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Bradley C. Martin, PharmD, PhD

OPIOID USE TRAJECTORIES

AN ANALYSIS OF OVER 1 MILLION NON-CANCER PATIENTS INITIATING OPIOIDS

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Chronic Pain and Prescription Opioids

- **11% of Americans experience daily (chronic) pain**
- **Opioids frequently prescribed for chronic pain**
- **Primary care providers commonly treat chronic, non-cancer pain**
  - account for ~50% of opioid pain medications dispensed
  - report concern about opioids and insufficient training

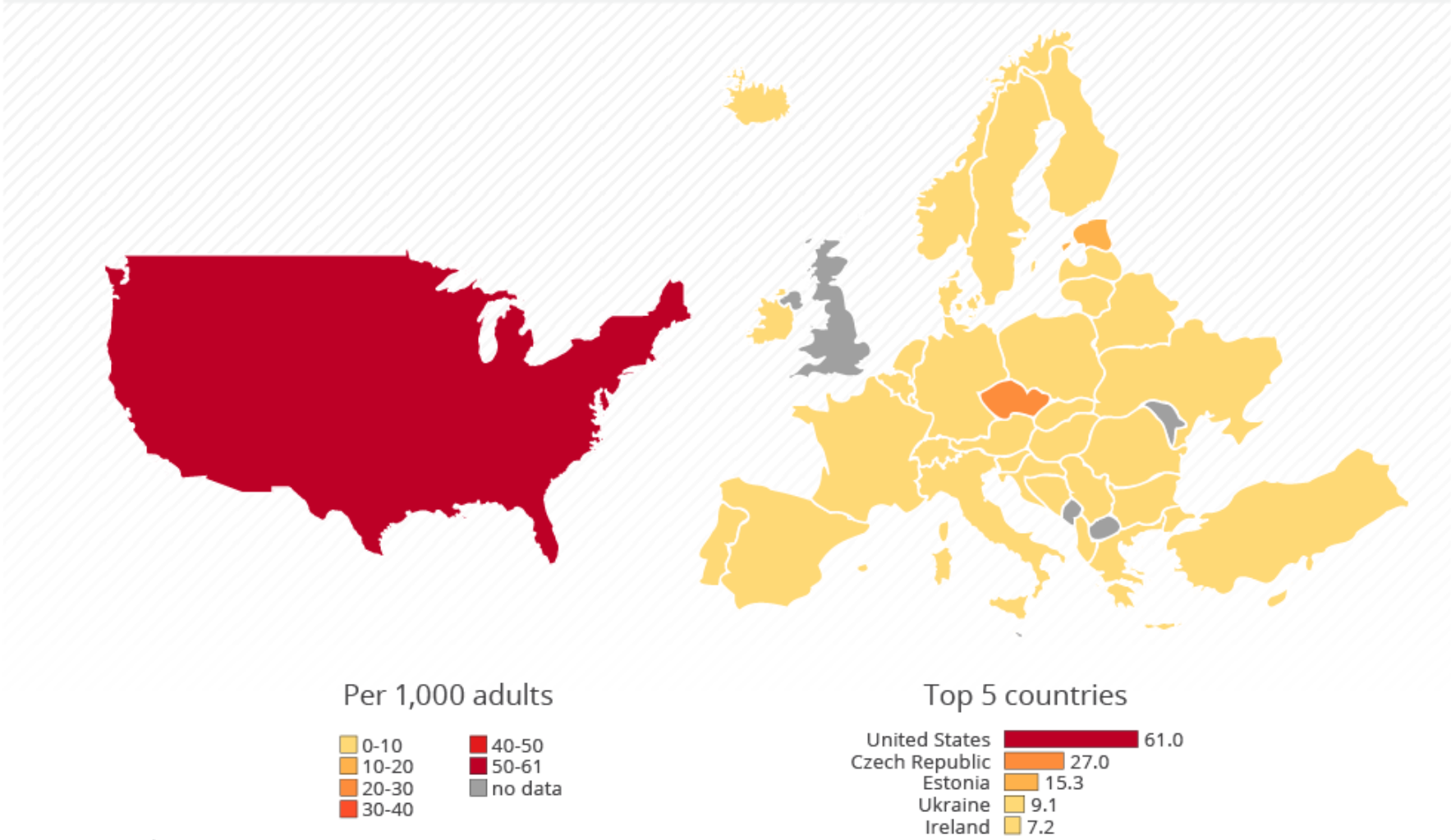
Managing Pain

- American Pain Society
  - 1995 Pain as fifth a vital sign
- Veterans Health Administration / JCAHO
  - Adopted guidance to more aggressively monitor and treat pain 1999-2000
    - 90% of American Pain Society Funding from PhRMA

BUSINESS NEWS | Mon May 15, 2017 | 8:59pm EDT

New York county sues Purdue, J&J over opioid marketing

Prevalence of opioid use at least once during past year



Source: http://data.unodc.org/, 2000–2012

U.S. State Prescribing Rates, 2016

‹ U.S. State Prescribing Rates, 2015

U.S. Prescribing Rate Maps

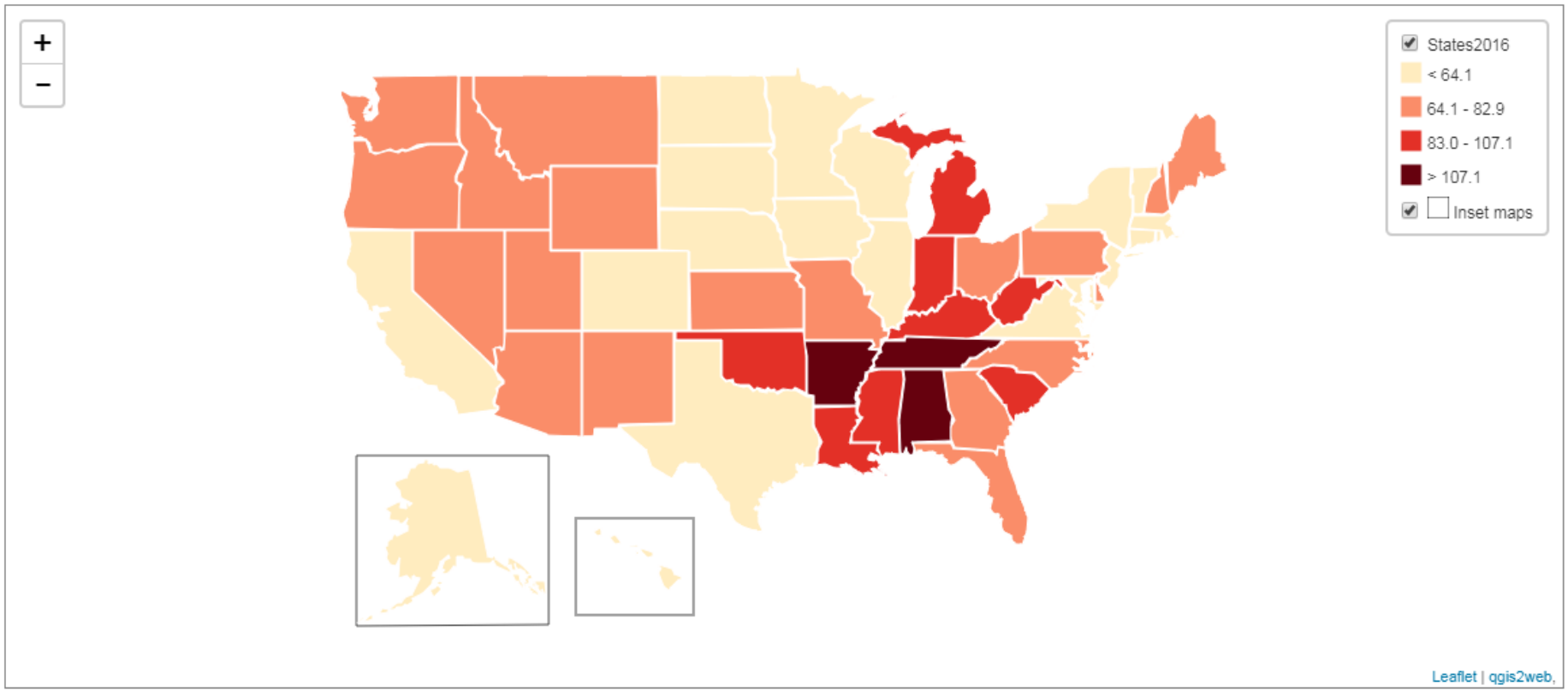
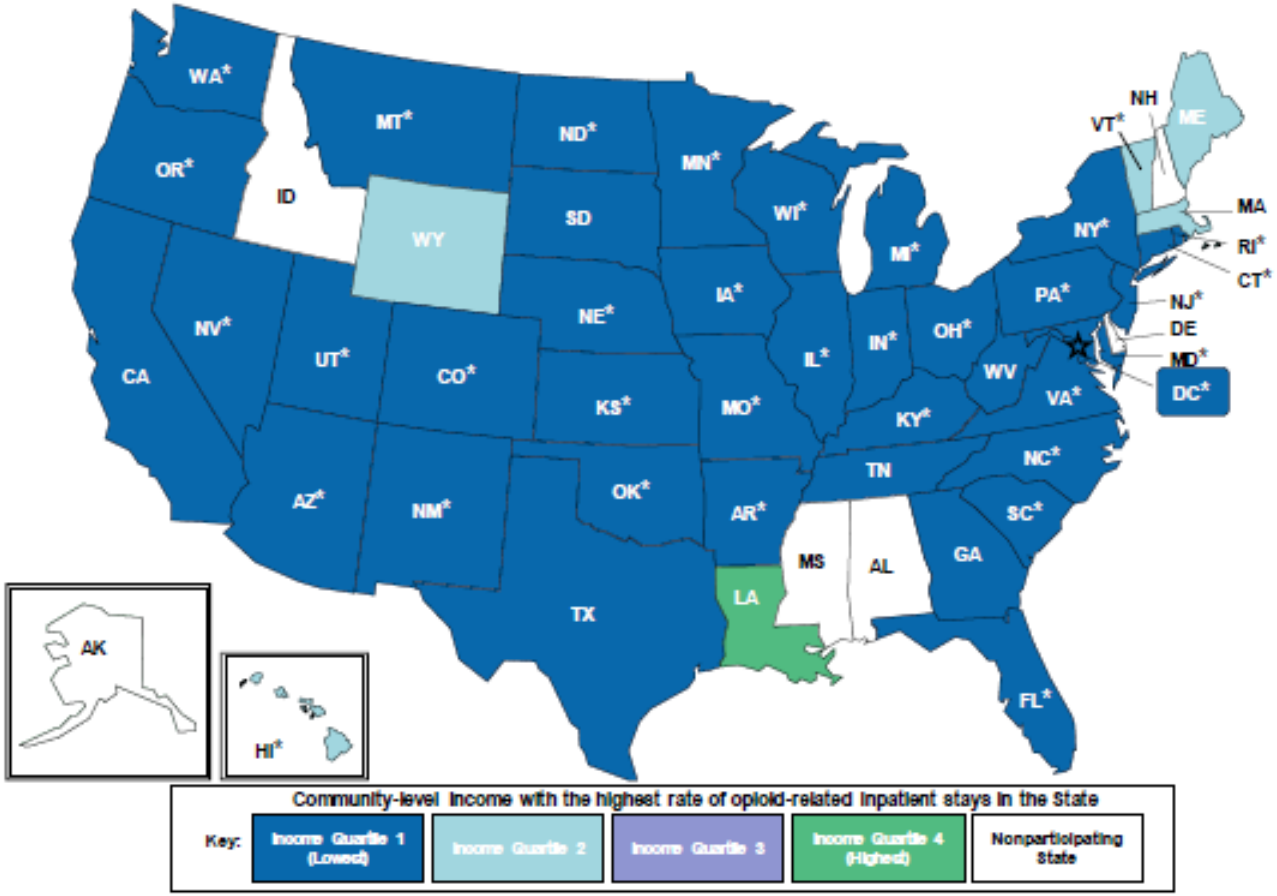


