

The Opioid Crisis and Its Effect on Transplantation

Greg J. McKenna, M.D.
Simmons Transplant Institute
Baylor University Medical Center
Dallas, TX

The Opioid Epidemic

How Bad is it ?

Opioid Epidemic

How Bad Is It ?

Overwhelming

July 5th 2016 Akron, Ohio

“The day carfentanil hit the streets of Akron. On that day, 17 people overdosed and one person died in a span of 9 hours....”

“....In 2016, Summit County (Akron) had 312 drug deaths — more than triple the 99 cases two years before. There were so many last year, that on three separate occasions the county had to request refrigerated trailers to store the bodies because they’d run out of space in the morgue.”

Opioid Epidemic

How Bad Is It ?

Futile

“First responders are finding that, with fentanyl and carfentanil, the overdoses can be so severe that multiple doses of naloxone — the anti overdose medication that goes by the brand name Narcan — are need to pull people out...”

“....E.M.S. crews are hitting them with 12, 13, 14 hits of Narcan with no effect” said Mr. Burke, likening a shot of Narcan to “a squirt gun in a house fire”

Opioid Epidemic

How Bad Is It ?

Desperate

“Across the country, someone dies of an opioid overdose every 24 minutes. In Massachusetts, the death toll is five people a day...”

“In the face of this epidemic, Cambridge could become the first city to take a step that until recently might have seemed unthinkable: It might place lockboxes on street corners to give the public easy access to naloxone, a medication that can rapidly revive people who have overdosed”

Opioid Epidemic

How Bad Is It ?

Desperate



An overdose simulation organized by a group of doctors, police officers and students testing Narcan dispensaries proposed for Cambridge, Mass. Erik Jacobs for The New York Times

Source: NYTimes 5/9/17

Opioid Epidemic

How Bad Is It ?

Ingenuity

“One clinic has installed an intercom, and requires people to respond...”

“Another clinic has designed a reverse-motion detector that sets off an alarm if there is no movement in the bathroom once the door is closed.”

Opioid Epidemic

How Bad Is It ?

Necessity

“Some clinics and restaurants check on bathroom users by having staff knock on the door after 10 or 15 minutes”

Opioid Epidemic

How Bad Is It ?

Frustration

“As overdose deaths pile up, a medical examiner quits the morgue”

“It’s almost as if the Visigoths are at the gates, and the gates are starting to crumble. I’m not an alarmist by nature, but this is not overhyped. It has completely overwhelmed us.”

“It makes me feel like my hair is on fire, and I don’t even have hair”

Opioid Epidemic

How Bad Is It ?

Frustration

As Overdose Deaths Pile Up, a Medical Examiner Quits the Morgue

By KATHARINE Q. SEELYE OCT. 7, 2017



Source: NYTimes 10/7/17

The Opioid Epidemic

So What Is It ?

Opioids - A Primer

- Oral Opioid Analgesics:
 - Morphine, hydrocodone, hydromorphone, oxycodone
 - Vary in potency, duration and onset of action
- Heroin: “Pure” Heroin
 - White powder, can be smoked or snorted
 - South America and Southeast Asia origin
 - Found in US markets east of Mississippi River
- Black Tar Heroin
 - Sticky, must be dissolved, diluted and injected
 - Mexican origin
 - Found in US markets west of Mississippi River
- Synthetic Opioids:
 - Fentanyl
 - Used for cutting heroin as cheap, very potent
 - Carfentanil
 - Extremely potent analogue of fentanyl
- Opioid Substitute:
 - Methadone
 - Partial agonist of opioid receptor. Useful for treating addiction

Introduction

- The opioid epidemic is a national tragedy that is growing
- It has led to many deaths from overdoses and other drug related diseases, numbers that are growing exponentially
- It has affected populations, communities, and even politics and an end is not in sight. It is causing significant impacts on medical resources.
- Possibly most of all, the field of transplantation has been markedly affected by the opioid epidemic and it is leading to dramatic changes in practice

Outline

The relationship between the opioid crisis and transplantation is complex and multifaceted and I will examine it in four parts

- 1) The Opioid Epidemic and the Impact on Organ Donation
- 2) The Opioid Epidemic and HCV+ Donors
- 3) Opioids and the Pretransplant Patient
- 4) Opioids and Posttransplant Patient Management

Opioid Epidemic and the Impact on Organ Donation



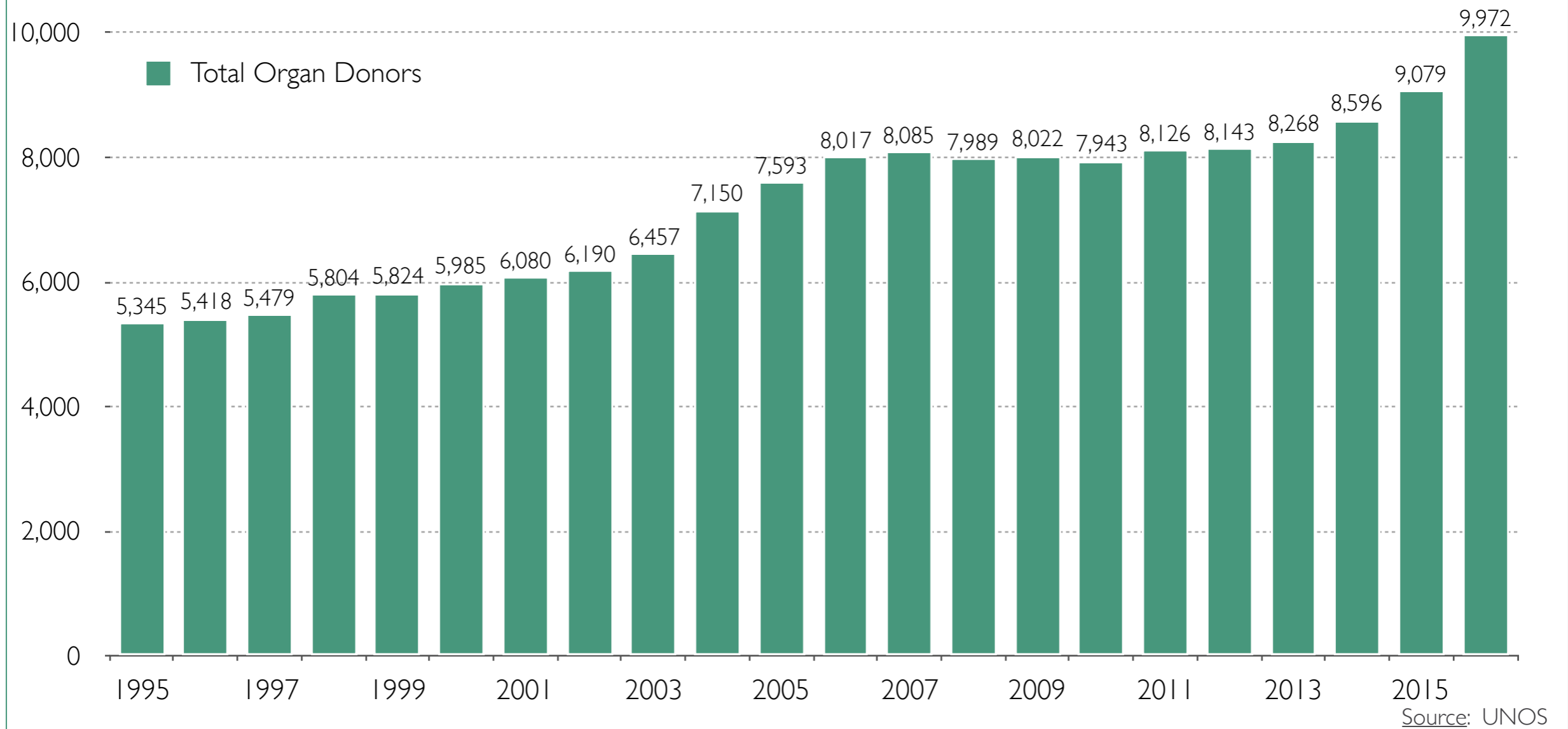
Opioid Epidemic Overview

- Drug Overdose → Most common cause of death for people < 50 yrs
→ More deaths than MVA and firearms combined
- Demographics → Impacts primary poor, rural, white males
→ Appalachian, Northeast, Southwest

