
65 years and over	0.4	0.3	0.4	0.6	0.6	0.7	0.8	0.9	2.3	1
Sex²										
Male	2.0	2.1	2.5	3.3	3.7	4.2	4.5	5.8	2.9	1
Female	0.9	1.1	1.4	1.9	2.1	2.5	2.8	3.3	3.7	1
Race and Hispanic origin²										
Hispanic	1.7	1.2	1.2	1.5	1.6	1.5	1.6	2.0	1.2	1
Non-Hispanic white	1.6	1.8	2.4	3.2	3.7	4.3	4.7	5.8	3.6	1
Non-Hispanic black	0.9	0.9	1.1	1.3	1.3	1.5	1.8	2.7	3.0	1

* Figure does not meet standards of reliability or precision. Rate is based on fewer than 20 deaths and is considered unreliable.

0.0 Quantity more than zero but less than 0.05.

¹Interpret the ratio of 2006 to 1999 for the total number of deaths as follows: the number of deaths in 2006 was 3.4

From: Warner, et al, "Increase in Fatal Poisonings Involving Opioid Analgesics in the United States, 1999–2006", NCHS Data Brief ■ No. 22 ■ September 2009

Medical Use Fraction of OpA Overdose Deaths

From: Aron J. Hall; Joseph E. Logan; Robin L. Toblin; et al. **Patterns of Abuse Among Unintentional Pharmaceutical Overdose Fatalities** *JAMA*. 2008;300(22):2613-2620 (doi:10.1001/jama.2008.802)

Table 3. Substance Abuse Indicators Among Unintentional Pharmaceutical Overdose Deaths Involving Pharmaceutical Diversion and Doctor Shopping, West Virginia, 2006

Substance Abuse Indicator	All Deaths, No. (%)	Any Diverted Pharmaceuticals ^a		≥5 Clinicians ^b	
		No. (%) ^c	OR (95% CI) ^d	No. (%) ^c	OR (95% CI) ^d
History of substance abuse	231 (78.3)	153 (82.3)	1.8 (1.0-3.4)	49 (77.8)	1.0 (0.5-2.0)
Any diverted pharmaceuticals ^a	186 (63.1)	NA	NA	24 (38.1)	0.3 (0.1-0.5)
Nonmedical route of administration	66 (22.4)	49 (26.3)	1.9 (1.0-3.8)	9 (14.3)	0.5 (0.2-1.1)
≥5 Clinicians prescribed controlled substances ^b	63 (21.4)	24 (12.9)	0.3 (0.1-0.5)	NA	NA
Contributory alcohol	51 (17.3)	34 (18.3)	1.2 (0.6-2.4)	5 (7.9)	0.3 (0.1-0.9)
Previous overdose	50 (16.9)	29 (15.6)	0.8 (0.4-1.5)	19 (30.2)	2.8 (1.4-5.6)
Contributory illicit drug ^e	47 (15.9)	36 (19.4)	2.1 (1.0-4.9)	9 (14.3)	0.9 (0.3-1.9)
Current OTP enrollment	12 (4.1)	4 (2.2)	0.3 (0.1-1.1)	2 (3.2)	0.7 (0.1-3.5)
Any indicator ^f	279 (94.6)	167 (89.8)	1.5 (0.7-3.3)	55 (87.3)	0.5 (0.2-1.5)
Total	295 (100)	186 (100)		63 (100)	

Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio; OTP, opiate treatment program.

^aDiverted pharmaceuticals include those that contributed to death but that were not prescribed to the decedent.

^bIncludes clinicians who prescribed controlled substances to the decedent during the year prior to death, based on Controlled Substances Monitoring Program records.

^cPercentages among those with any diverted pharmaceuticals or ≥5 clinicians (column percentages) are reported.

^dOdds ratio compares those with given substance abuse indicator vs those without as the reference group.

^eIncludes cocaine, heroin, and methamphetamines.

^fExcludes not applicable indicators, as noted.

- **Limited, state-level data without trends.**

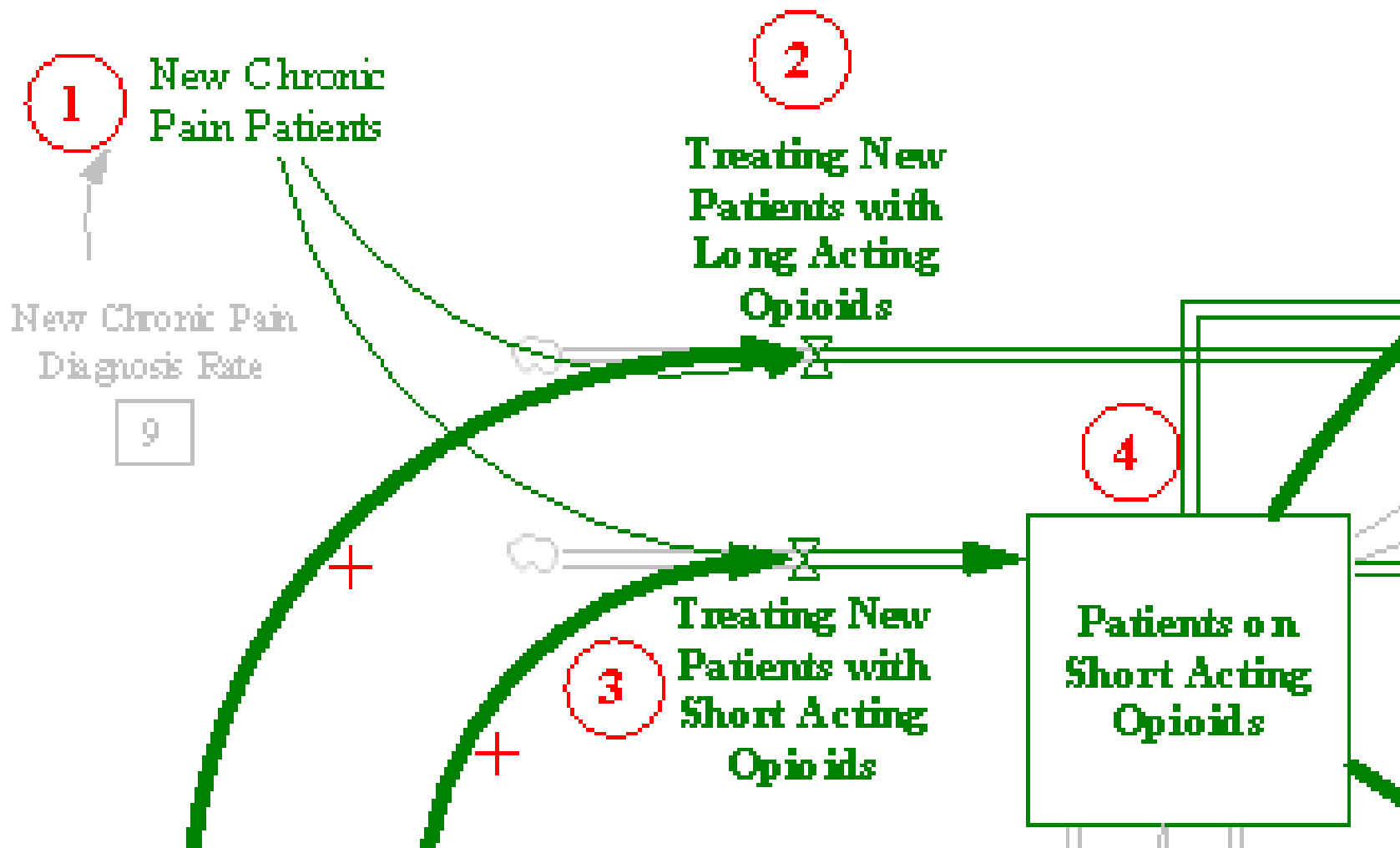
- **W. Virginia data in 2006 indicate that ~45% of decedents involving opioid analgesics had a prescription within the past year.**