Figure 5. Community-level income with the highest rate[a] of opioid-related inpatient stays, by State, 2014



Note: Asterisks denote States where the difference between the highest and second highest rates in the State was at least 10 percent.

* Opioid-related inpatient rates are per 100,000 population. State-level inpatient rates by community-level income are provided in Appendix A.

Source: Agency for Healthcare Research and Quality (AHRQ), Center for Delivery, Organization, and Markets, Healthcare Cost and Utilization Project (HCUP), HCUP Fast Stats, Opioid-Related Hospital Use (www.hcup-us.ahrq.gov/faststats/landing.jsp) based on the HCUP State Inpatient Databases (SID)

EARLY ASSOCIATION BETWEEN CUMULATIVE OPIOID DOSE AND OPIOID DEATH

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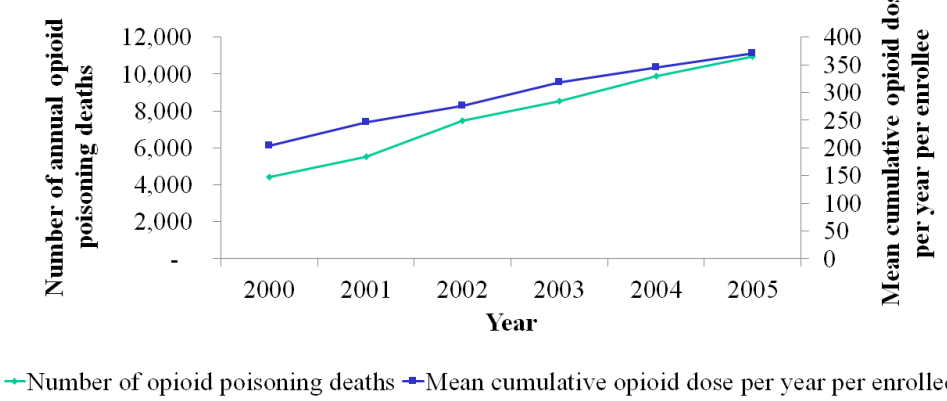
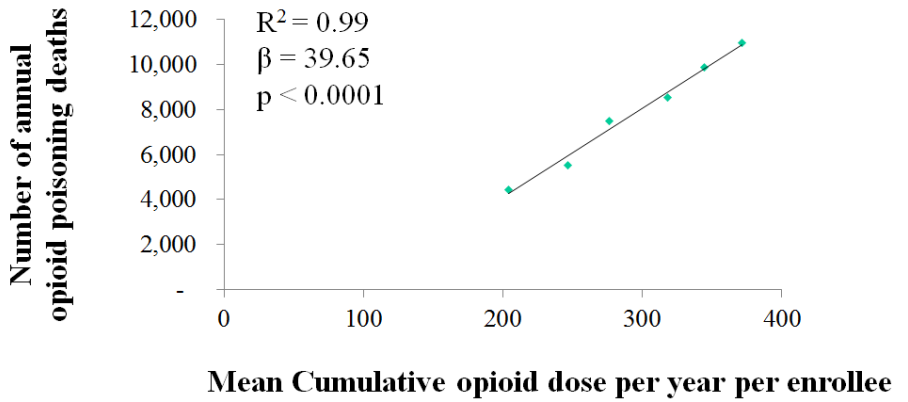
Number Of Opioid Poisoning Deaths and Mean Cumulative Opioid Dose Per Year Per Enrollee Across 2000-2005



OLS Regression Between Mean Cumulative Opioid Dose on the Number Of Annual Opioid Poisoning Deaths



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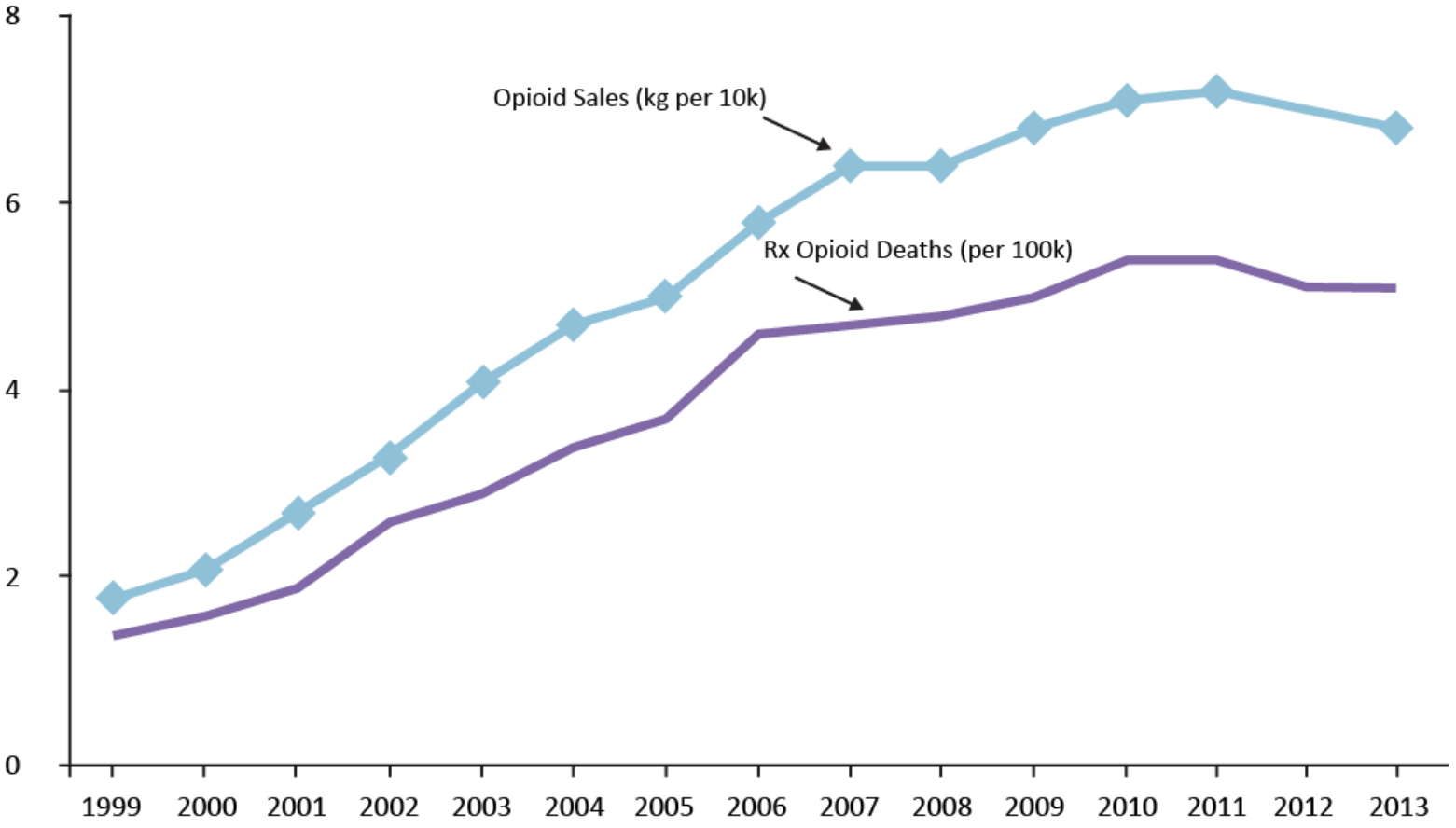
SHARP INCREASE IN OPIOID PRESCRIPTIONS → INCREASE IN DEATHS