Opioids and Organ Donation

Organ Donors

Number of Organ Donors By Year

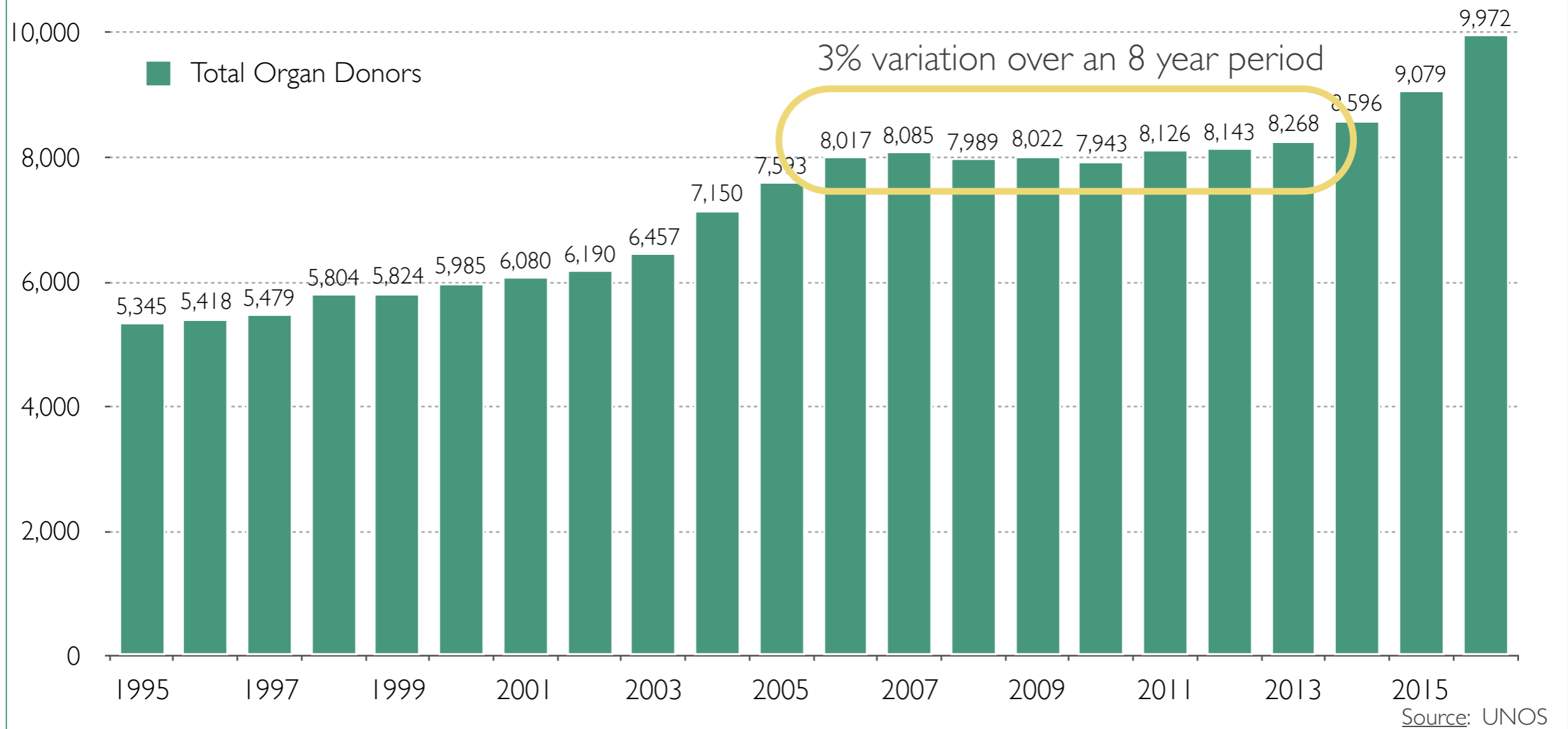


Source: UNOS

Opioids and Organ Donation

Organ Donors

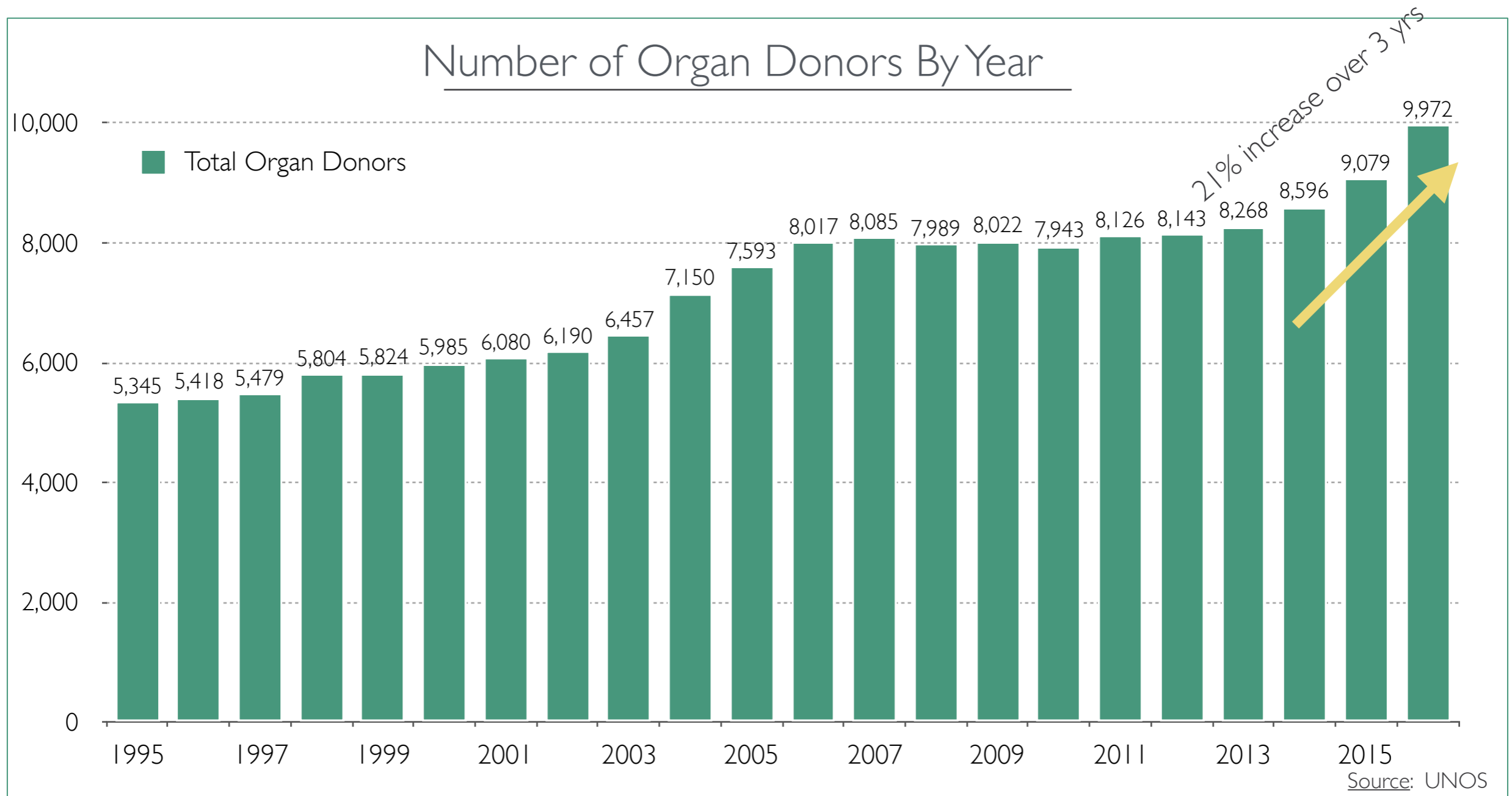
Number of Organ Donors By Year



Source: UNOS