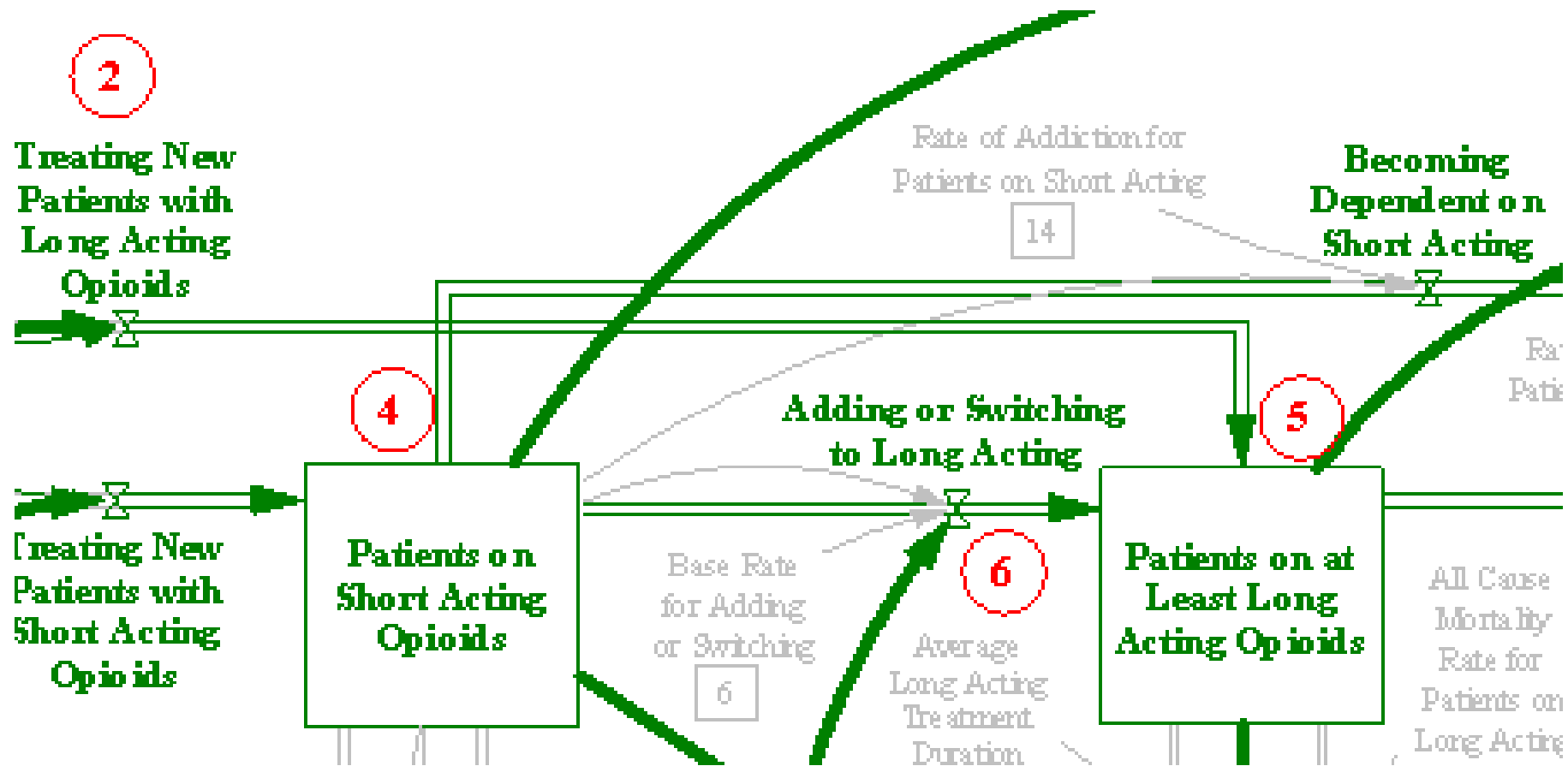
...using centralized prescription records maintained by the state's prescription drug monitoring program, we also were able to assess the [decedents' prescription histories in the year before their deaths.](#)

particularly prevalent among drug diverters. Multiple contributory substances were implicated in 234 deaths (79.3%). Opioid analgesics were taken by 275 decedents (93.2%), of whom only 122 (44.4%) had ever been prescribed these drugs.

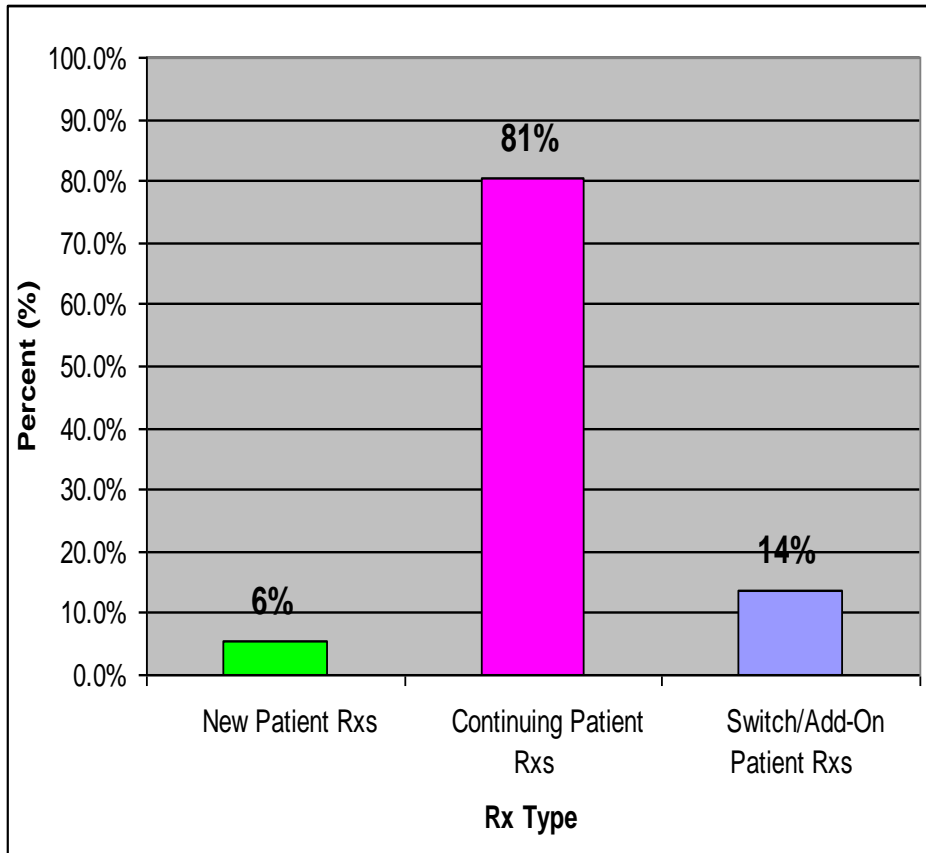
What to do?

- Need effective interventions
- Need tools to identify policies to reduce opioid abuse, addiction, and overdose deaths.
- Would a system dynamics (SD) model meet this need?
 - SD model structure features stocks and flows
 - Auxiliary variables, equations, parameters





MU Add/Switch Rates to Long-Acting Rx Opioid oxycodone ER



*3 month look-back period

- ~81% of new Rx dispensed to those had previous Rx for ER oxycodone product within past 3 months
- ~6% had no previous Rx
- ~14% of new Rx switched or added-on from another pain therapy product, including other long-acting opioids

SA, LA, and SA+LA Utilization Pattern (White Study)

Direct Costs of Opioid Abuse in an Insured Population in the United States

(population ~2M covered by 16 employer health plans)

TABLE 4 Comparison of Drug Utilization Patterns, 1998-2002 (Patients Aged 12-64 Years)

	Opioid Abusers (N=740)					Nonabusers (N=2,220)					Relative Risk Ratio [†]
	Number (%) of Patients With at Least 1 Claim	Number of Claims per Patient			Number (%) of Patients With at Least 1 Claim	Number of Claims per Patient					
		Mean*	SD	Median		Mean*	SD	Median			
	[A]				[B]				[C]= [A]/[B]		
Prescription drugs											
All prescription drugs	643	86.9%	41.6 ^a	41.9	27.0	1,369	61.7%	13.8 ^a	19.3	7.0	1.4 ^a
All nonopioids	637	86.1%	32.4 ^a	32.7	23.0	1,353	60.9%	13.0 ^a	17.5	7.0	1.4 ^a
Prescription opioids											
SAOs [‡] only	304	41.1%	9.4 ^a	11.9	4.0	421	19.0%	2.3 ^a	3.6	1.0	2.2 ^a
LAOs [§] only	7	0.9%	6.9	5.6	9.0	3	0.1%	11.3	14.6	5.0	7.0 ^a
Both SAOs and LAOs	127	17.2%	25.7	15.5	24.0	8	0.4%	32.1	32.4	23.0	47.6 ^a

* t tests were conducted to compare the mean number of claims per patient between opioid abusers and nonabusers; ^a denotes significance at the 1% level (P < 0.01).