National Vital Statistics System, DEA's Automation of Reports and Consolidated Orders System

Population: 197,000

Role of Prescribing Opioids and Overdose Deaths

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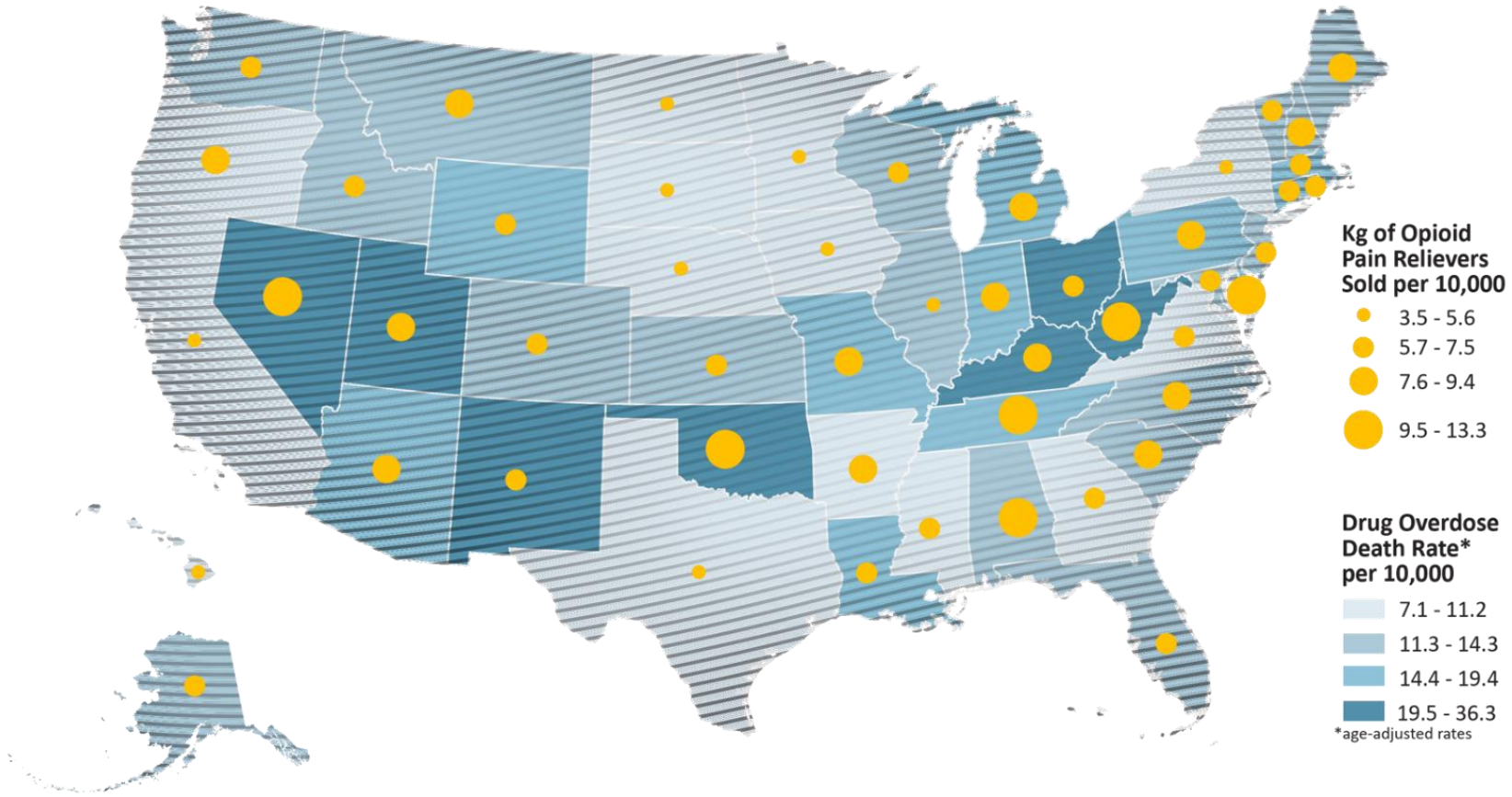

*Death rate, 2013, National Vital Statistics System. Opioid pain reliever sales rate, 2013, DEA's Automation of Reports and Consolidated Orders System

TURN THE TIDE

PRESCRIBING OPIOIDS FOR CHRONIC PAIN

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ADAPTED FROM CDC GUIDELINE

Opioids can provide short-term benefits for moderate to severe pain. Scientific evidence is lacking for the benefits to treat chronic pain.

IN GENERAL, DO NOT PRESCRIBE OPIOIDS AS THE FIRST-LINE TREATMENT FOR CHRONIC PAIN (for adults 18+ with chronic pain > 3 months excluding active cancer, palliative, or end-of-life care).

BEFORE PRESCRIBING

OPIOID SELECTION, DOSAGE, DURATION, FOLLOW-UP, AND DISCONTINUATION

CLINICAL REMINDERS

- Use immediate-release opioids when starting
- Start low and go slow
- When opioids are needed for acute pain, prescribe no more than needed
- Do not prescribe ER/LA opioids for acute pain
- Follow-up and re-evaluate risk of harm; reduce dose or taper and discontinue if needed

4 When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids.

5 When opioids are started, clinicians should prescribe the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when considering increasing dosage to ≥50 morphine milligram equivalents (MME)/day, and should avoid increasing dosage to ≥90 MME/day or carefully justify a decision to titrate dosage to ≥90 MME/day.

6 Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than seven days will rarely be needed.

7 Clinicians should evaluate benefits and harms with patients within 1 to 4 weeks of starting opioid therapy for chronic pain or of dose escalation. Clinicians should evaluate benefits and harms of continued therapy with patients every 3 months or more frequently. If benefits do not outweigh harms of continued opioid therapy, clinicians should optimize other therapies and work with patients to taper opioids to lower dosages or to taper and discontinue opioids.

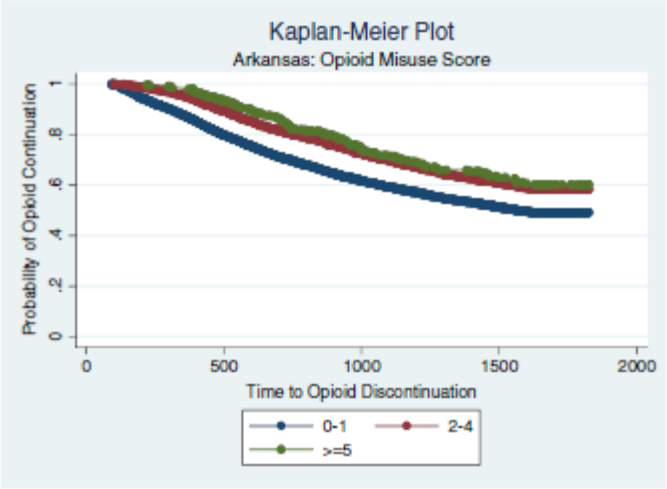
Long-Term Chronic Opioid Therapy Discontinuation Rates from the TROUP Study

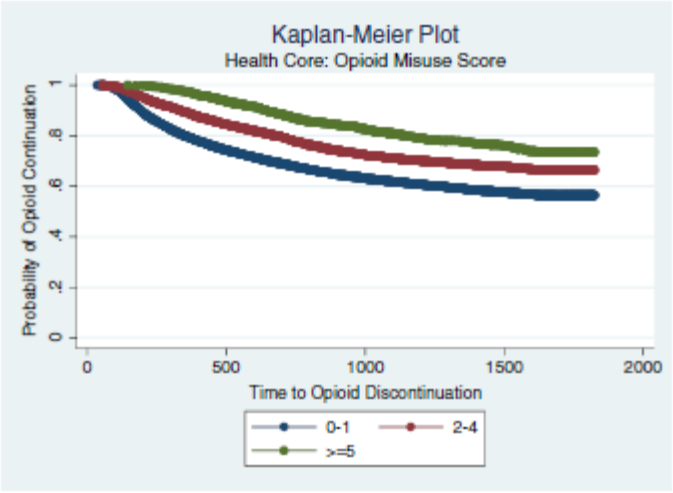
Bradley C. Martin, PharmD, PhD[1], Ming-Yu Fan, PhD[2], Mark J. Edlund, MD, PhD[3], Andrea DeVries, PhD[4], Jennifer Brennan Braden, MD, MPH[2], and Mark D. Sullivan, MD, PhD[2]

[1]College of Pharmacy, Division of Pharmaceutical Evaluation and Policy, University of Arkansas for Medical Sciences, Little Rock, AR, USA; [2]Department of Psychiatry and Behavioral Sciences, Division of Consultation-Liaison Psychiatry, University of Washington, Seattle, WA, USA; [3]Department of Psychiatry and Behavioral Sciences, University of Arkansas for Medical Sciences, Little Rock, AR, USA; [4]HealthCore, Wilmington, DE, USA.

- The study was designed to report chronic opioid therapy discontinuation rates after five years and identify factors associated with discontinuation.
  - Commercially insured population (HealthCore plans)
  - Publicly Insured population (Arkansas Medicaid).

Days until opioid discontinuation by misuse score for Arkansas Medicaid and HealthCore, 2001-2005





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CDC A-Z INDEX

Morbidity and Mortality Weekly Report (*MMWR*)

CDC > MMWR

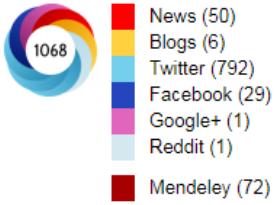
Characteristics of Initial Prescription Episodes and Likelihood of Long-Term Opioid Use — United States, 2006–2015

Weekly / March 17, 2017 / 66(10);265–269

Format: Select One

Anuj Shah[1]; Corey J. Hayes, PharmD[1,2]; Bradley C. Martin, PharmD, PhD[1] (View author affiliations)

View suggested citation



Study Aims

- Identify opioid prescribing characteristics prognostic for long term opioid use.