Opioids and Organ Donation

Organ Donors



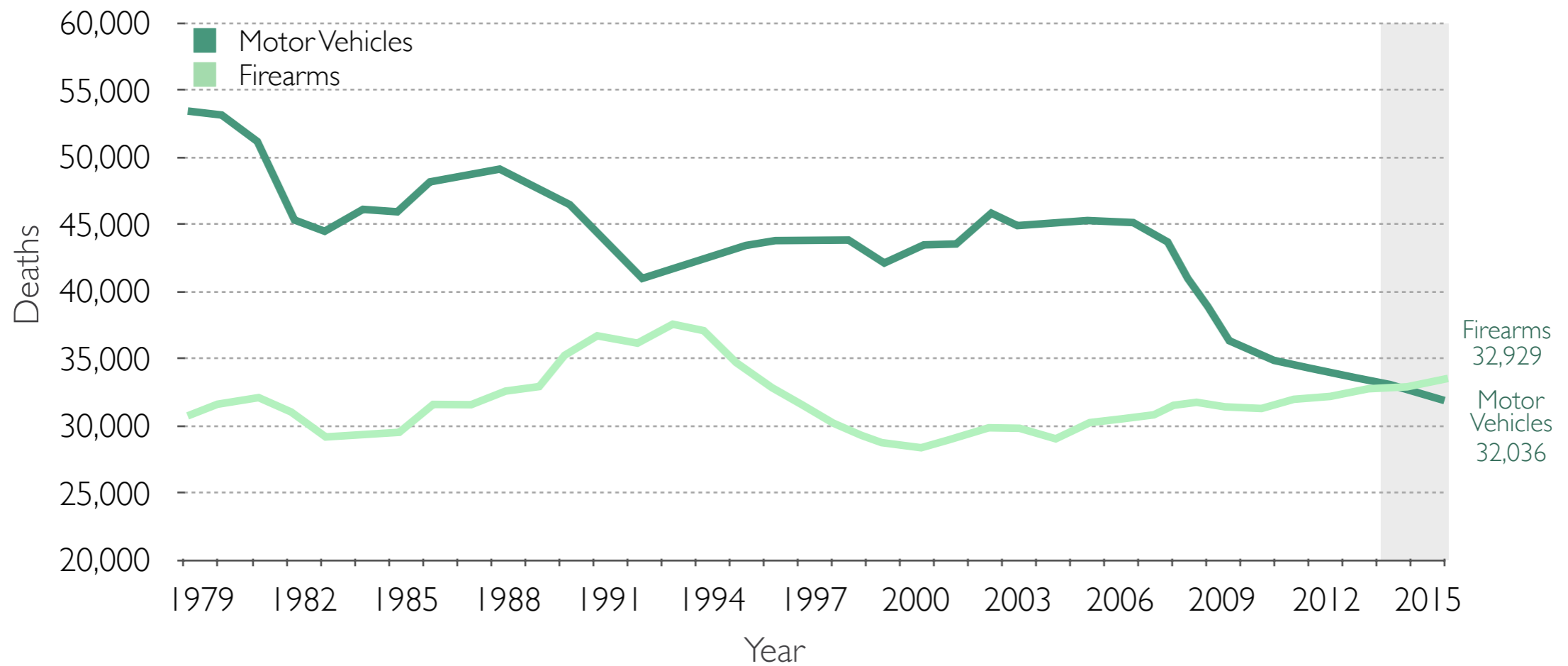
Opioid Epidemic

Impact on Mortality



Opioid Epidemic

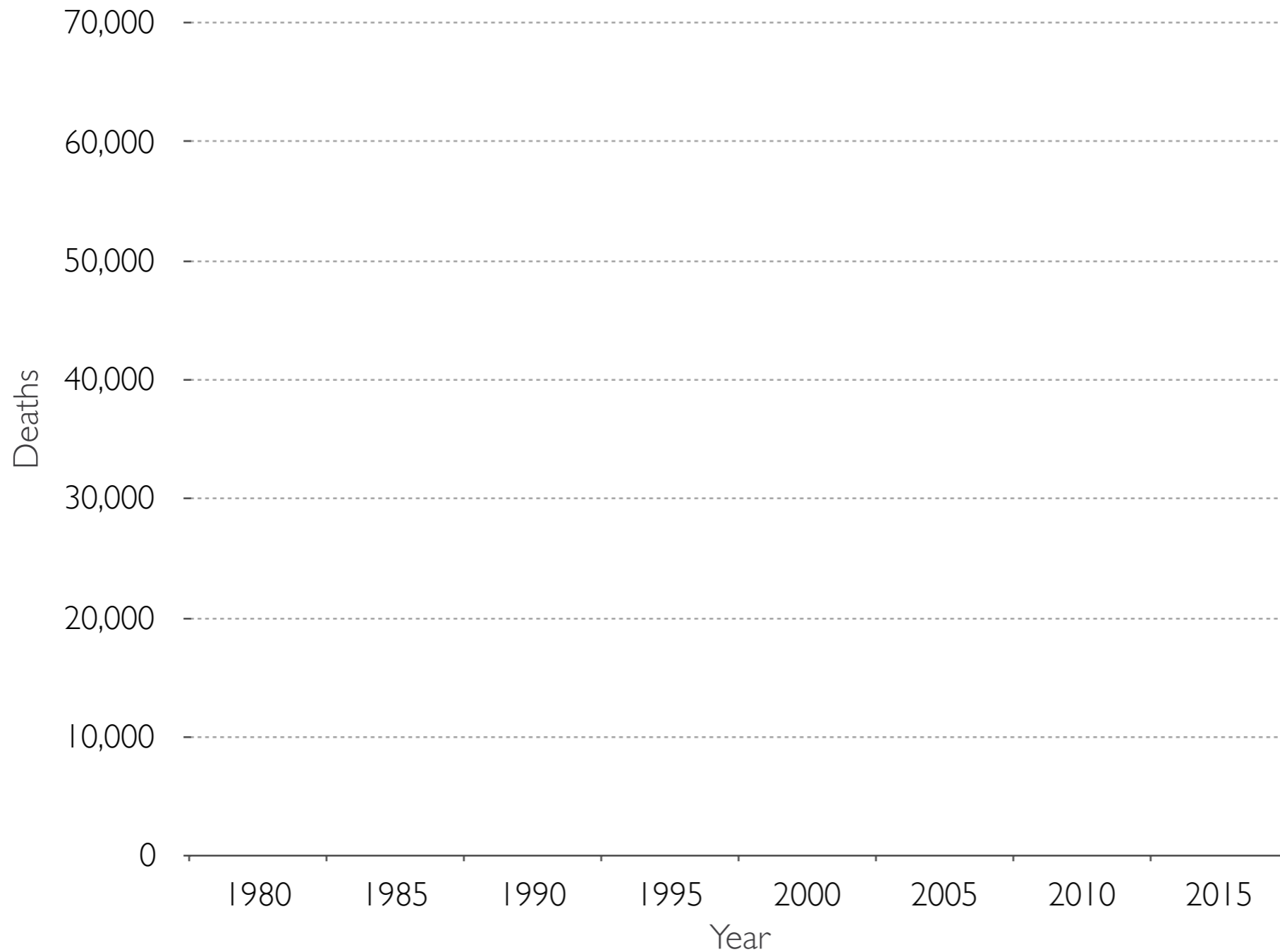
Common Causes of Death in US



Source: CDC and Bloomberg

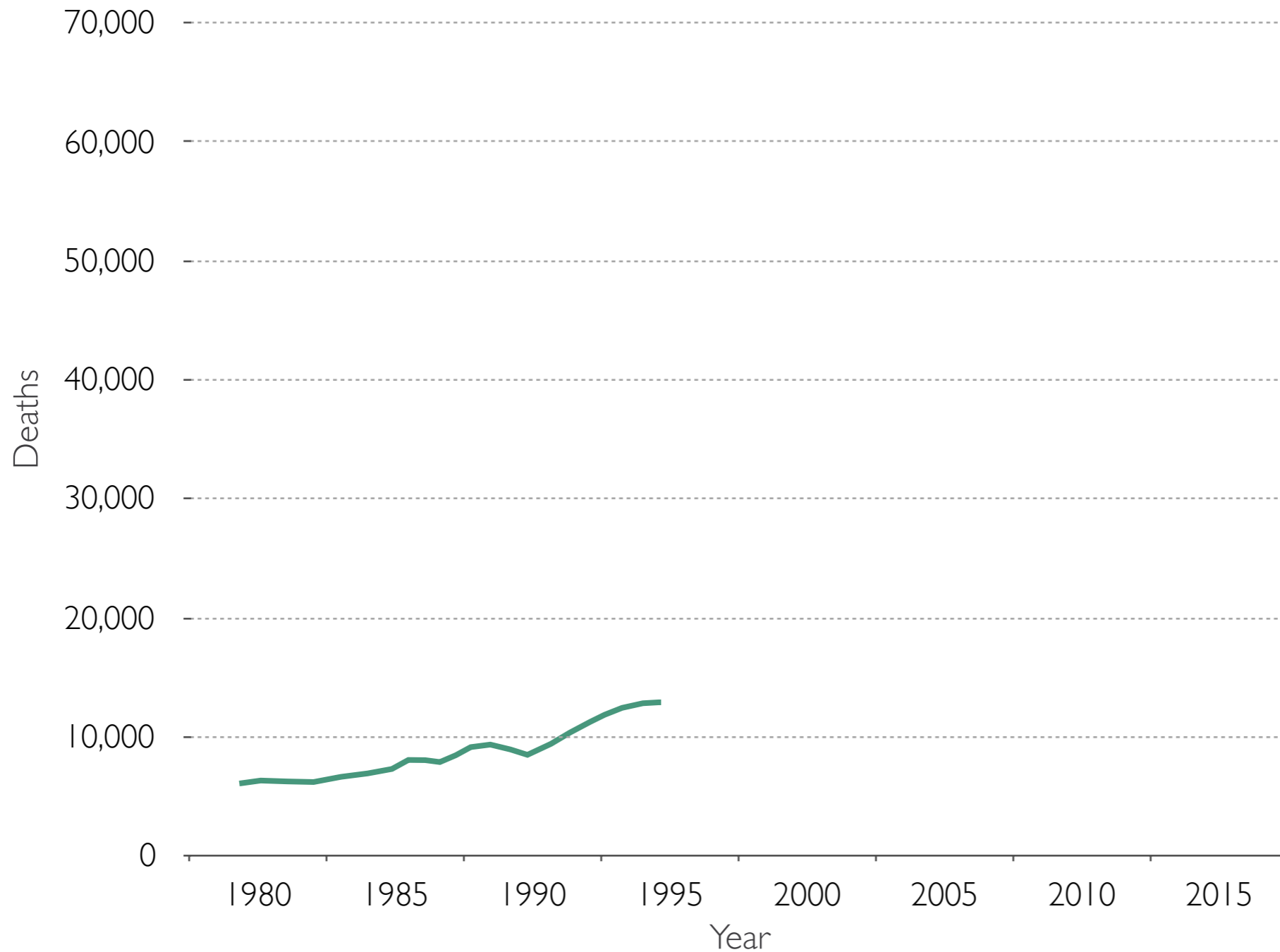