† Chi-square tests were conducted to compare the prevalence rates of drug claims between opioid abusers and nonabusers; ^a denotes significance at the 1% level (P < 0.01).

‡ Short-acting (prescription) opioids (SAOs): any prescription drug with these active ingredients: hydrocodone (308 patients), oxycodone (153), tramadol (88), codeine (110), propoxyphene (93), and other SAOs (78, meperidine, butorphanol, fentanyl, hydromorphone, buprenorphine, morphine, pentazocine, dihydrocodeine, opium, sufentanil, nalbuphine or drugs administered as a medical procedure with the following HCPCS codes: J0592, J0745, J1170, S0092, J2175, J2180, J2270, J2271, J2300, and J3010). "SAOs only" includes patients with claims only for SAOs.

§ Long-acting (prescription) opioids (LAOs): oxycodone ER (97 patients), fentanyl transdermal system (38), methadone (29), extended-release morphine (16, including the claims for brand names Kadian, Avinza, MS Contin, Oramorph, Astramorph PF, Duramorph, and Infumorph or extended-release morphine administered as a medical procedure with the following HCPCS codes: J2275 and S0093). "LAOs only" includes patients with claims only for LAOs.

Are there other claims database analyses that can be used to validate the above splits?

From: White AG, et al, "Direct Costs of Opioid Abuse in an Insured Population in the United States,"

J Manag Care Pharm. 2005;11(6):469-79

MU OpA Dependence & Abuse

Who develops opioid abuse/dependence among those receiving opioid therapy for chronic non-cancer pain?

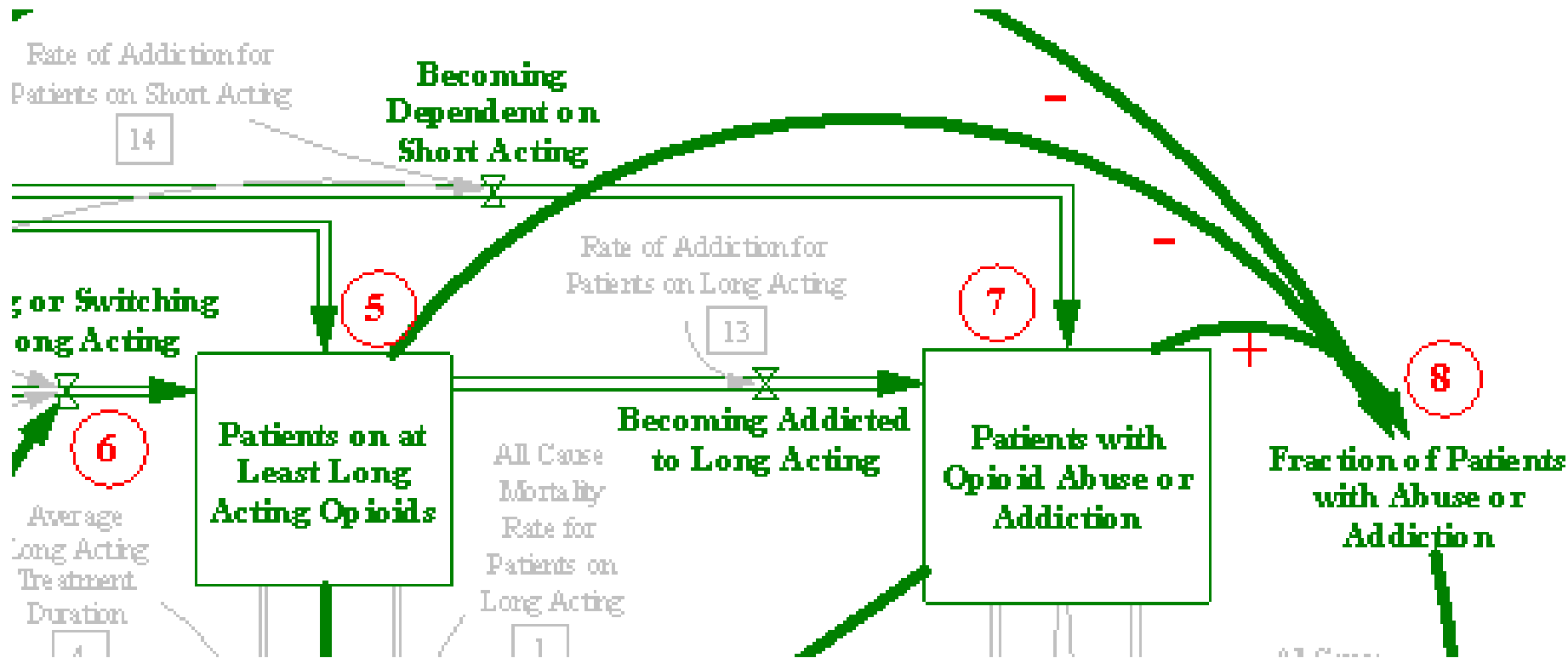
Using pharmacy and diagnostic codes from VA VISN-16 data warehouse for 2000-2005 to identify individuals with at least 91+ days of opioid use in 2002. [N= 15,162; ~5% of all pts]

Excluded individuals with opioid abuse diagnosis in 2000-2002, to ensure that predictors preceded the outcome.

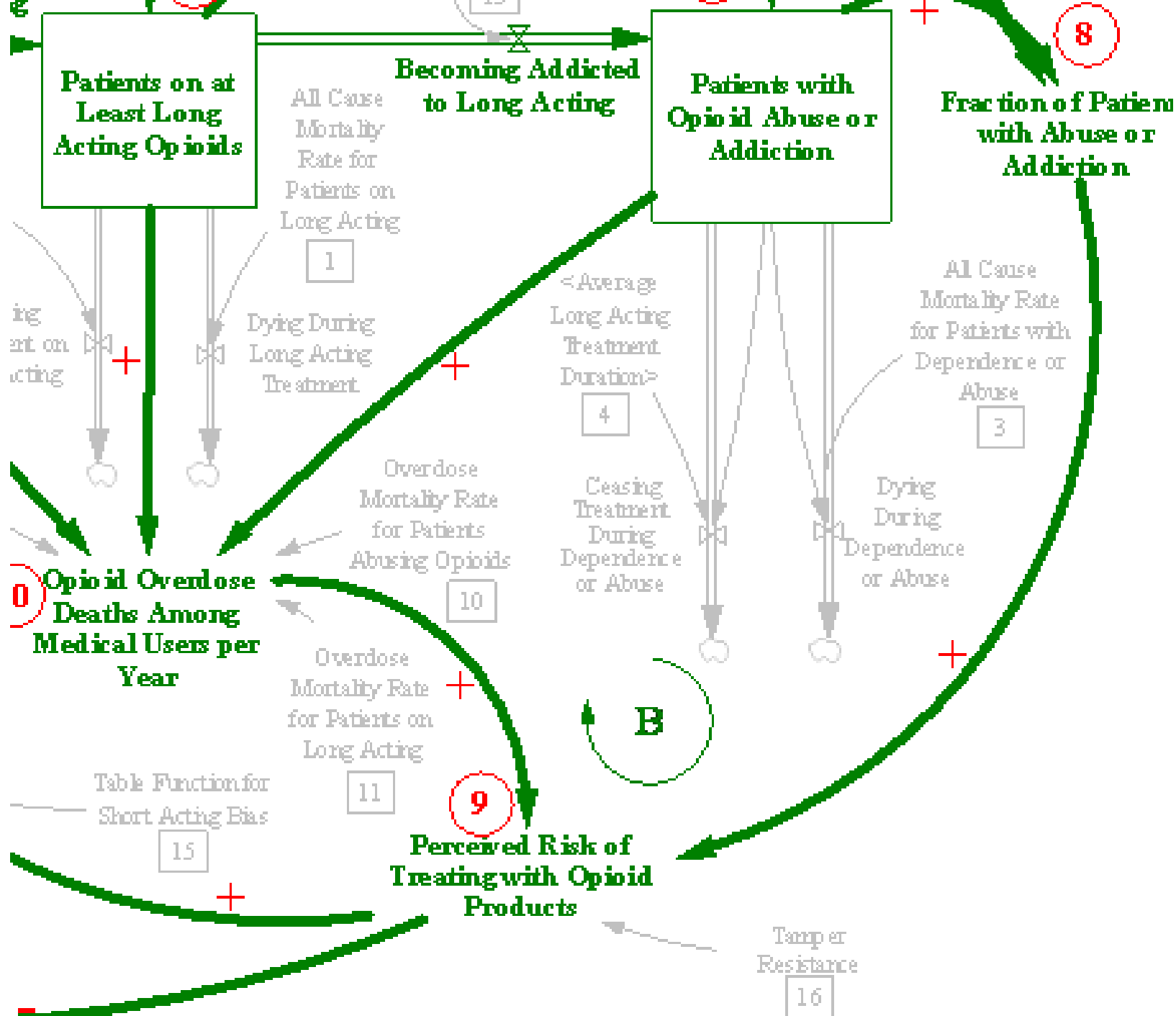
Dependent Variable:

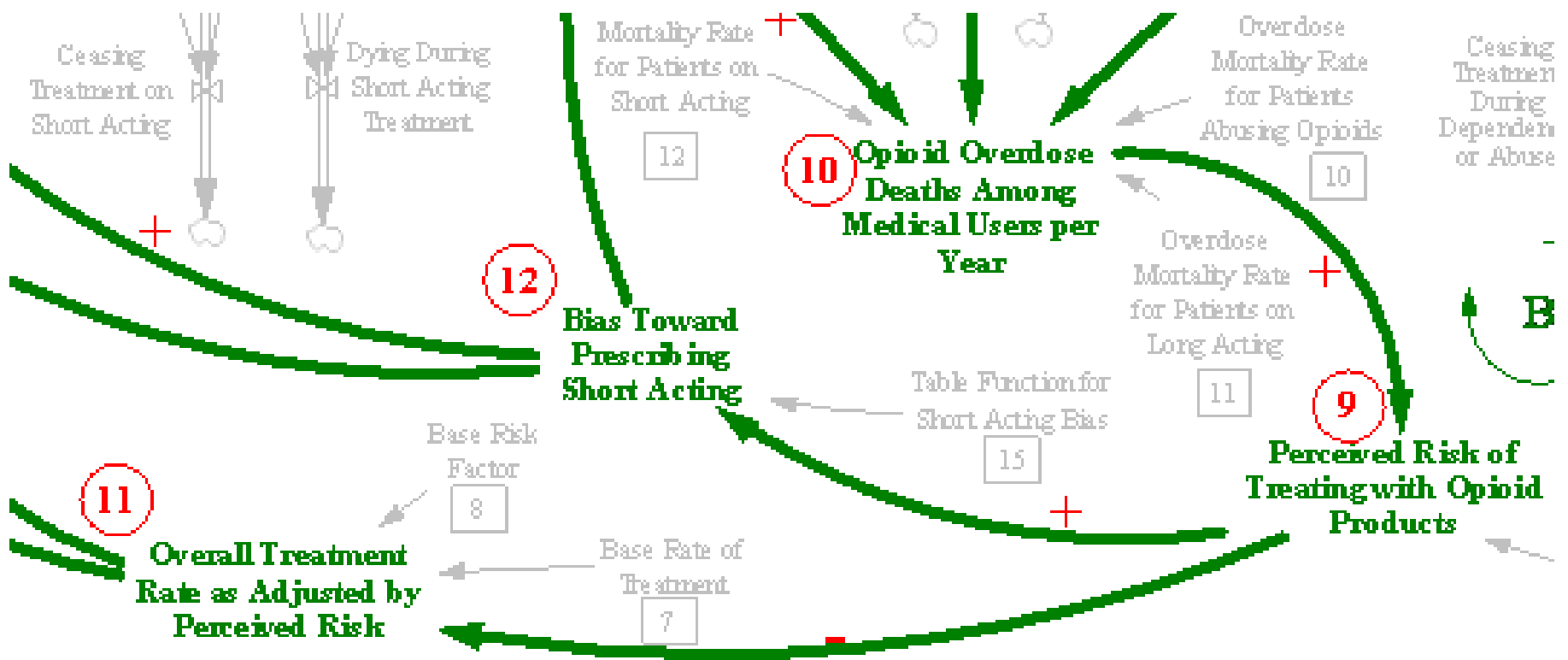
Diagnosis of Opioid Abuse or Dependence in Years 2003-2005. [N=298; ~2% chronic users]