  - Specifically, we determined the probability of continued opioid use at one and three years by:
    - duration of therapy
    - number of prescriptions
    - cumulative dose
    - days' supply of the first prescription
    - choice of first opioid prescription

Data, Subjects, Key Study Measures

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- Data: IMS Lifelink+ database for 2006-2015
- Subjects: Opioid naïve, cancer and substance abuse free patients
- Study Measures:
  - Opioid Discontinuation at 1 and 3 years
  - Opioid Prescription Characteristics
    - Initial Days of Opioid Use
    - Number of opioid prescriptions
    - Cumulative dose
    - Type of opioid
    - Initial Days Supply of Opioid

Subjects

Total = 1,294,247	N / Mean (% / s.d.)
Age	44.52 (14.56)
Gender	
Females	698950 (54.00)
Enrollment duration (years)	2.48 (2.04)
Pain Diagnoses	
Back Pain	226681 (17.51)
Neck Pain	90352 (6.98)
Head Pain	30123 (2.33)
Joint Pain	389700 (30.11)
Patient Region	
South	476565 (36.74)
Midwest	376520 (29.09)
East	279595 (21.60)
West	142698 (11.03)
Missing/Other	19869 (1.54)
Payer Type	
Commercial	866815 (66.97)
Self-Insured	387122 (29.91)
Other / Unknown	40310 (3.11)
Opioid Episode Characteristics	
First Prescription >= 90 MEQ	89438 (6.91)
First Prescription >= 120 MEQ	22895 (1.77)
First Prescription of Long Acting Opioid	6588 (0.51)
Duration of first episode	14.81 (65.00)

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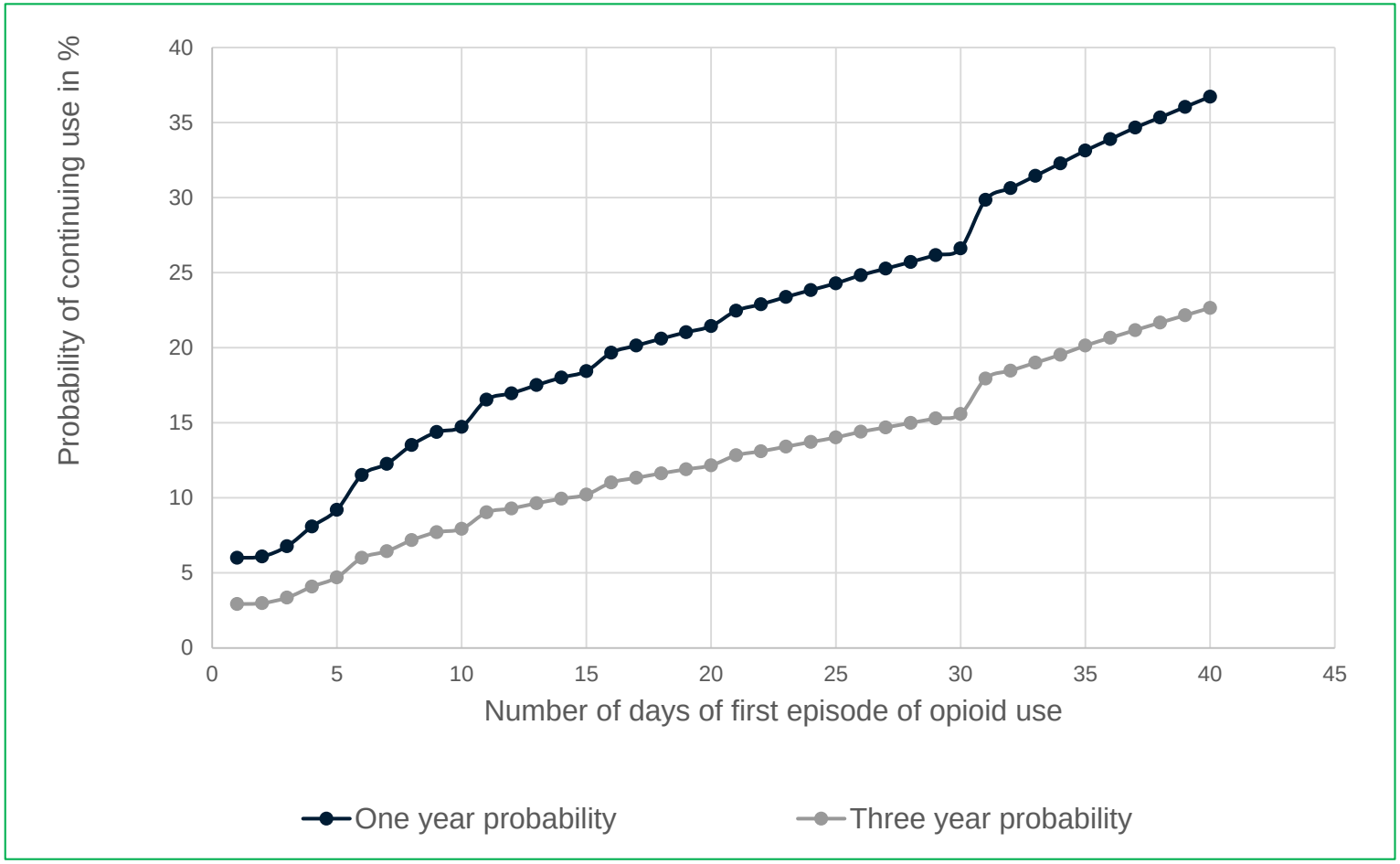
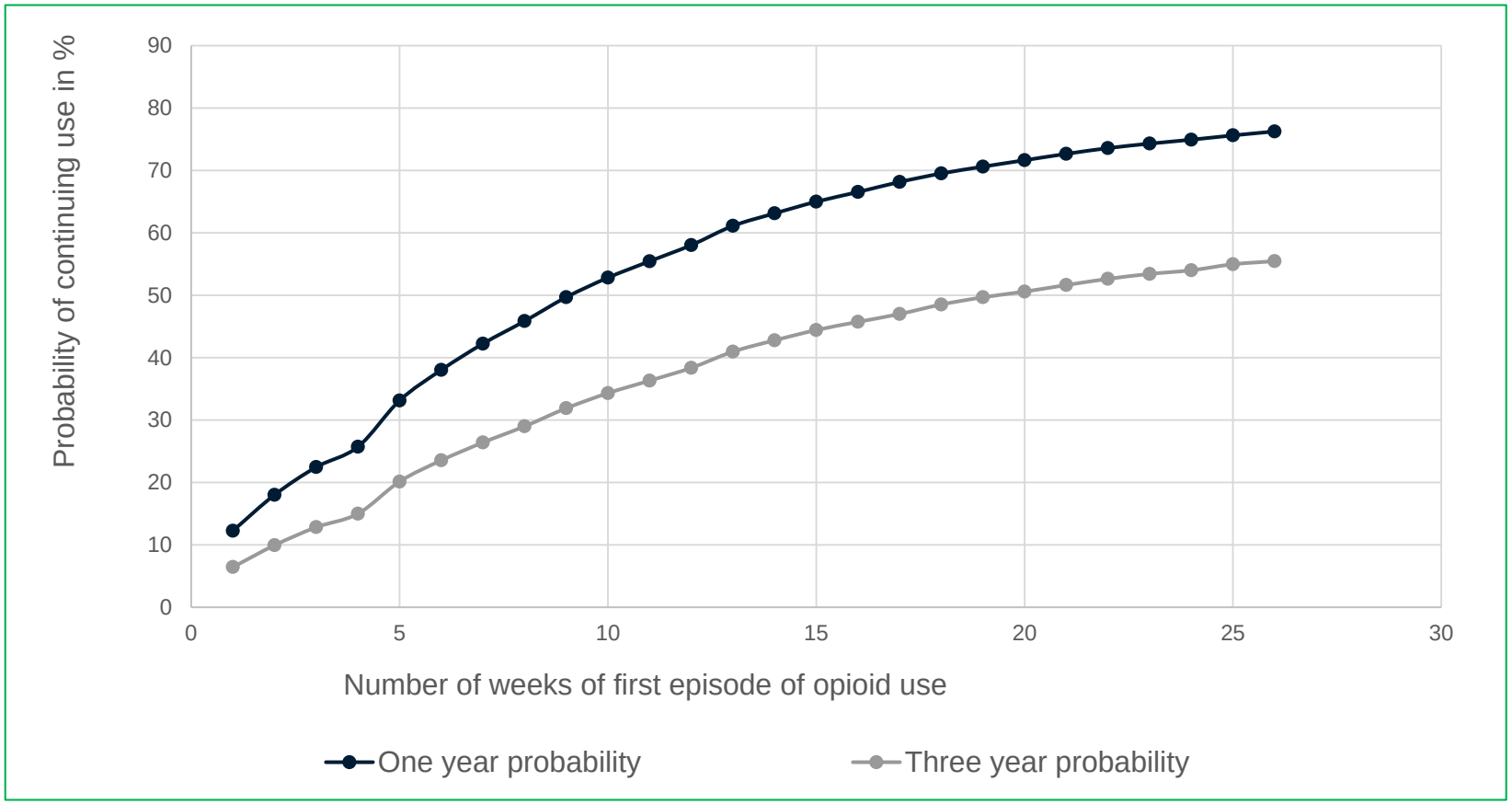
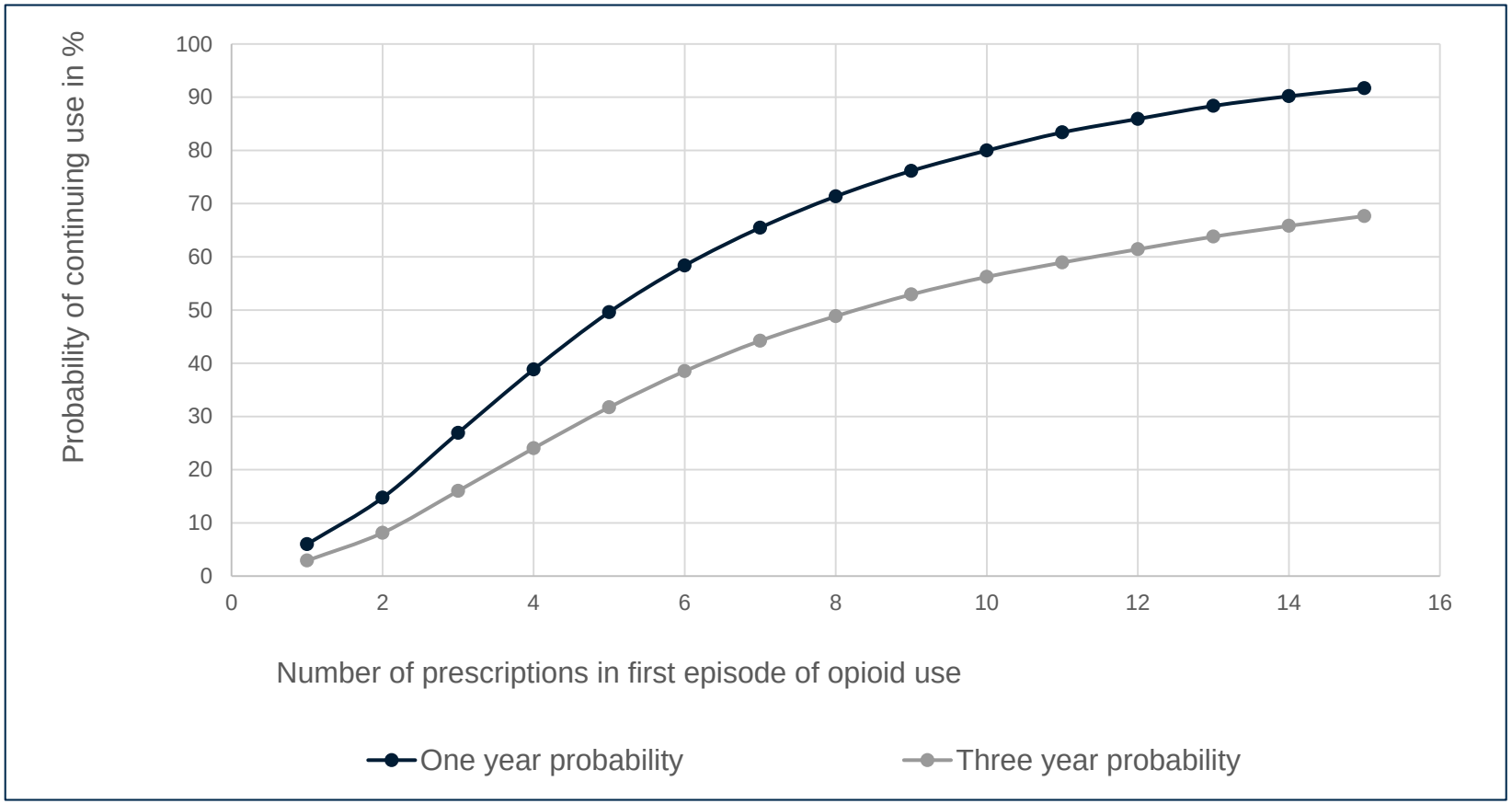
Continued Use by Initial Days of Therapy (n=1,294,247)