Opioid Epidemic

Drug Overdose Deaths 1980 - 2016



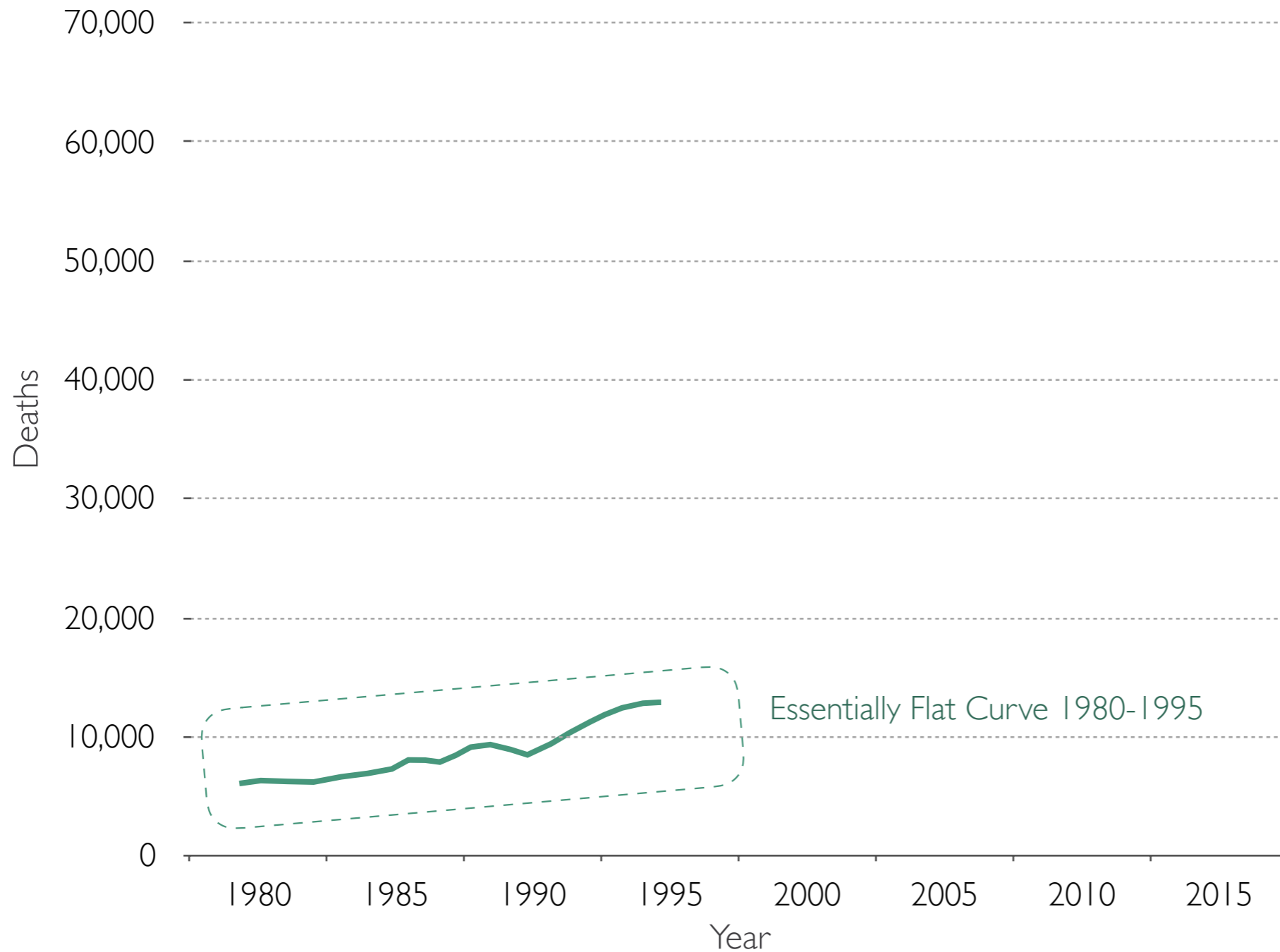
Opioid Epidemic

Drug Overdose Deaths 1980 - 2016



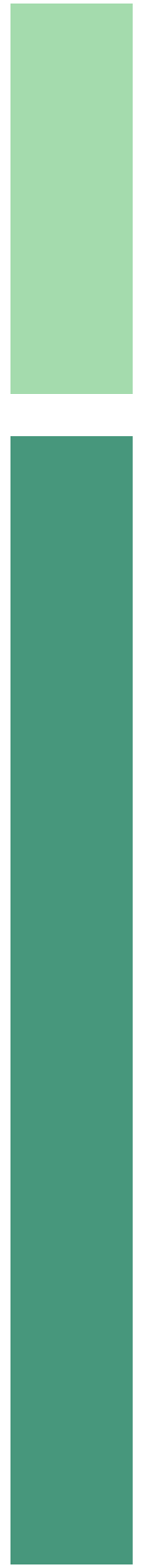
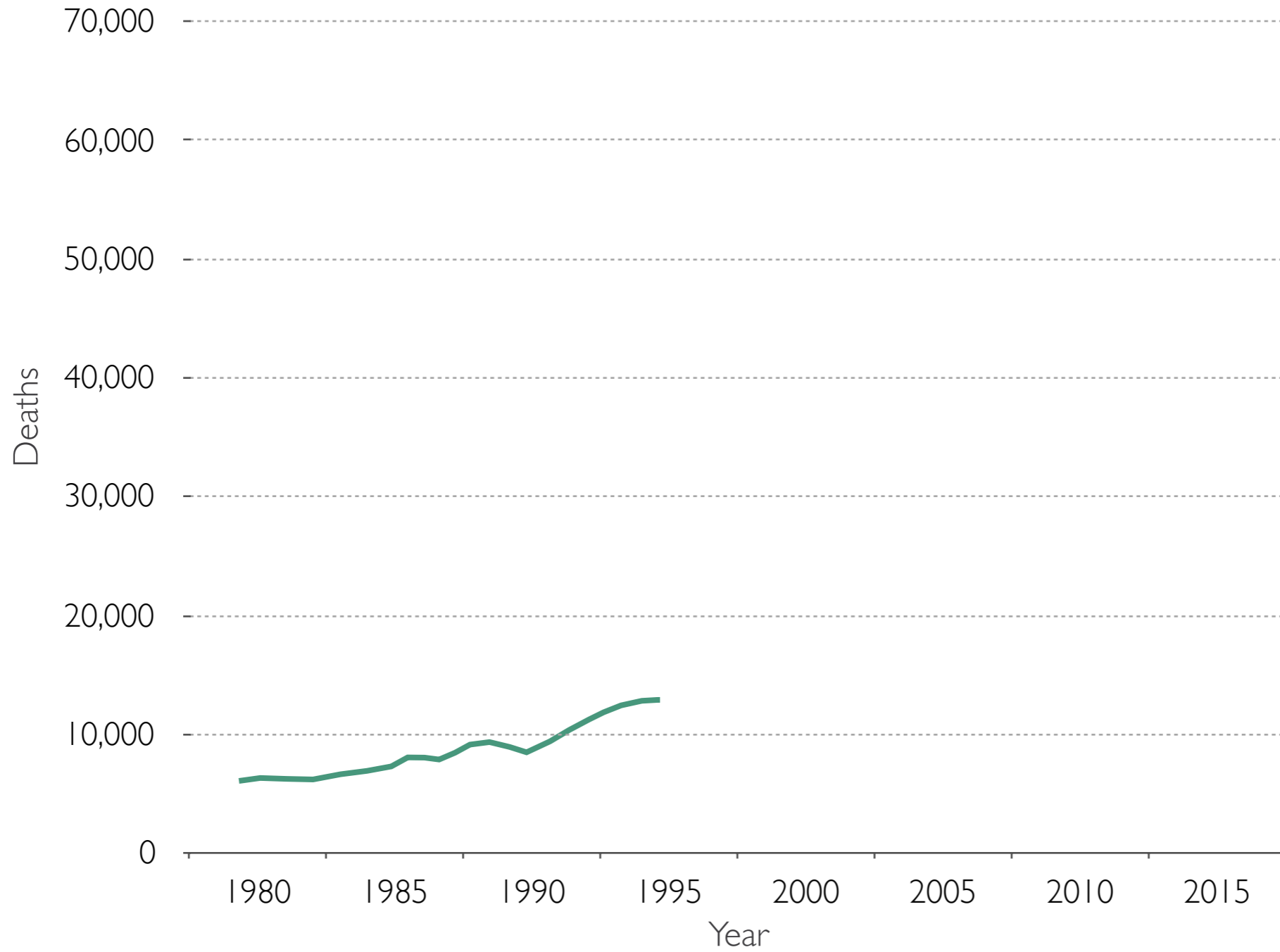
Opioid Epidemic