Edlund ME et al. *Pain* In Press

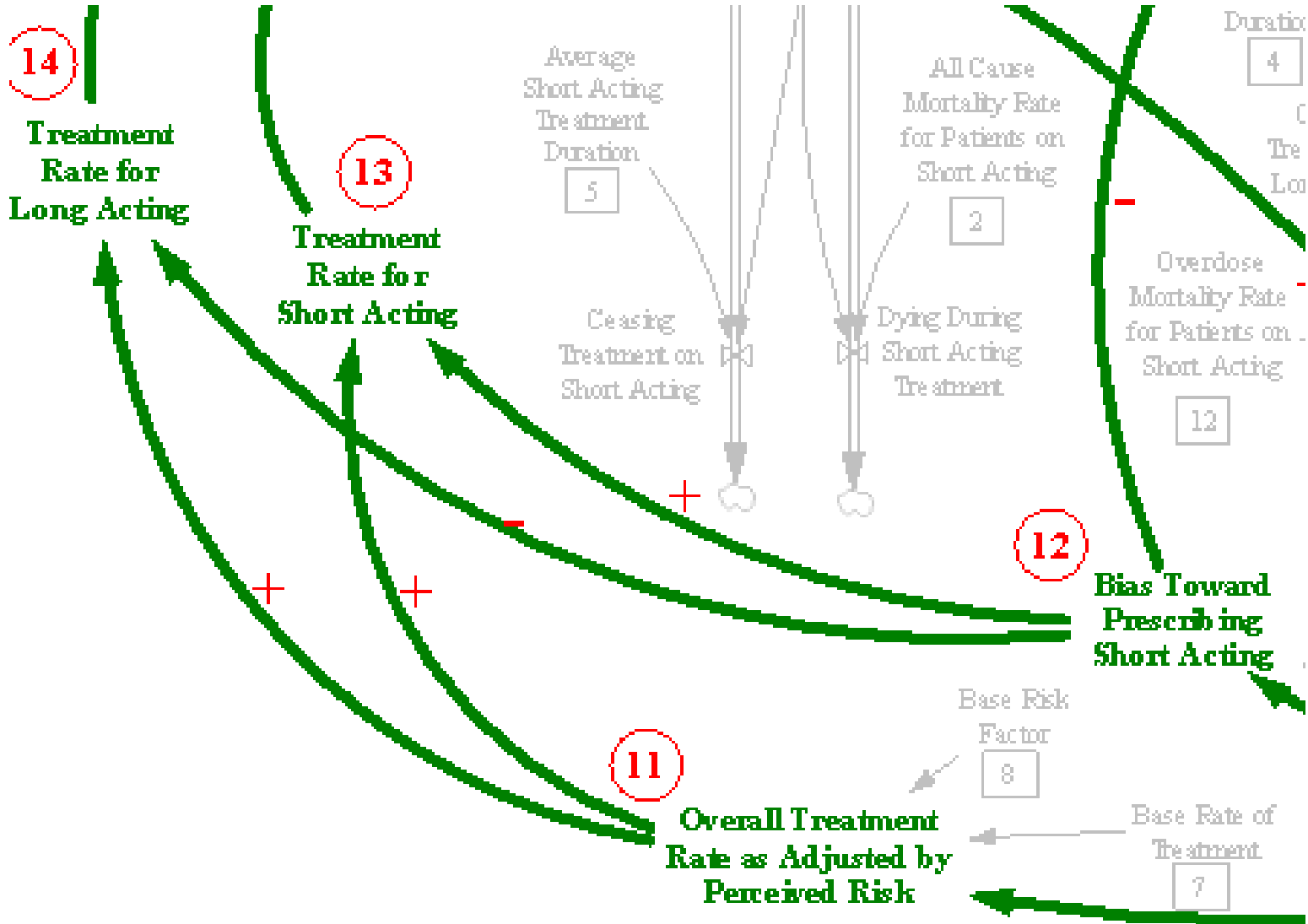


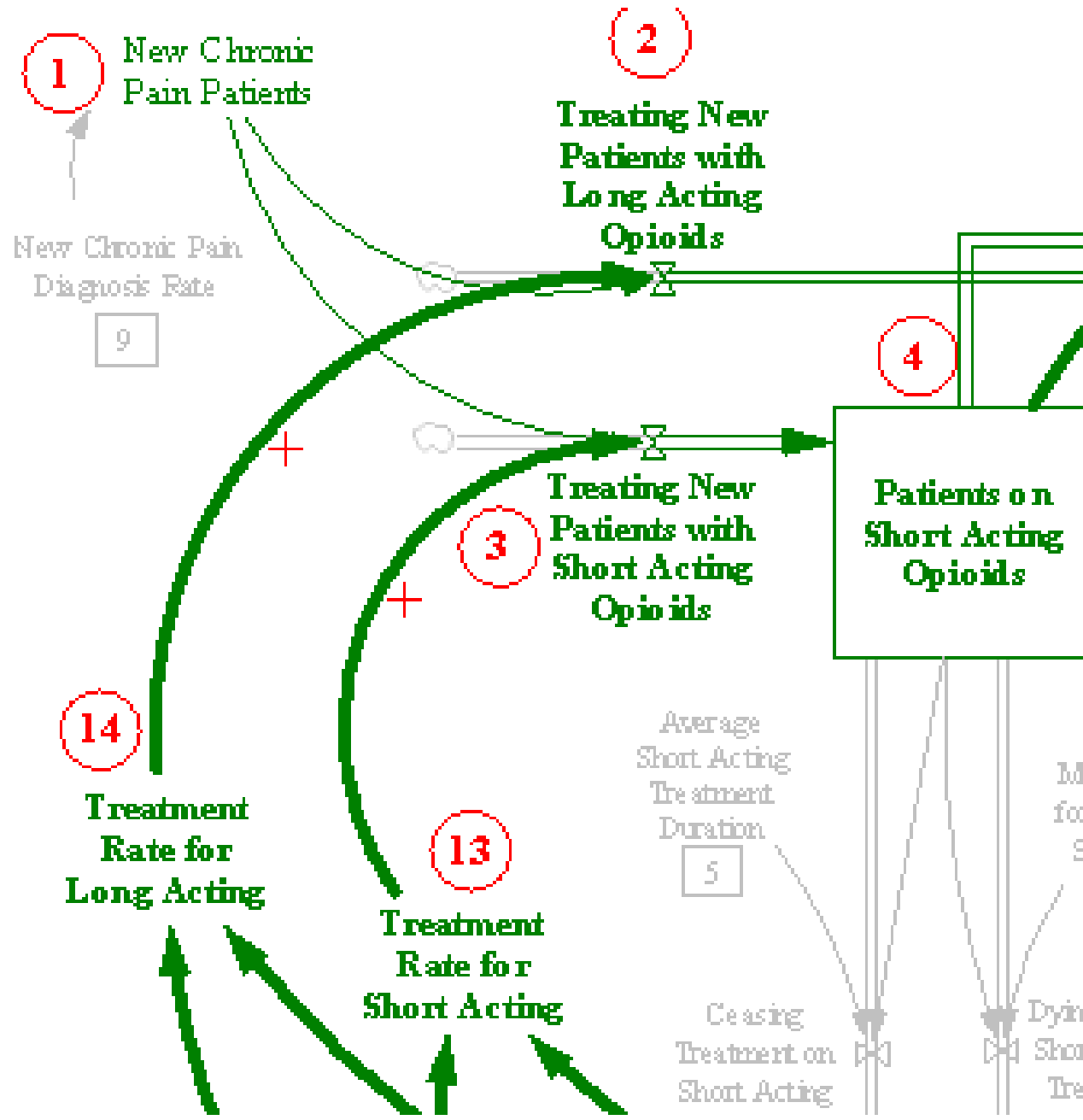
© 2008

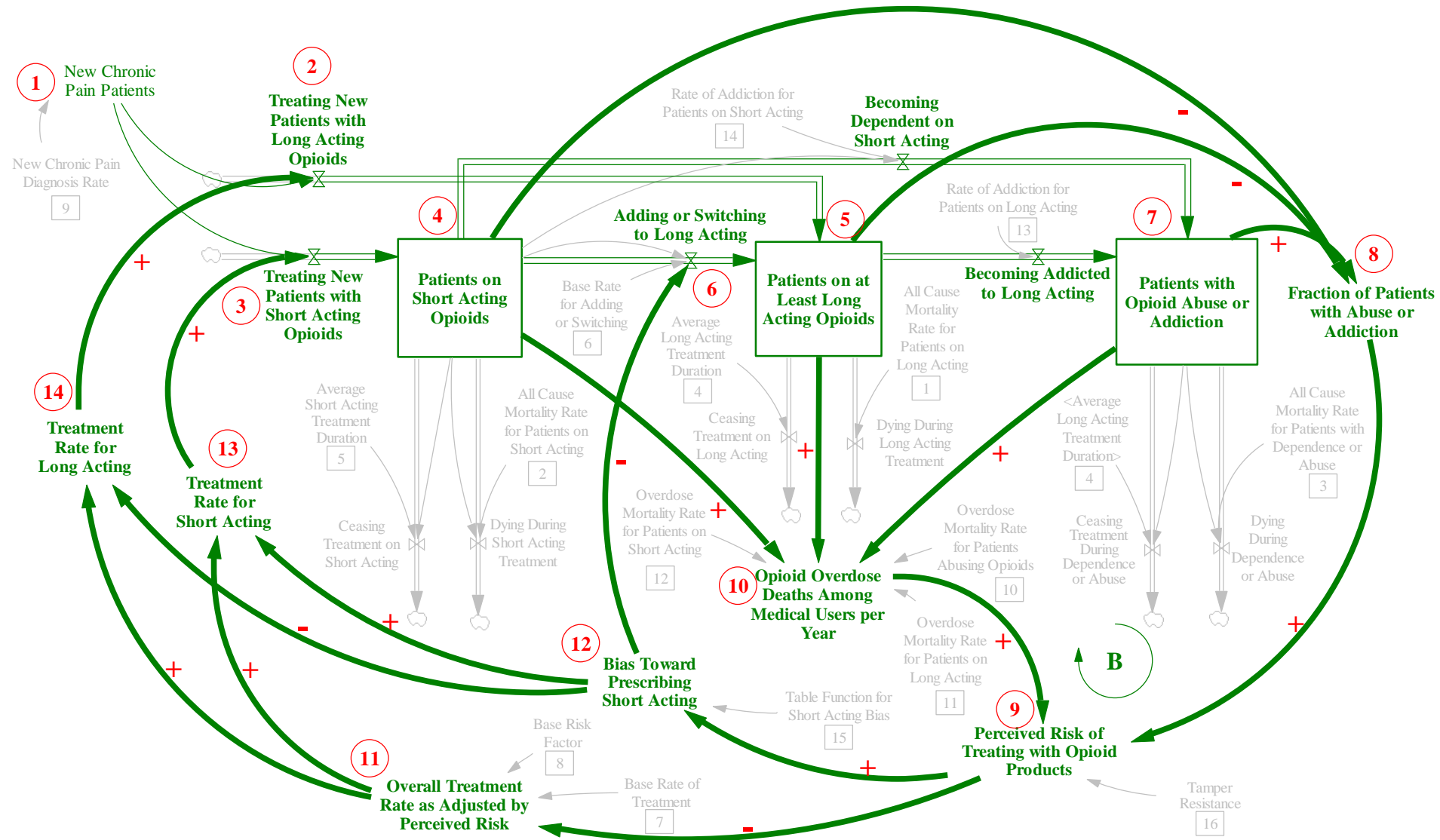




Prescribers concerned about the risk of abuse and addiction and possible regulatory action are likely to prescribe fewer opioids overall (Wolfert et al., 2010) and to more cautiously prescribe long-acting products (Potter et al., 2001)