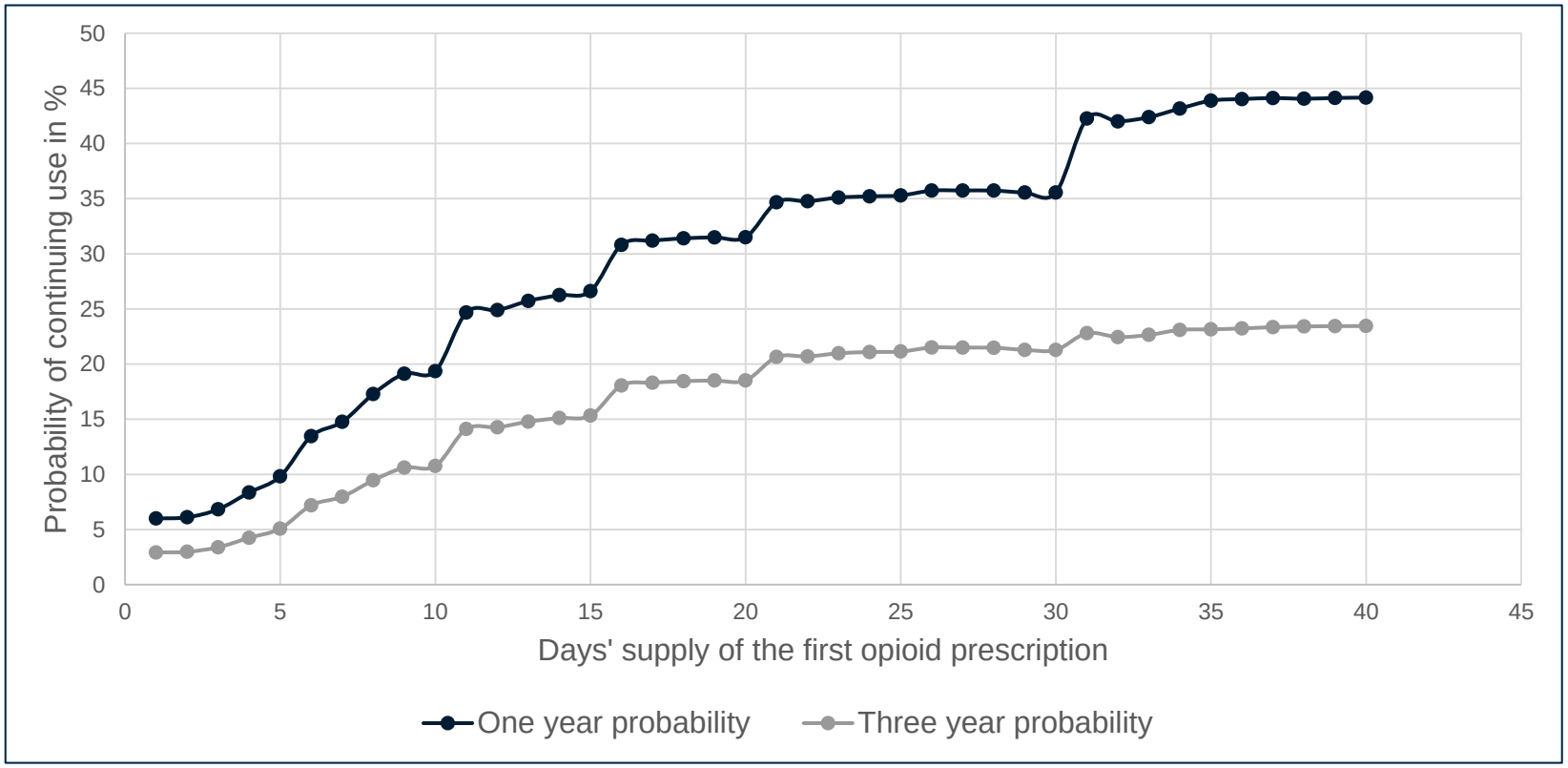
Continued Use by Initial Weeks of Therapy



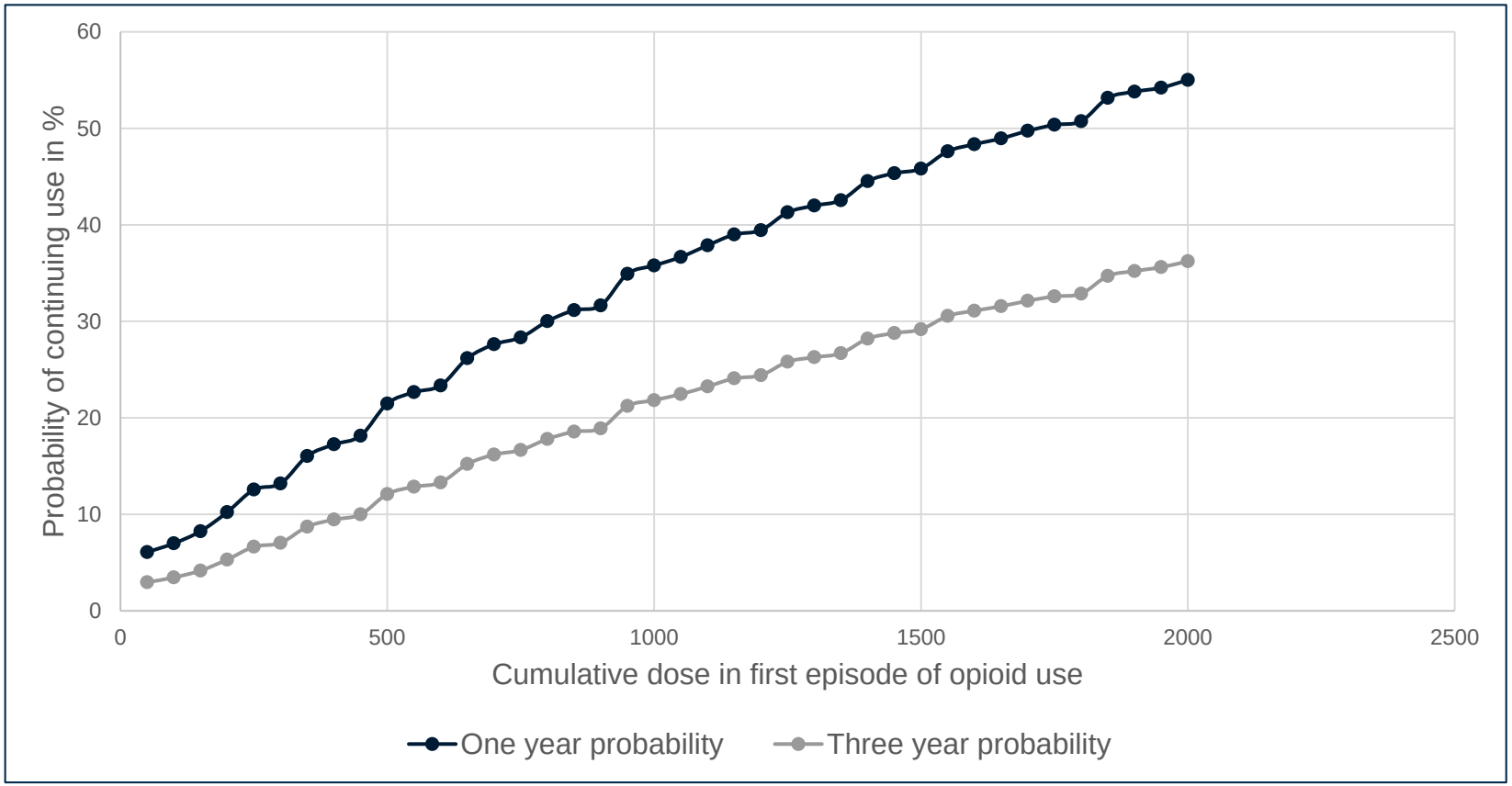
Continued Use by Number of Prescriptions