Drug Overdose Deaths 1980 - 2016



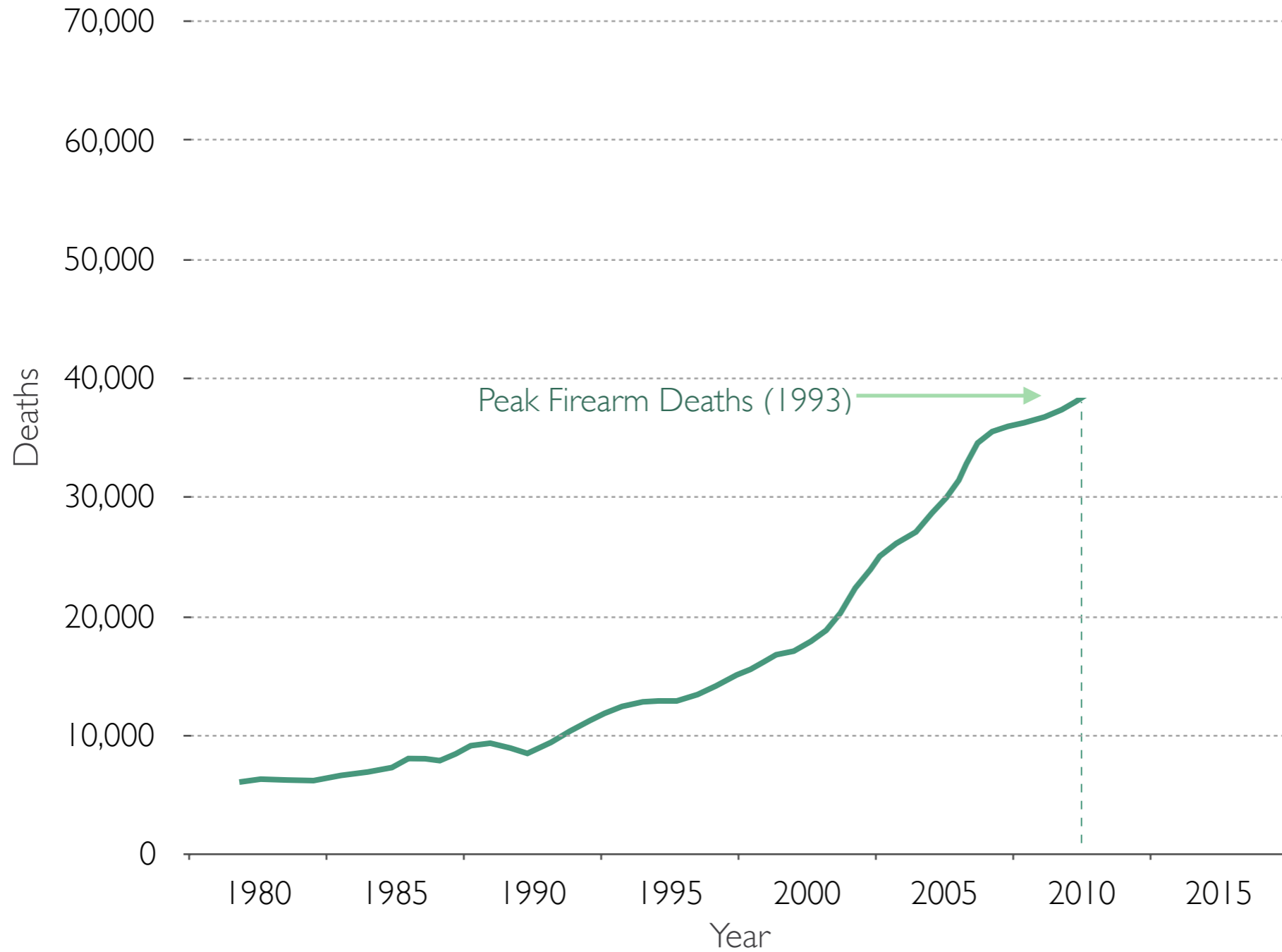
Opioid Epidemic

Drug Overdose Deaths 1980 - 2016



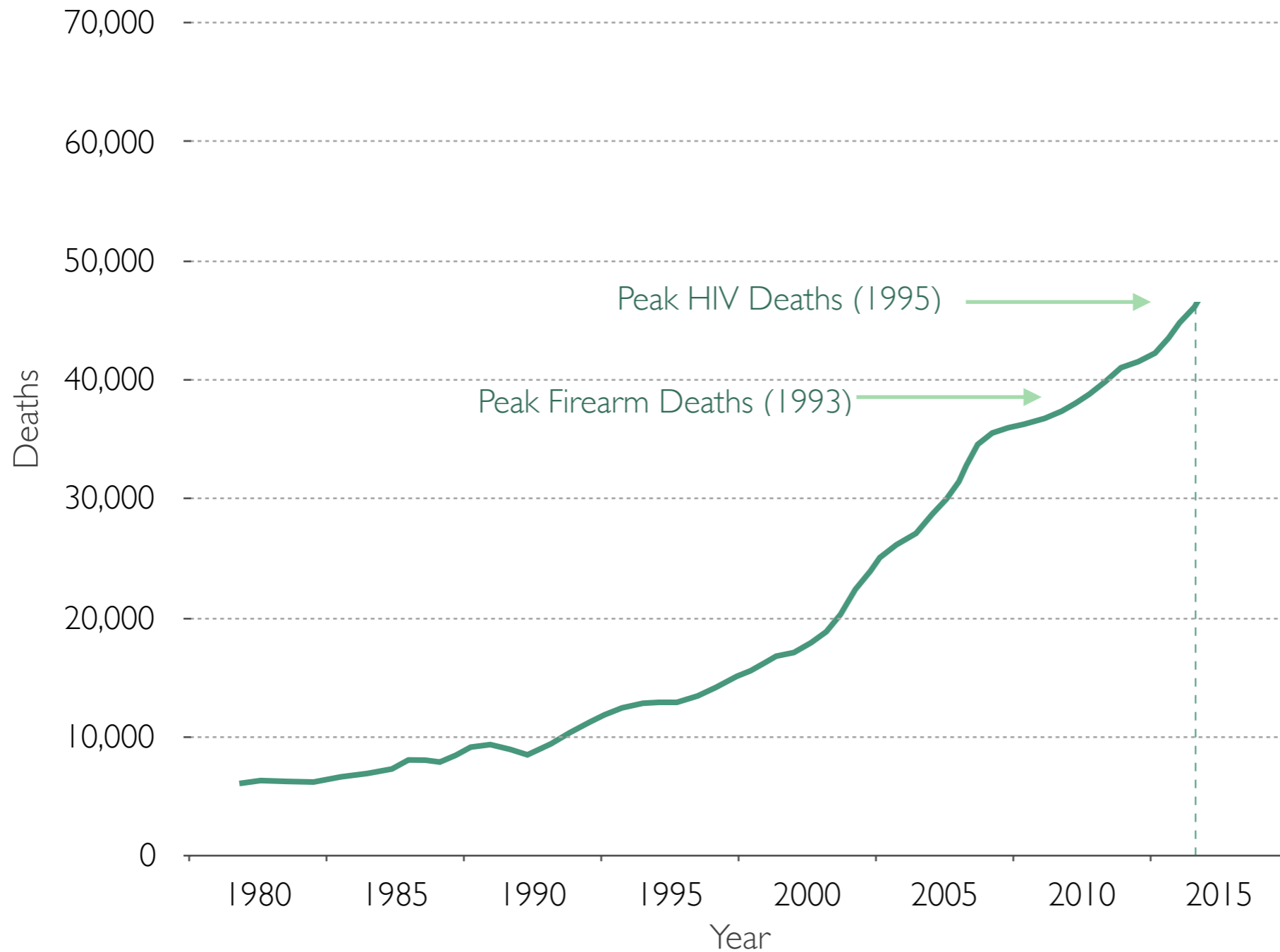
Opioid Epidemic

Drug Overdose Deaths 1980 - 2016



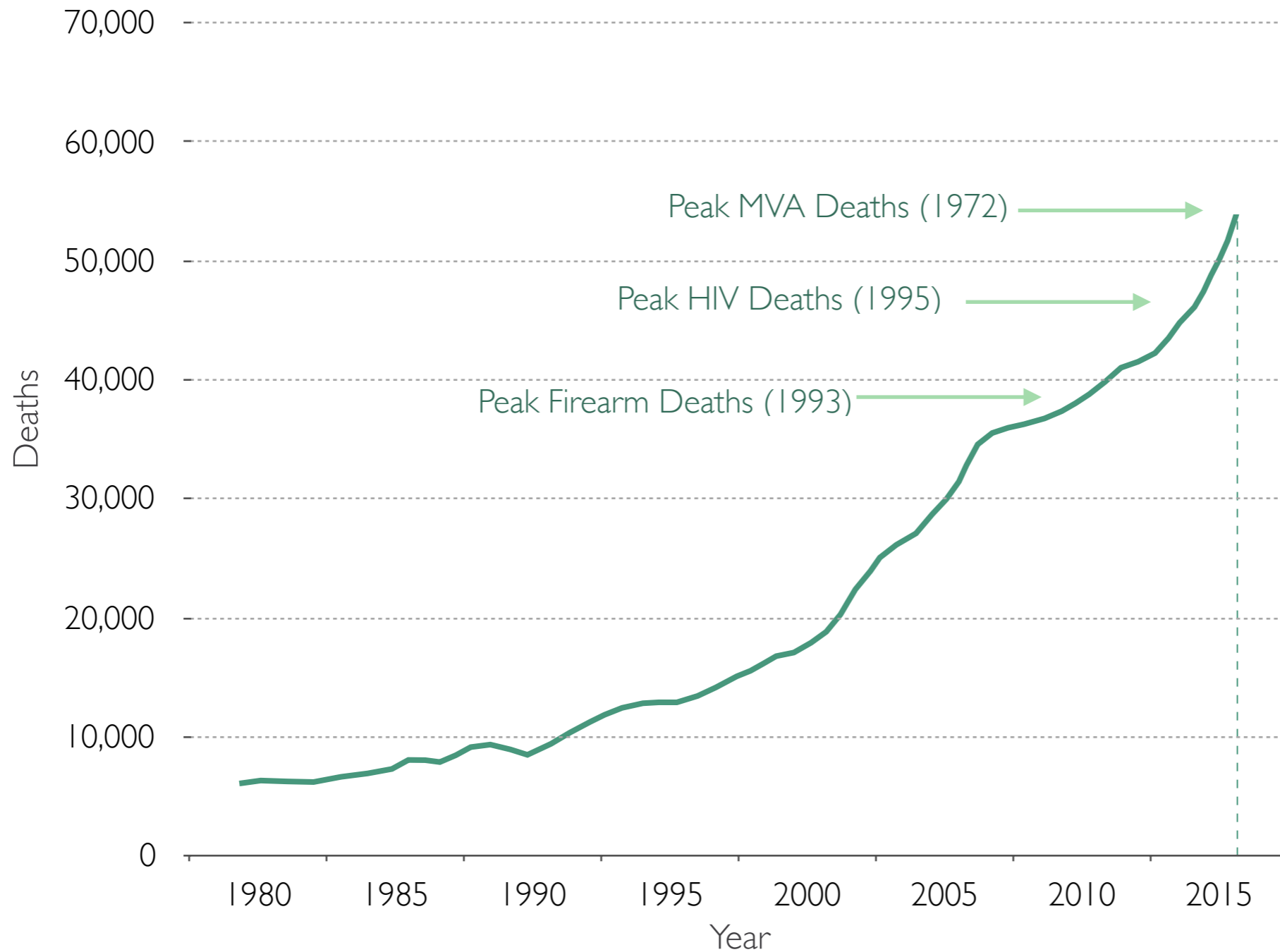
Opioid Epidemic

Drug Overdose Deaths 1980 - 2016



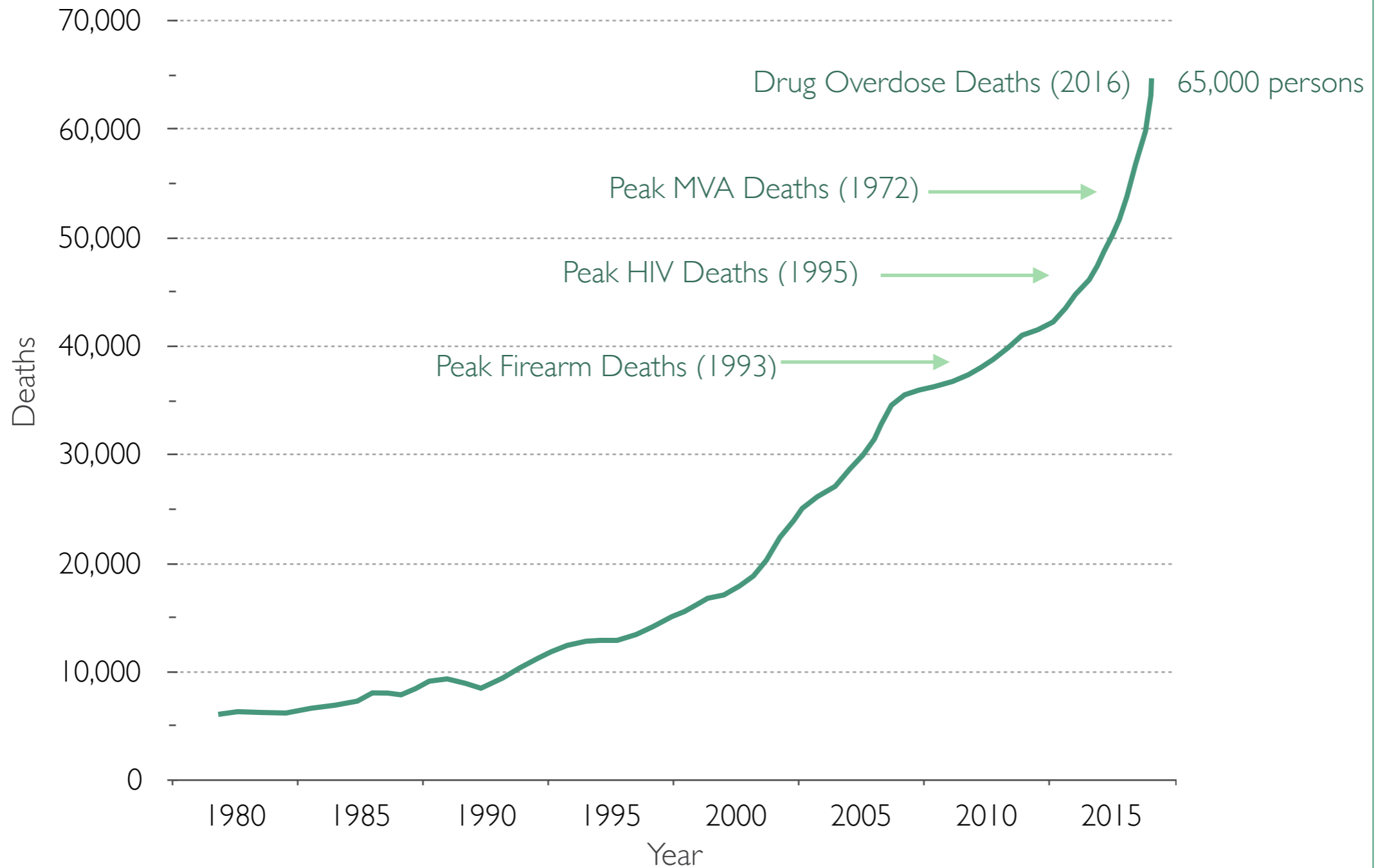
Opioid Epidemic