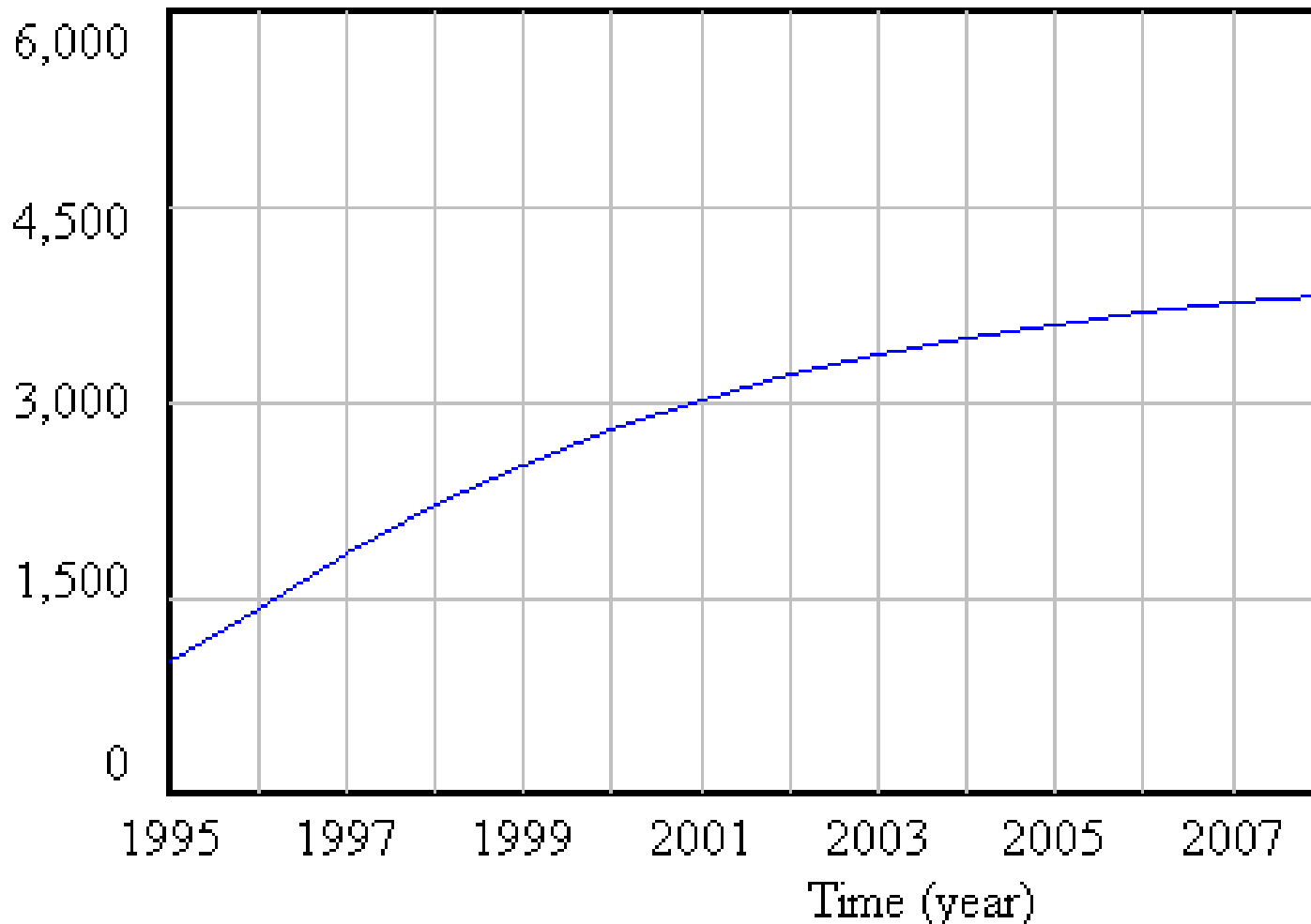


Model Parameters

Parameter	Value	Support
All Cause Mortality Rate for Patients on Long-acting	0.012	Modeling Team Judgment
All Cause Mortality Rate for Patients on Short-acting	0.01	Panel Consensus
All Cause Mortality Rate for Patients with Dependence or Abuse	0.015	Panel Consensus
Average Long-acting Treatment Duration (in years)	7	Panel Consensus
Average Short-acting Treatment Duration (in years)	2	Panel Consensus
Base Rate for Adding or Switching	0.03	Extrapolation from outcome data: Verispan, LLC, SDI Vector One®: National (VONA; see Governale, 2007)
Base Rate of Treatment	0.25	Panel Consensus
Base Risk Factor	1.5	Modeling Team Judgment
New Chronic Pain Diagnosis Rate	0.112	WHO (World Health Organization; see Gureje et al., 2001)
Overdose Mortality Rate for Patients Abusing Opioids	0.0015	Extrapolation from Heroin Research (see Fisher et al., 2004)
Overdose Mortality Rate for Patients on Long-acting	0.0025	CONSORT study (Consortium to Study Opioid Risks and Trends; see Dunn et al., 2010)
Overdose Mortality Rate for Patients on Short-acting	0.00005	CONSORT study (Consortium to Study Opioid Risks and Trends; see Dunn et al., 2010)
Rate of Addiction for Patients on Long-acting	0.05	Meta-Analyses (see Fishbain et al., 2008; Højsted & Sjøgren, 2007)
Rate of Addiction for Patients on Short-acting	0.02	VISN16 data (South Central Veterans Affairs Health Care Network; see Edlund et al., 2007)