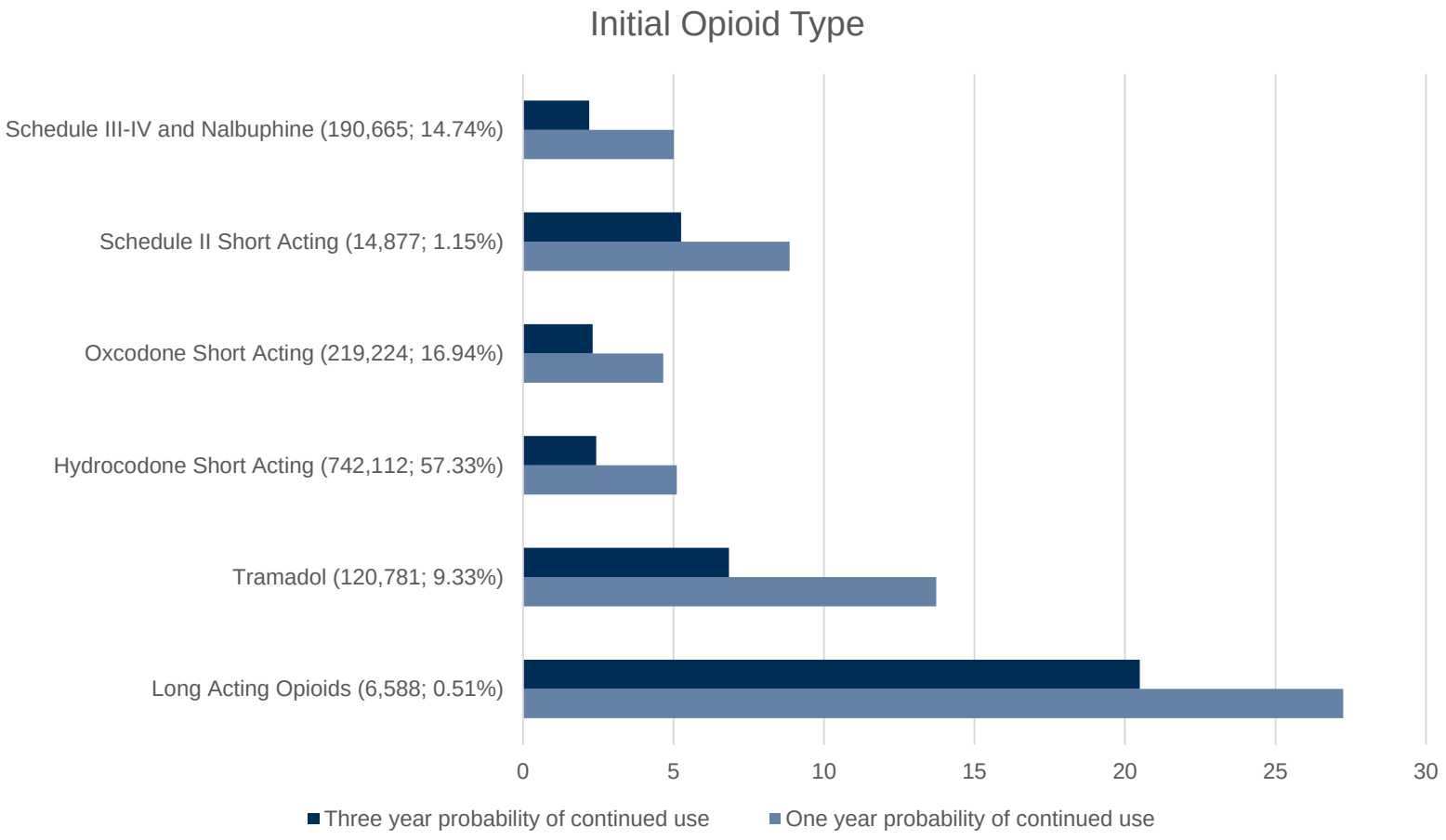
Continued Use by Days Supplied of First Prescription



Continued Use by Cumulative Dose (MEQ) of First Episode



Continued Use by Initial Opioid Type



Thoughts

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- Each additional day of opioid therapy increases the risk of chronic opioid use starting with the 3rd day
  - 1 or more days 6.00%
  - 8 or more days 13.52%
  - 31 or more days 29.85%
- No clear thresholds based on weeks of initial opioid use or cumulative dose
- Tramadol appears to be used sometimes when clinicians are thinking of a long term analgesic strategy
- Opioids for 13 weeks have high probabilities of long term use (61.11%) and nearly constant after that.

Limitations

- Data do not capture pain intensity or duration
- Did not account for the etiology of pain
  - Acute (post-op, trauma) or chronic pain conditions
- Unable to account for opioids that were paid for out of pocket or obtained illicitly
- Unable to separate intentional and un-intentional long term chronic opioid use

ELSEVIER

The Journal of Pain

Available online 13 July 2017

In Press, Corrected Proof

Original Report

Factors Influencing Long-Term Opioid Use Among Opioid Naive Patients: An Examination of Initial Prescription Characteristics and Pain Etiologies

Anuj Shah *, Corey J. Hayes *, †, Bradley C. Martin *

⊞ Show more

https://doi.org/10.1016/j.jpain.2017.06.010

- Explore the association between characteristics of the first opioid prescription, patient level factors and the pain etiology on the probability of opioid discontinuation among opioid naïve patients

Data and Subjects

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- IMS Lifelink+ database for 2006-2015
  - 10% random sample (approximately 6.5M lives)

- Opioid naïve, cancer and substance abuse free patients
  - at least one OPR prescription between June 06 and Dec 14
  - at least 6 months of continuous enrollment without an opioid prescription prior to first opioid prescription
  - at least **14** years of age
  - Excluded:
    - any non-melanoma cancer, substance abuse diagnosis or buprenorphine/naloxone prescription in the 6 month prior period
    - **Missing data on demographics (gender, region, age, payer)**