Drug Overdose Deaths 1980 - 2016



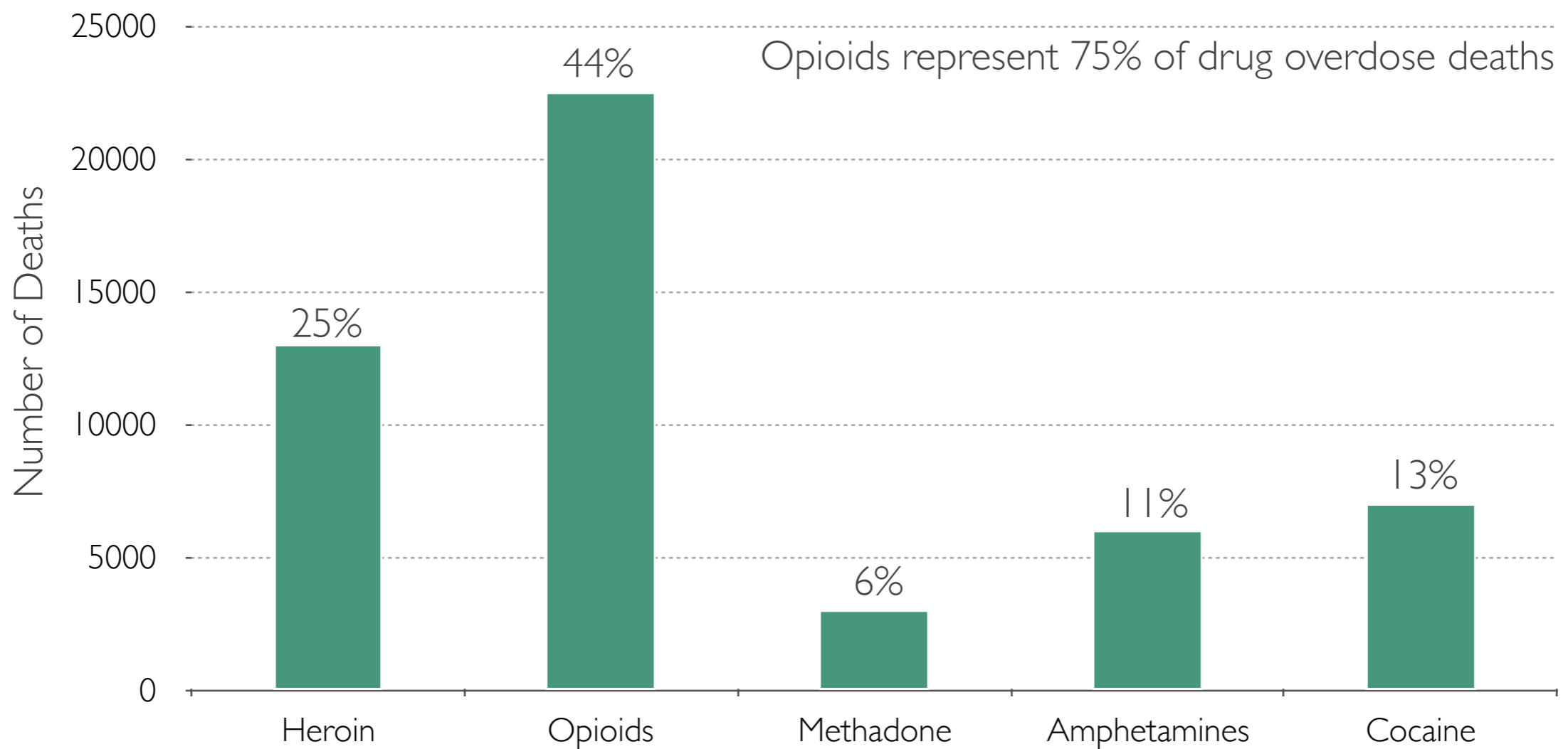
Opioid Epidemic

Drug Overdose Deaths 1980 - 2016



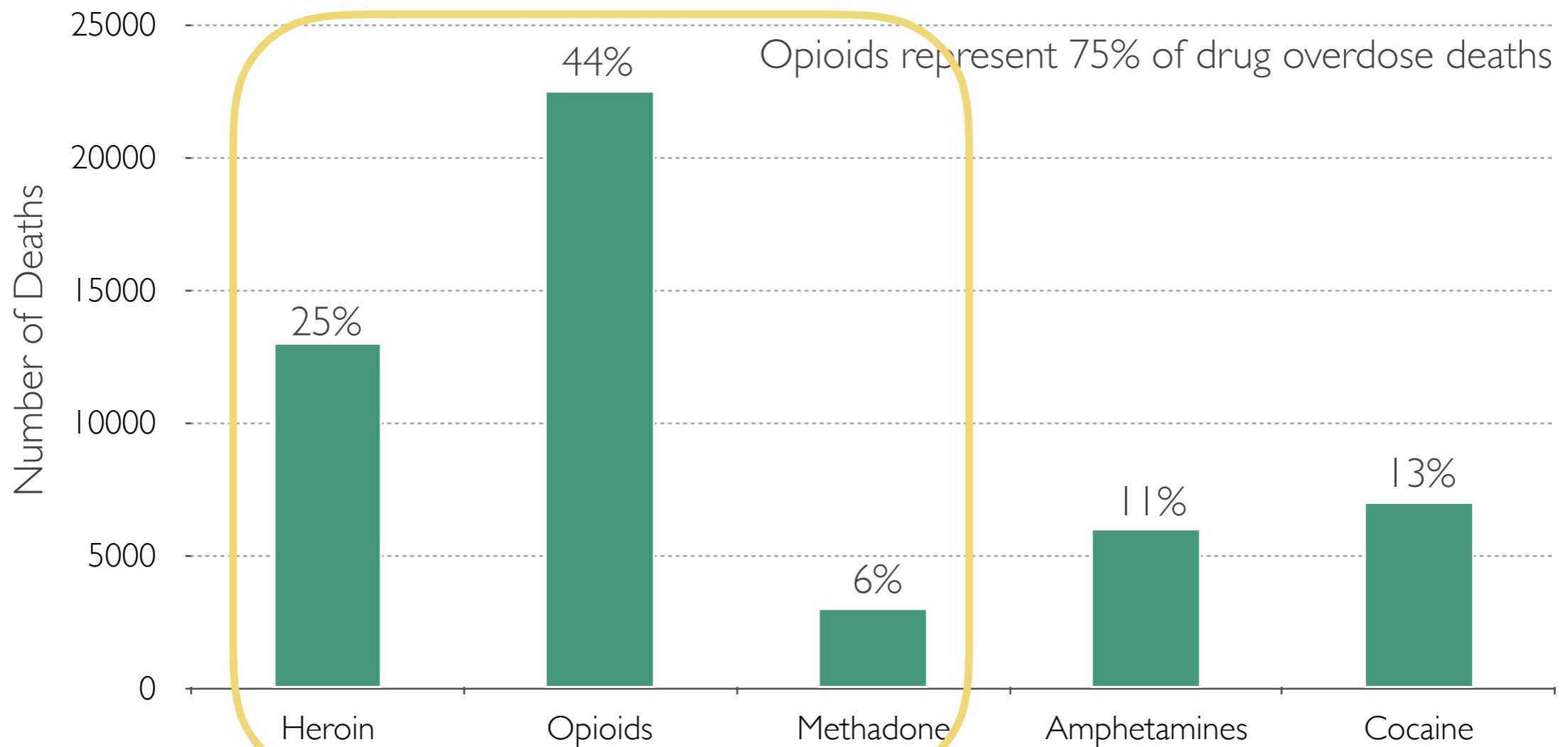
Opioid Epidemic

Overdose Deaths by Drug in 2016



Opioid Epidemic

Overdose Deaths by Drug in 2016



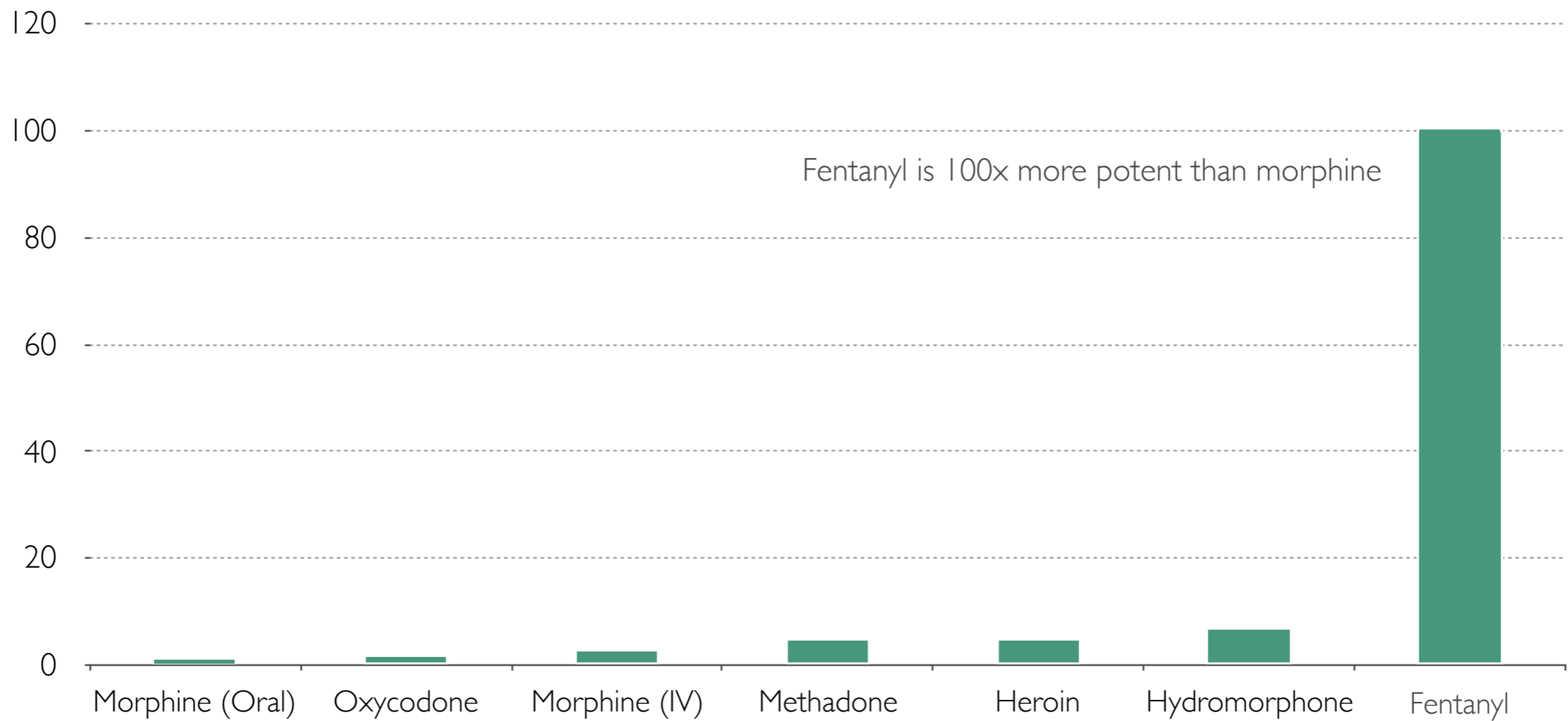
What is Causing These Overdose
Deaths ?

What is Causing These Overdose Deaths ?