Baseline Results

MU Opioid OD deaths per year

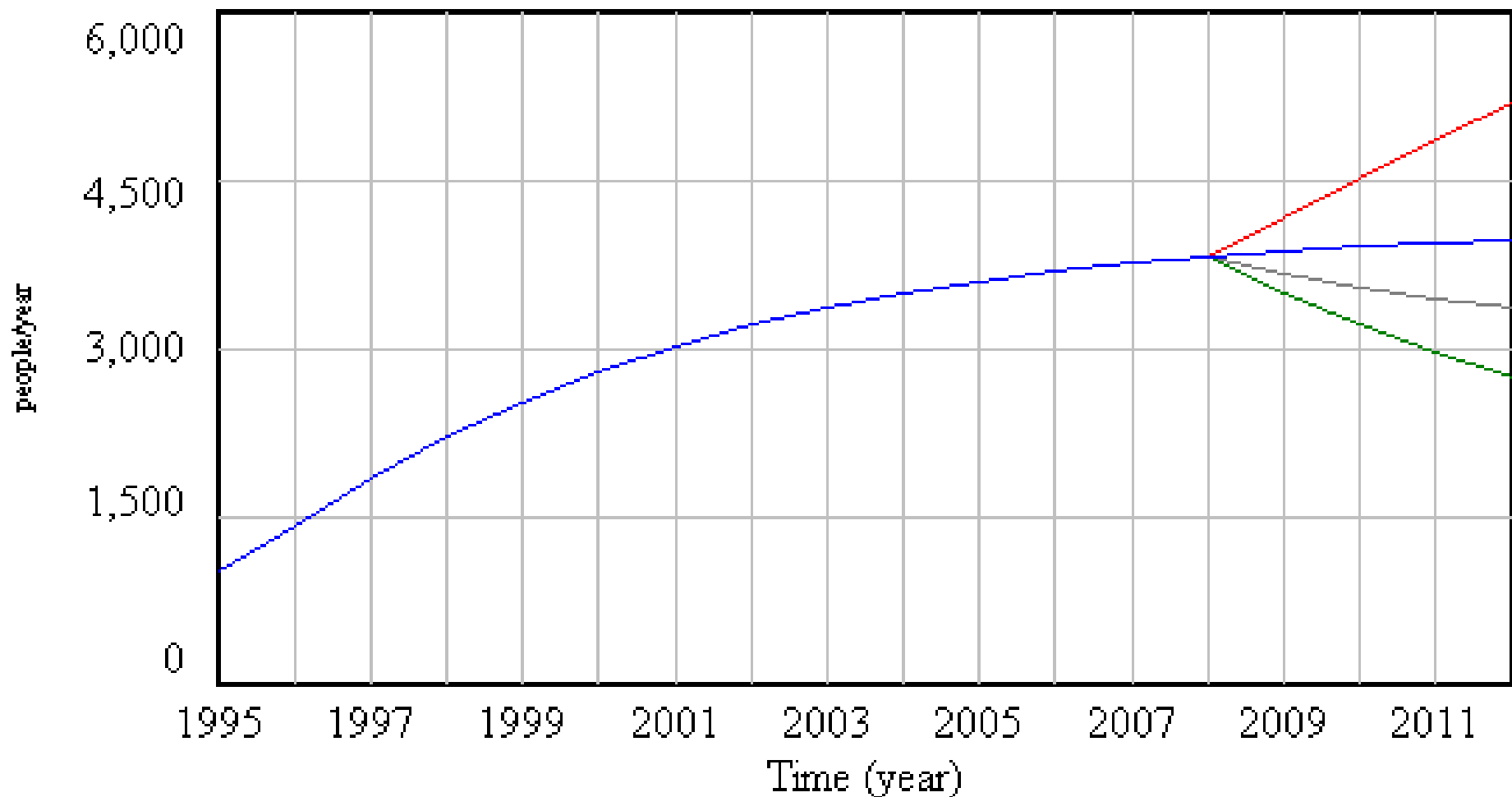


MU Opioid OD deaths per year : baseline

Interventions

1. New highly tamper resistant LA formulation
 - Reduces risk AND risk perception
2. Prescriber education program
 - More cautious prescribing
3. Reduced rate of abuse/addiction
 - But w/o changing prescriber baseline perceived risk