Study Measures

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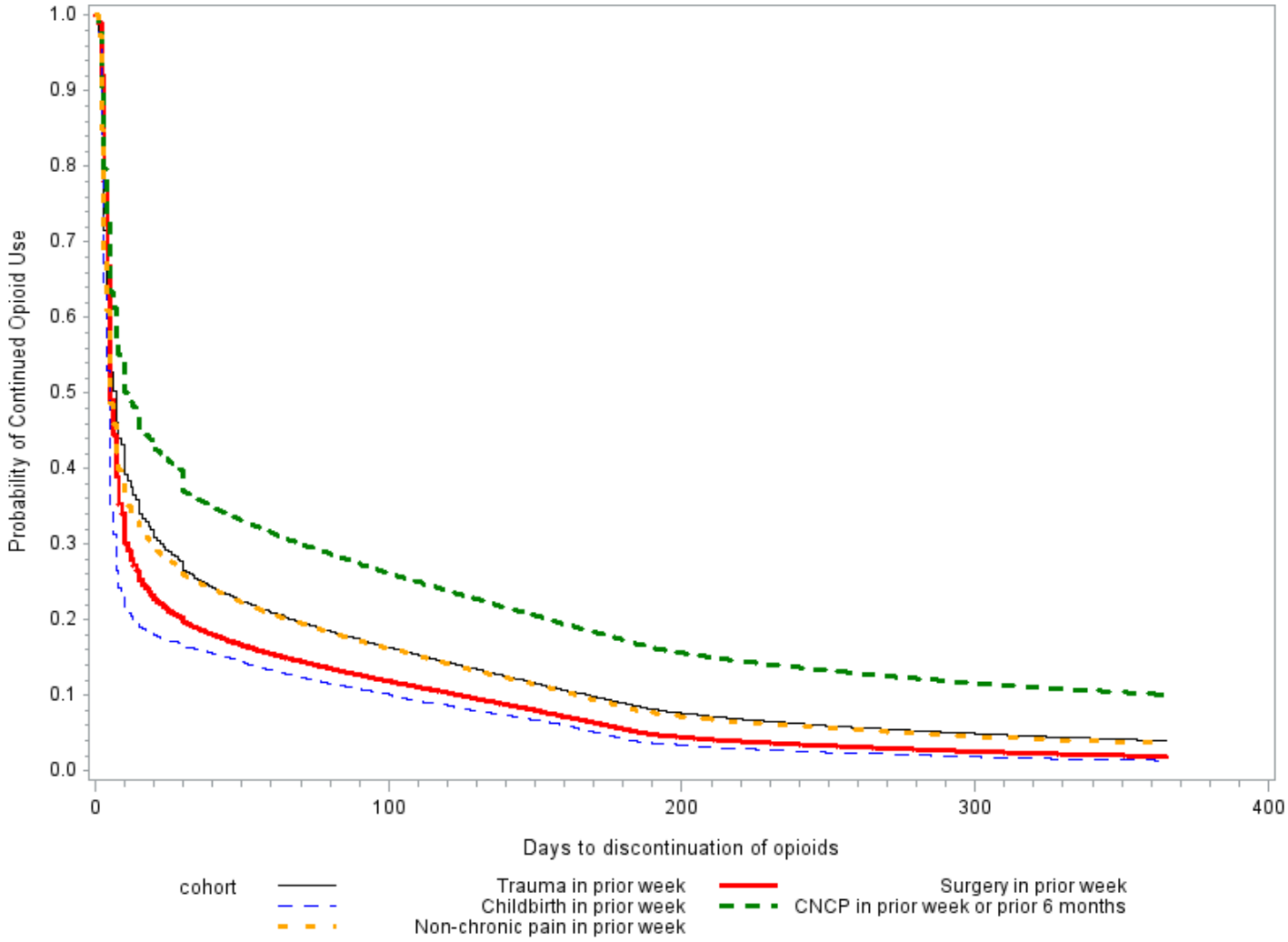
- Opioid Discontinuation
- Initial Opioid Episode
  - Days supply of first prescription, average daily dose, opioid type
- Pain etiology
  - (a)Trauma and Surgery (b)Trauma (c)Surgery (d)Burn (e)Childbirth (f)Dental procedure (g)Chronic pain conditions (headache, back/neck pain, joint pain, neuropathic pain, fibromyalgia) (h)Other pain conditions (chest pain, abdominal pain, others) (i)Other inpatient admission (j)Other Emergency Department visit (k)Unknown
- Patient and System Characteristics
  - Age, Gender, Region, Year, Insurance Type (Medicaid, Medicare, Commercial), Mental Health (mood, personality, adjustment, anxiety), Prior Benzodiazepine / Muscle Relaxant.

Subject Characteristics
n=1,353,902

- Over half were women and over a quarter were 31-44 years old
- A quarter had chronic pain
- A quarter had surgery and or trauma
- Could not determine pain etiology for 1/3rd of sample
- Hydrocodone most frequently prescribed opioid initially
  - Long acting least frequently prescribed
- About ½ the sample had an initial opioid for 4 days or less

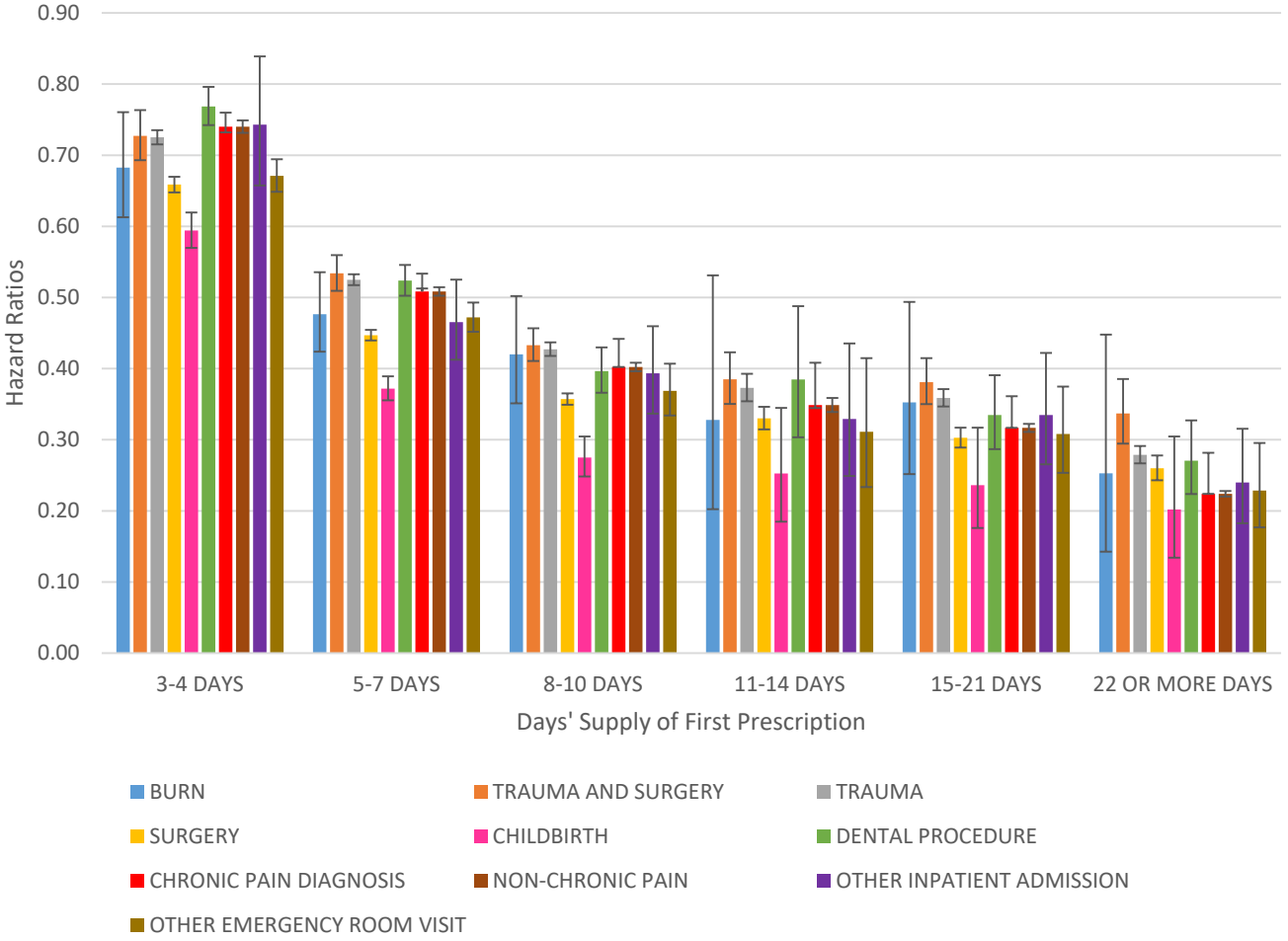
Time to Opioid Discontinuation by Pain Etiology



Longer Opioid Use is Associated with:

- Modest Associations (0.8 < HR <1.0)
  - Women, Elderly, Living in South or West, All Mental Health Disorders Studied, Pain types **except** chronic pain, childbirth, and surgery, Benzodiazepine and Muscle Relaxant Use, High Daily Dose, Use of Oxycodone, Hydrocodone, Tramadol Short Acting Schedule II
- Moderate Associations (0.6 < HR < 0.8)
  - Medicaid, Long Acting Opioid, Chronic Pain, 3-4 days supplied
- Strong Associations (HR < 0.6)
  - Days supplied greater that 4

Hazard of Opioid Discontinuation by Days Supplied interacted with pain etiology



Thoughts

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- Days Supply of Initial Opioid is the STRONGEST Predictor of Long Term Opioid Use
  - Persons prescribed 5-7 days are TWICE as Likely to Continue Opioids than persons prescribed 1-2 days
  - Persons prescribed 11-14 days are THREE times as Likely to Continue Opioids
- The Effect of Days Supplied persisted across all pain etiologies
- Persons with mental health disorders and those prescribed muscle relaxants or benzodiazepines used opioids longer

Implications

- Clinical
  - The Initial Days Supplied of Opioids is the strongest modifiable factor prognostic for long term use
    - Supports CDC guidelines limiting initial opioids to 3 days or less and rarely more than 7 days
  - Extra Caution for persons with mental health disorders and those prescribed muscle relaxants or benzodiazepines

- Policy
  - States are implementing initial days supply limits – usually 7 days or less
    - PBMs are implementing similar restrictions

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Access to the Data was supported by the UAMS Translational Research Institute (**UL1TR000039)**

Back Up Slides with Additional Methods and Data

Data and Subjects

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- IMS Lifelink+ database for 2006-2015
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- Opioid naïve, cancer and substance abuse free patients
    - at least one OPR prescription between June 06 and Sept 15
    - at least 6 months of continuous enrollment without an opioid prescription prior to first opioid prescription
    - at least 18 years of age
  - Excluded:
    - any non-melanoma cancer, substance abuse diagnosis or buprenorphine/naloxone prescription in the 6 month prior period

Study Measures

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- Opioid Discontinuation
  - At least 180 days without opioid use
  - Followed until loss of enrollment, study end date, or discontinuation of opioids.

- Initial Opioid Episode
  - Continuous use of opioids with a gap no greater than 30 days
  - Duration (days and weeks)
  - Number of opioid prescriptions
  - Cumulative dose (expressed in morphine milliequivalents)

- Initial Prescription
  - Days supply
  - Average daily dose (MME)
  - Prescription type
    - Long Acting, Oxycodone Short Acting, Hydrocodone Short Acting, Other Schedule II Short Acting; Schedule III-IV, Tramadol

Analysis

- Kaplan Meier curves
  - Median time to discontinuation
  - Probability of continued OPR use at one and three years

- Sensitivity analyses
  - Discontinuation required 90 instead of 180 opioid free days
  - Initial opioid episode used 7 instead of 30 day maximum gap
  - Excluded patients who's initial prescription exceeded 90 MME

Subjects

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- Patient and System Characteristics
  - Age, Gender, Region, Year, Insurance Type (Medicaid, Medicare, Commercial), Mental Health (mood, personality, adjustment, anxiety), Prior Benzodiazepine / Muscle Relaxant.