Potency of synthetic opioids

Opioid Epidemic

Relative Strength of Opioid Analgesics



Opioid Epidemic

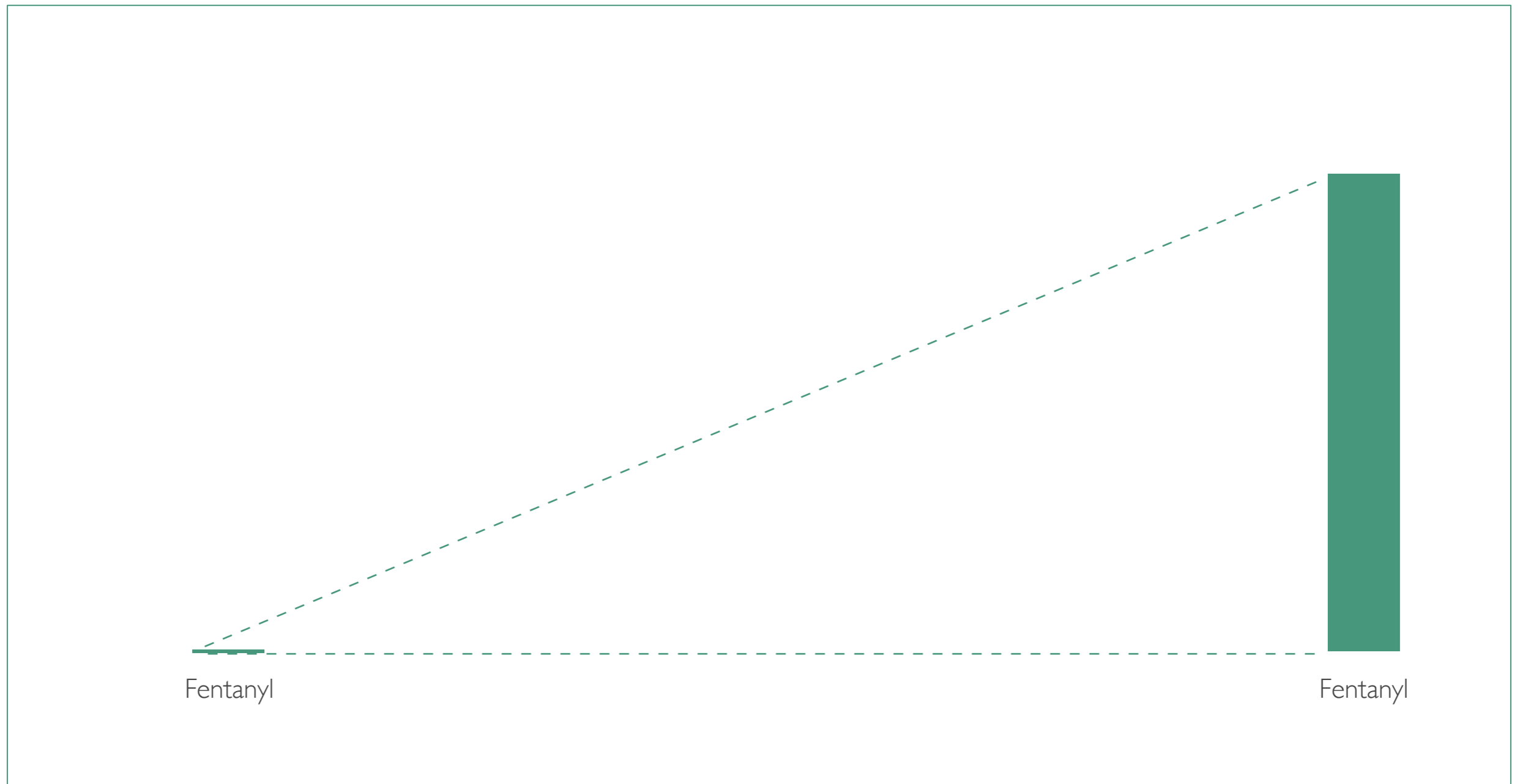
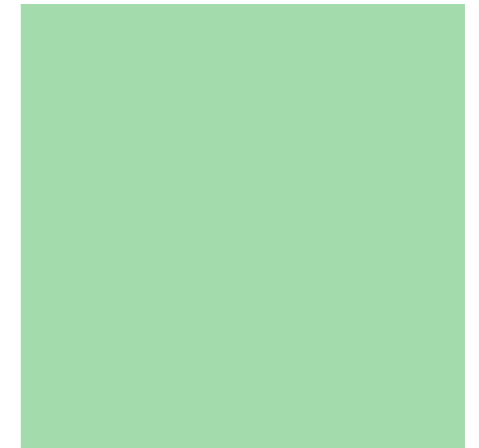
Relative Strength of Opioid Analgesics



Fentanyl

Opioid Epidemic

Relative Strength of Opioid Analgesics



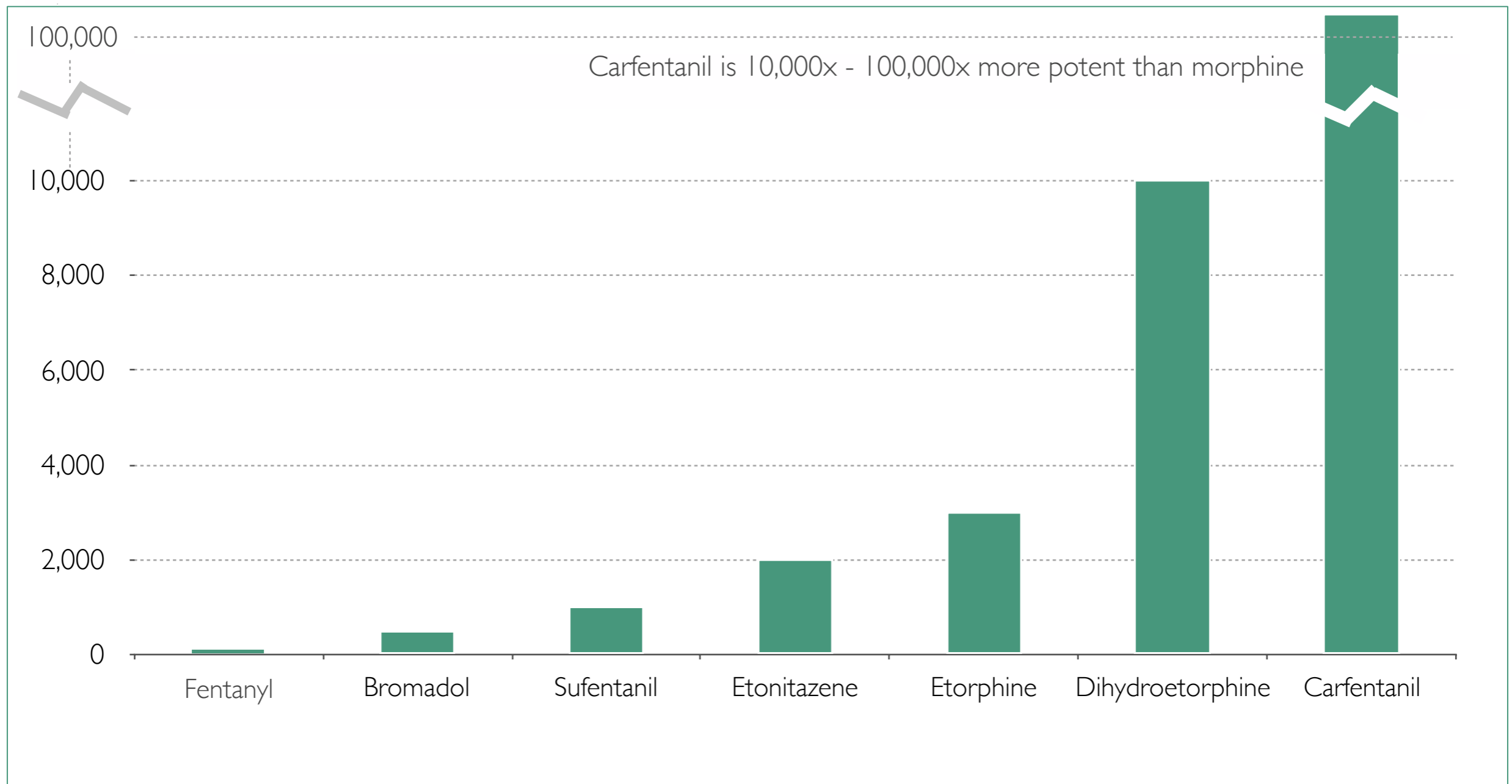
Opioid Epidemic

Relative Strength of Opioid Analgesics

—
Fentanyl

Opioid Epidemic

Relative Strength of Opioid Analgesics



Opioid Epidemic

Relative Strength of Opioid Analgesics



Lethal Dose
of Heroin



Lethal Dose
of Fentanyl

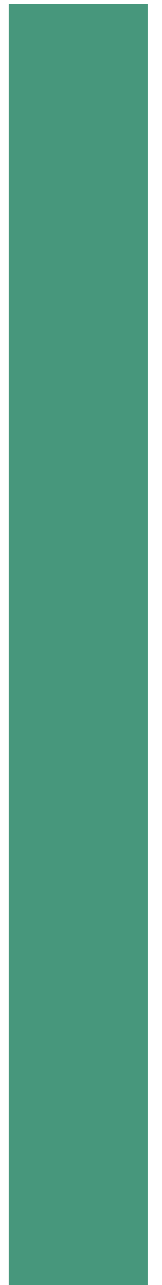
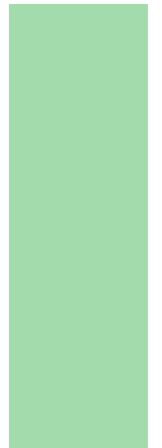


Lethal Dose of
Carfentanil

Less Potent



More Potent



The Opioid Epidemic

Who is Most Impacted ?

Opioid Epidemic

Mortality Rate by Ethnicity

	All-Cause Mortality	All External Causes	Poisonings
White Non-Hispanics	33.9	32.8	22.2
Black Non-Hispanics	-214.8	-6.0	3.7
Hispanics	-63.6	-2.9	4.3
WNH Education Class			
High School or Less	134.4	68.7	44.3
Some College	-3.3	18.9	14.6
College Degree	-57.0	3.6	4.6

White vs Hispanic > 4 x higher ≤ High School vs ≥ College > 8 x higher

Source: Case et al. PNAS. 2015

Opioid Epidemic

Mortality Rate by Ethnicity

	All-Cause Mortality	All External Causes	Poisonings
White Non-Hispanics	33.9	32.8	22.2
Black Non-Hispanics	-214.8	-6.0	3.7
Hispanics	-63.6	-2.9	4.3
WNH Education Class			
High School or Less	134.4	68.7	44.3
Some College	-3.3	18.9	14.6
College Degree	-57.0	3.6	4.6