MU Opioid OD deaths per year



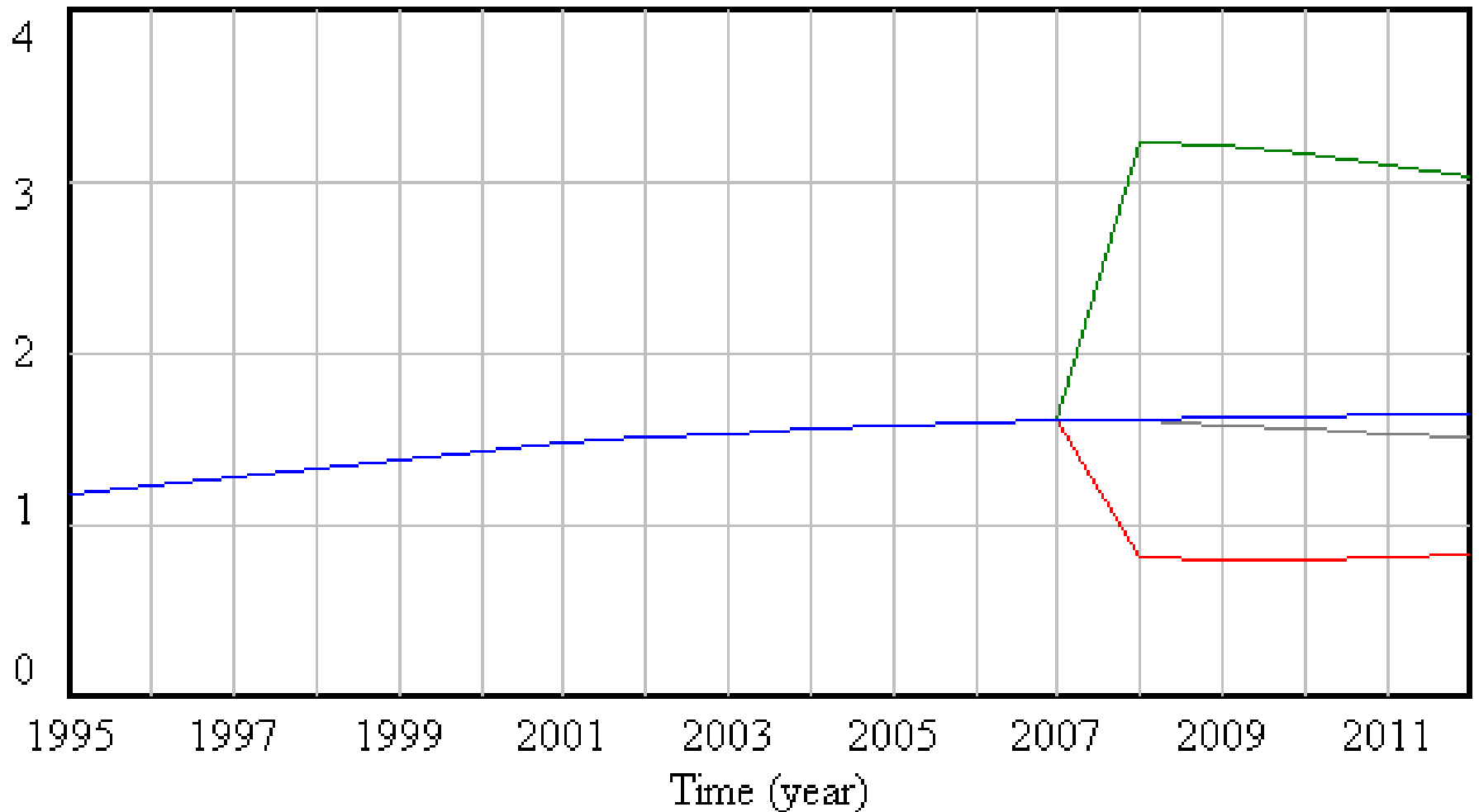
MU Opioid OD deaths per year : baseline

MU Opioid OD deaths per year : tamper_resist_2in2008

MU Opioid OD deaths per year : PhysicianEdImpactonPE_to2in2008andLessDep

MU Opioid OD deaths per year : ReduceOnlyAbuse Potential in2008

Perceived Risk of Opioid Tx



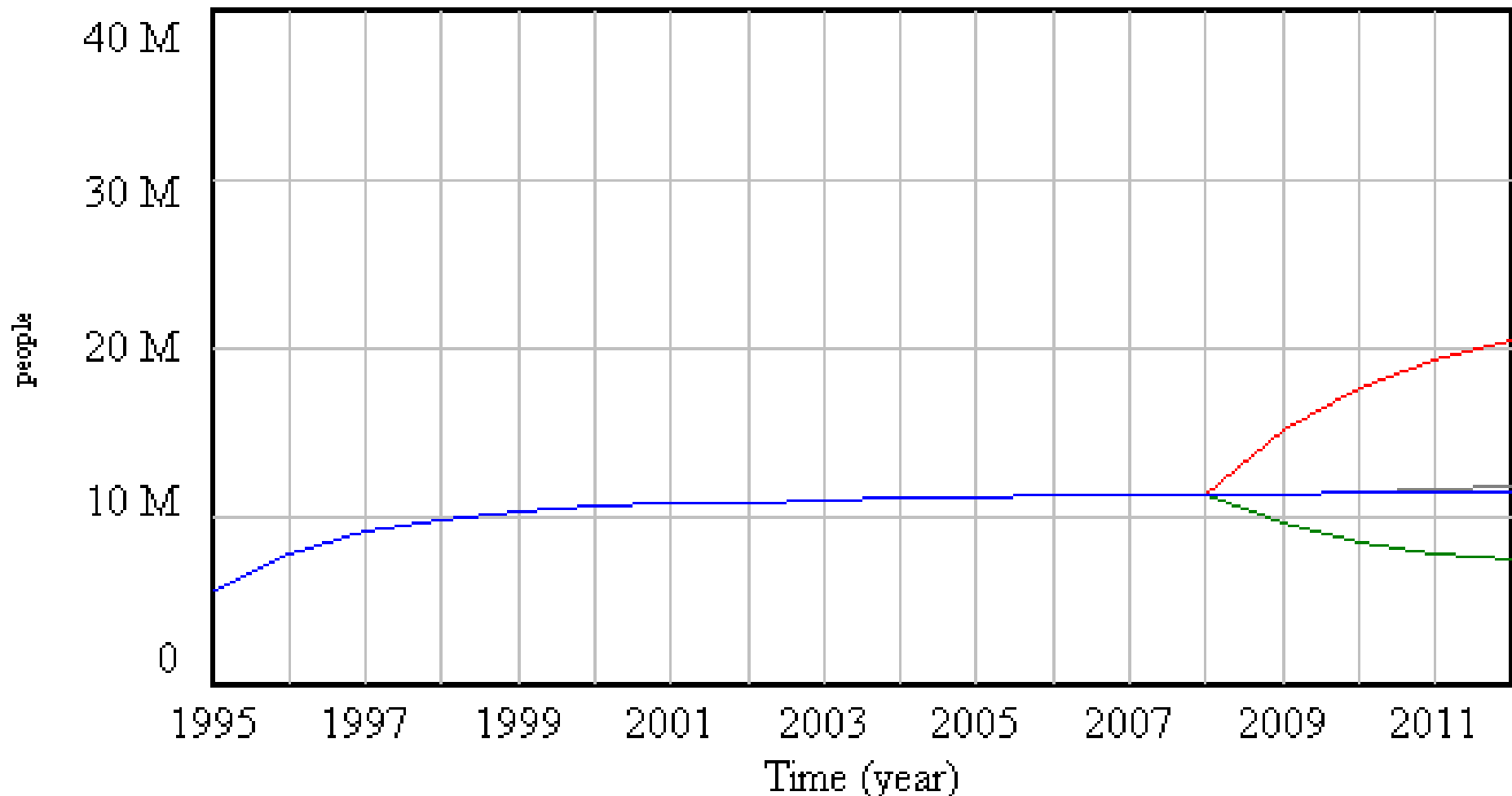
Perceived Risk of Opioid Tx : baseline —————

Perceived Risk of Opioid Tx : tamper_resist_2in2008 —————

Perceived Risk of Opioid Tx : PhysicianEdImpactonPE_to2in2008andLessDep —————

Perceived Risk of Opioid Tx : ReduceOnlyAbusePotentialin2008 —————

TOTAL CP PTS on OpA



TOTAL CP PTS on OpA : baseline

TOTAL CP PTS on OpA : tamper_resist_2m2008

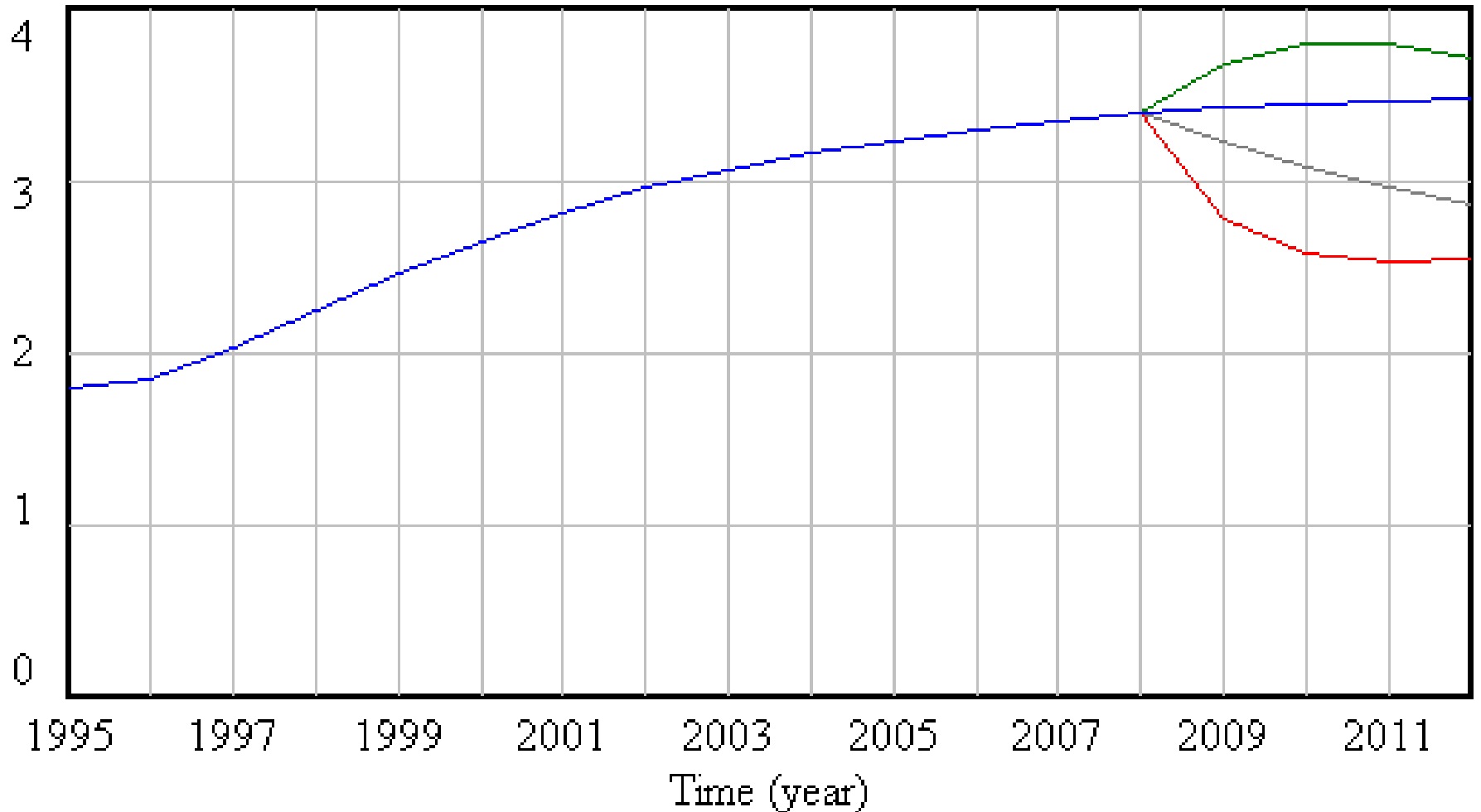
TOTAL CP PTS on OpA : PhysicianEdImpactonPE_to2m2008andLessDep

TOTAL CP PTS on OpA : ReduceOnlyAbuse Potential in2008

An Alternative Metric

- Deaths per 10,000 patients

Deaths per 10000 Pts



Deaths per 10000 Pts : baseline —
Deaths per 10000 Pts : tamper_resist_2in2008 —
Deaths per 10000 Pts : PhysicianEdImpactonPE_to2in2008andLessDep —
Deaths per 10000 Pts : ReduceOnlyAbuse Potential in2008 —

Discussion

- System dynamics modeling has promise
 - Tool for understanding the public health problem of PO-related mortality
 - Tool for evaluating policy options and regulations to address the problem
- May be difficult to minimize negative outcomes without reduced CP patient access to PO treatment
- Important to choose the right metric(s)
- Need to consider multiple metrics

Study Strengths and Weaknesses

- 😊 Systems perspective
- 😊 Empirical support for many parameter values
- 😊 Highlights need to carefully consider metrics
- 😊 Recognizes need for policy makers to make value judgments to balance access to treatment and reducing adverse outcomes
- 😞 Excludes acute pain
- 😞 Assumes all pain patients are legitimate
- 😞 Weak data support for some parameter values
- 😞 Does not consider impacts of poly-drug use
- 😞 Does not consider impact of drug abuse treatment programs
- 😞 Excludes alternative treatments for pain

Questions?

- Comments?
- Suggestions?