Analysis

- Kaplan Meier Curves

- Cox Proportional Hazards Models
  - General Model
  - Interacted Model
    - Pain etiology and days supplied
  - Stratified Model
    - Chronic vs Non-Chronic Pain

	PATIENTS WHO USED OPIOID <365 DAYS (N = 1,320,883; 97.56%)*	PATIENTS WHO USED OPIOID ≥365 DAYS (N = 33,019; 2.44%)*
CHARACTERISTIC	N (%)	N (%)
AGE IN YEARS AT THE TIME OF FIRST OPIOID PRESCRIPTION		
A. 14-17	85,176 (6.45%)	254 (0.77%)
B. 18-21	106,626 (8.07%)	519 (1.57%)
C. 22-30	202,016 (15.29%)	2,685 (8.13%)
D. 31-44	352,056 (26.65%)	7,946 (24.06%)
E. 45-54	277,909 (21.04%)	9,584 (29.03%)
F. 55-64	221,938 (16.80%)	8,399 (25.44%)
G. ≥65	75,162 (5.69)	3,632 (11.00%)
FEMALE GENDER	708,925 (53.67%)	18,484 (55.98)
REGION OF RESIDENCE		
A. EAST	288,890 (21.88%)	6,098 (18.47%)
B. MIDWEST	393,006 (29.75%)	9,656 (29.24%)
C. SOUTH	486,699 (36.85%)	13,552 (41.04%)
D. WEST	152,198 (11.52%)	3,713 (11.25%)
PAYER TYPE		
A. COMMERCIAL	888,034 (67.23%)	20,568 (62.29%)
B. MEDICAID	400,451 (30.32%)	10,503 (31.81%)
C. MEDICARE	16,584 (1.26%)	788 (2.39%)
D. SELF-INSURED	15,184 (1.20%)	1,160 (3.51%)
MENTAL HEALTH CONDITIONS		
A. MOOD DISORDER	72,379 (5.48%)	3,138 (9.50%)
B. PERSONALITY DISORDER	1,052 (0.08%)	32 (0.10%)
C. ADJUSTMENT DISORDER	19,717 (1.49%)	473 (1.43%)
D. ANXIETY DISORDER	57,160 (4.33%)	2,472 (7.49%)
E. MISCELLANEOUS DISORDER	13,382 (1.01%)	512 (1.55%)

INDICATION FOR OPIOID PRESCRIPTION‡		
A. TRAUMA AND SURGERY	36,676 (2.78%)	299 (0.91%)
B. TRAUMA	166,331 (12.59%)	2,907 (8.80%)
C. SURGERY	178,126 (13.49%)	1,356 (4.11%)
D. BURN	2,539 (0.19%)	20 (0.06%)
E. CHILDBIRTH	18,059 (1.37%)	58 (0.18%)
F. DENTAL PROCEDURE	22,732 (1.72%)	197 (0.60%)
G. CHRONIC NON-CANCER PAIN	323,058 (24.46%)	17,340 (52.52%)
H. NON CHRONIC PAIN	85,527 (6.47%)	1,319 (3.99%)
I. OTHER INPATIENT ADMISSION	3,489 (0.26%)	92 (0.28%)
J. OTHER EMERGENCY DEPARTMENT VISIT	20,372 (1.54%)	180 (0.55%)
K. UNKNOWN INDICIATION	463,974 (35.13)	9,251 (28.02%)
CHOICE OF FIRST OPIOID PRESCRIPTION^		
A. LONG-ACTING OPIOID	5,675 (0.43%)	871 (2.64%)
B. SCHEDULE TWO SHORT ACTING OPIOID	14,801 (1.12%)	525 (1.59%)
C. SHORT ACTING OXYCODONE	224,814 (17.02%)	3,839 (11.63%)
D. SHORT ACTING HYDROCODONE	768,447 (58.18%)	16,446 (49.81%)
E. SCHEDULE III OR IV OR NALBUPHINE	198,943 (15.06%)	4,384 (13.28%)
F. TRAMADOL	108,203 (8.19%)	6,954 (21.06%)
DAYS' SUPPLY OF FIRST PRESCRIPTION		
A. 1-2	274,601 (20.79%)	2,580 (7.81%)
B. 3-4	490,737 (37.15%)	5,266 (15.95%)
C. 5-7	363,181 (27.50%)	7,336 (22.22%)
D. 8-10	99,417 (7.53%)	4,040 (12.24%)
E. 11-14	15,331 (1.16%)	1,056 (3.20%)
F. 15-21	39,205 (2.97%)	3,638 (11.02%)
G. ≥22	38,411 (2.91%)	9,103 (27.57%)
≥90 MME AVERAGE DAILY DOSE OF FIRST PRESCRIPTION†	115,396 (8.74%)	3,457 (10.47%)

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Time to Discontinuation

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INDICATION FOR FIRST OPIOID PRESCRIPTION**	ONE YEAR PROBABILITY OF CONTINUED OPIOID USE, %	THREE YEAR PROBABILITY OF CONTINUED OPIOID USE, %	MEDIAN DAYS TO DISCONTINUATION
TRAUMA AND SURGERY	1.97%	0.74%	7.00
TRAUMA	3.96%	1.71%	5.00
SURGERY	1.90%	0.64%	5.00
BURN	1.98%	0.89%	5.00
CHILDBIRTH	1.33%	0.45%	5.00
DENTAL PROCEDURE	2.29%	0.77%	5.00
CHRONIC NON-CANCER PAIN	10.07%	5.11%	11.00
NON CHRONIC PAIN	3.69%	1.48%	5.00
OTHER INPATIENT ADMISSION	6.60%	2.91%	8.00
OTHER EMERGENCY DEPARTMENT VISIT	2.47%	1.11%	4.00
UNKNOWN ETIOLOGY	4.47%	2.20%	5.00

CHARACTERISTIC	HAZARD RATIO	95% CI
AGE IN YEARS AT THE TIME OF FIRST OPIOID PRESCRIPTION (REF=31-44)		
A. 14-17	1.32	1.31-1.33
B. 18-21	1.16	1.14-1.16
C. 22-30	0.96	0.96-0.97
D. 45-54	0.98	0.98-0.99
E. 55-64	0.98	0.98-0.99
F. ≥65	0.91	0.91-0.92
FEMALE GENDER (REF=MALE)	0.99	0.98-0.99
REGION OF RESIDENCE (REF= MIDWEST)		
A. EAST	1.04	1.04-1.05
B. SOUTH	0.92	0.92-0.93
C. WEST	0.94	0.93-0.95
PAYER TYPE (REF= SELF-INSURED)		
A. COMMERCIAL	0.98	0.98-0.99
B. MEDICAID	0.69	0.68-0.70
C. MEDICARE	0.94	0.92-0.95
MENTAL HEALTH CONDITIONS		
A. MOOD DISORDER (REF=NO MOOD DISORDER)	0.88	0.87-0.88
B. PERSONALITY DISORDER (REF=NO PERSONALITY DISORDER)	0.94	0.88-1.01
C. ADJUSTMENT DISORDER (REF=NO ADJUSTMENT DISORDER	0.99	0.98-1.01
D. ANXIETY DISORDER (REF=NO ANXIETY DISORDER)	0.93	0.92-0.94
E. MISCELLANEOUS DISORDER (REF=NO MISCELLANEOUS DISORDER)	0.95	0.93-0.97

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BEZODIAZEPINE PRESCRIPTION IN PRIOR 6 MONTHS (REF=NO BEZODIAZEPINE PRESCRIPTION)	0.84	0.84-0.85
MUSCLE RELAXANT PRESCRIPTION IN PRIOR 6 MONTHS (REF=NO MUSCLE RELAXANT PRESCRIPTION)	0.91	0.90-0.91
INDICATION FOR OPIOID PRESCRIPTION (REF=SURGERY)‡		
A. TRAUMA AND SURGERY	0.91	0.90-0.92
B. TRAUMA	0.84	0.84-0.85
C. BURN	0.97	0.93-1.01
D. CHILDBIRTH	1.12	1.10-1.14
E. DENTAL PROCEDURE	0.90	0.89-0.92
F. CHRONIC NON-CANCER PAIN	0.78	0.77-0.78
G. NON CHRONIC PAIN	0.86	0.85-0.87
H. OTHER INPATIENT ADMISSION	0.82	0.79-0.86
I. OTHER EMERGENCY DEPARTMENT VISIT	0.93	0.92-0.95
J. UNKNOWN INDICIATION	0.93	0.93-0.94
CHOICE OF FIRST OPIOID PRESCRIPTION (REF= SCHEDULE III OR IV OR NALBUPHINE)†		
A. LONG-ACTING OPIOID	0.78	0.75-0.80
B. SCHEDULE TWO SHORT ACTING OPIOID	0.93	0.91-0.94
C. SHORT ACTING OXYCODONE	0.96	0.95-0.96
D. SHORT ACTING HYDROCODONE	0.95	0.94-0.95
E. TRAMADOL	0.90	0.89-0.91
DAYS' SUPPLY OF FIRST PRESCRIPTION (REF=1-2)		
A. 3-4	0.71	0.70-0.71
B. 5-7	0.48	0.47-0.48
C. 8-10	0.38	0.37-0.38
D. 11-14	0.33	0.32-0.33
E. 15-21	0.29	0.29-0.30
F. ≥22	0.20	0.19-0.20
≥90 MME AVERAGE DAILY DOSE OF FIRST PRESCRIPTION (REF=<90 MME AVERAGE DAILY DOSE OF FIRST PRESCRIPTION)^	0.95	0.94-0.95

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