White vs Hispanic > 4 x higher ≤ High School vs ≥ College > 8 x higher

Source: Case et al. PNAS. 2015

Opioid Epidemic

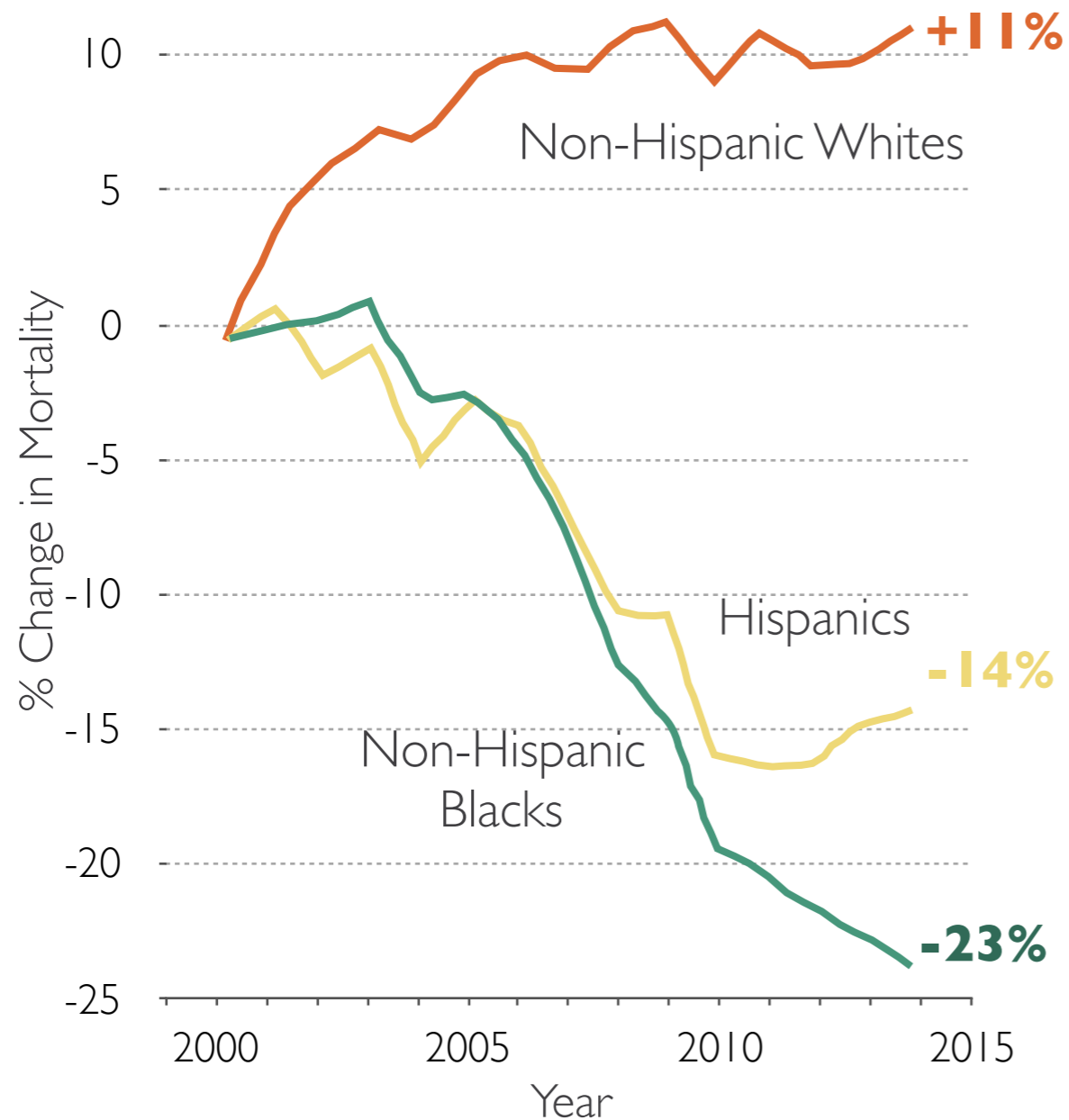
Mortality Rate by Ethnicity

	All-Cause Mortality	All External Causes	Poisonings
White Non-Hispanics	33.9	32.8	22.2
Black Non-Hispanics	-214.8	-6.0	3.7
Hispanics	-63.6	-2.9	4.3
WNH Education Class			
High School or Less	134.4	68.7	44.3
Some College	-3.3	18.9	14.6
College Degree	-57.0	3.6	4.6

White vs Hispanic > 4 x higher ≤ High School vs ≥ College > 8 x higher

Source: Case et al. PNAS. 2015

Opioid Epidemic Mortality Rate by Ethnicity

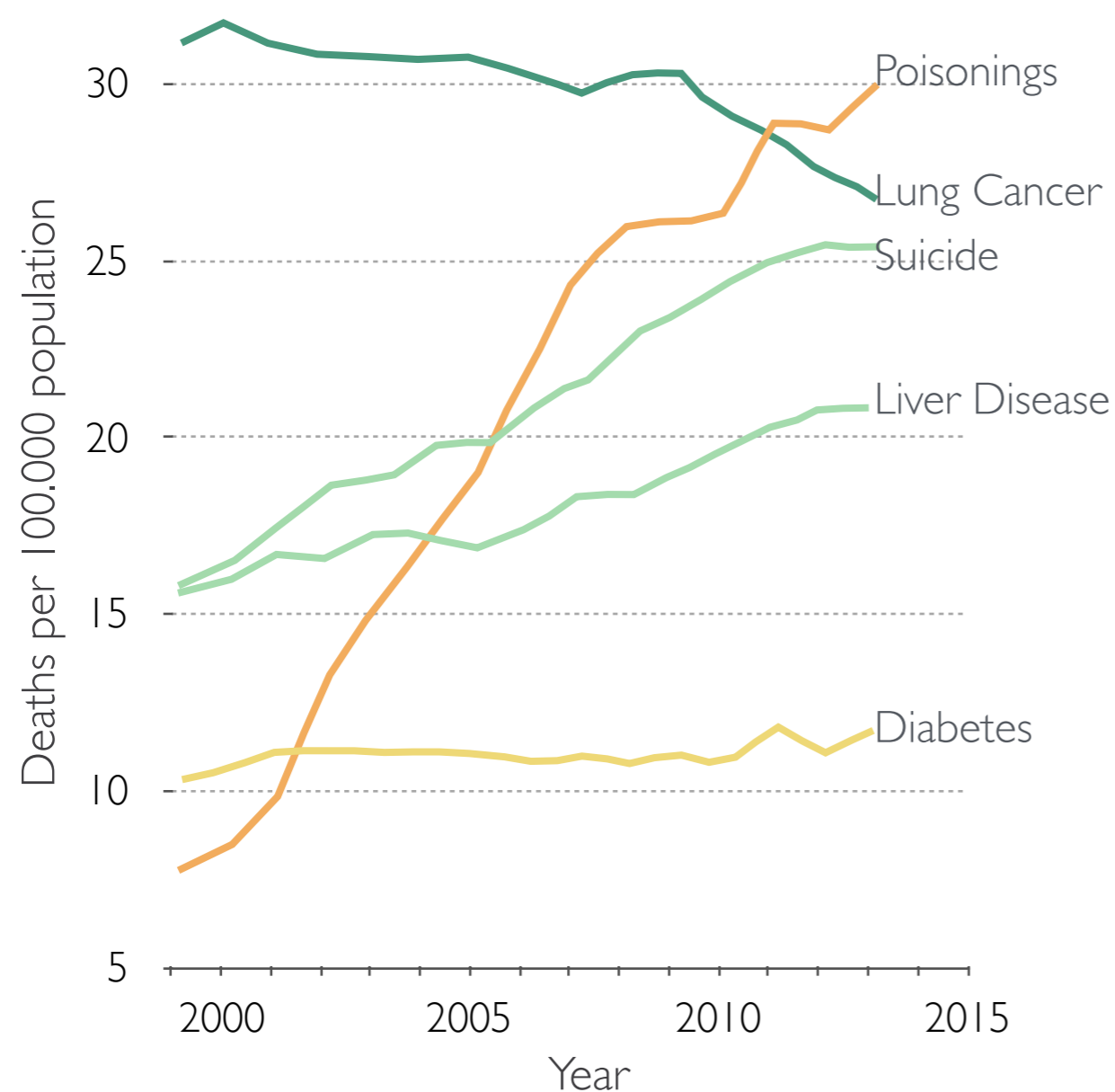


↑ mortality rate of non-Hispanic whites age 25-54 yrs over

Source: NY Times

Opioid Epidemic Mortality Rate by Cause

Mortality by Cause White Non-Hispanic Ages 45 - 54

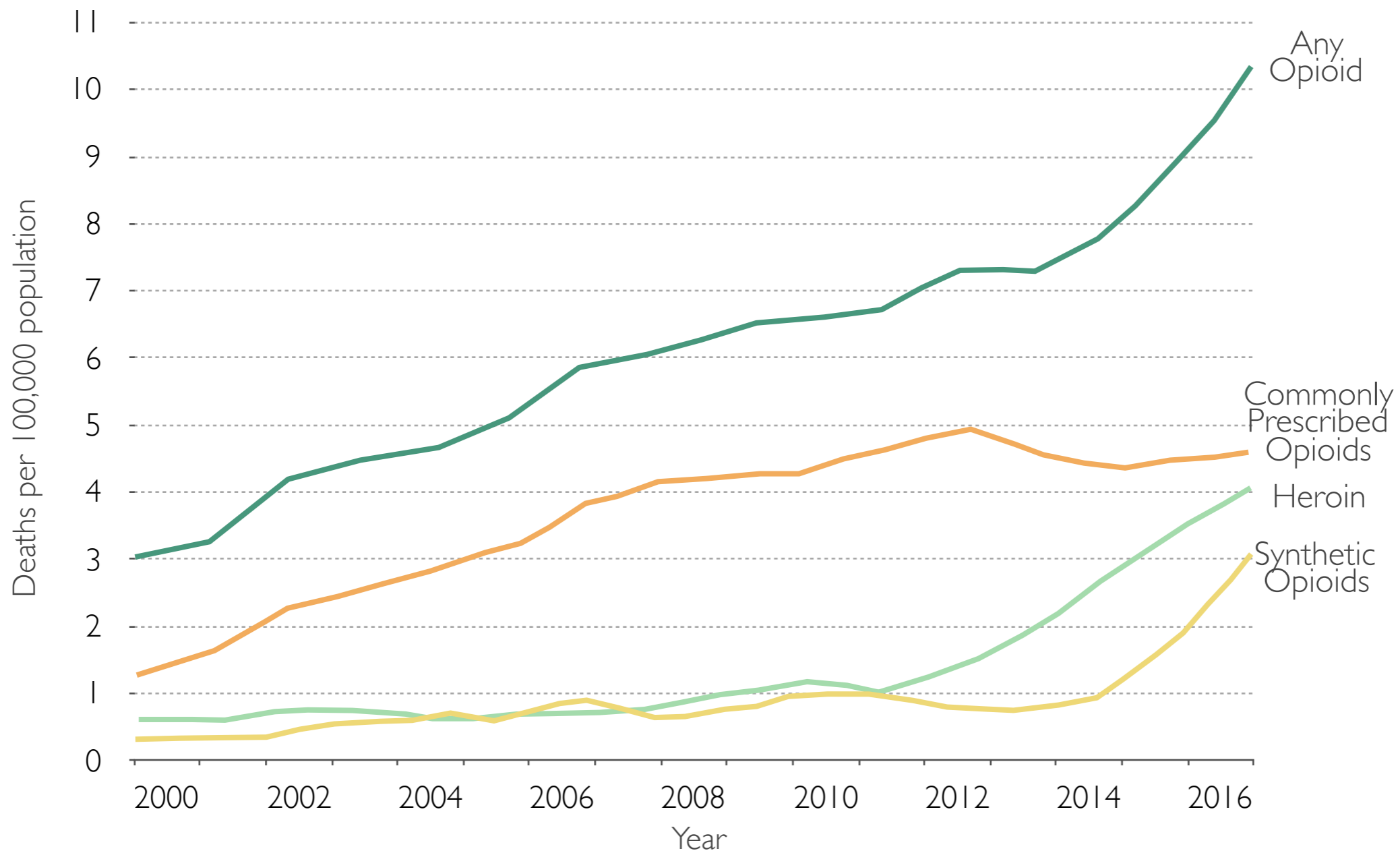


Drug overdoses are expected to remain the leading cause of death for Americans <50 yr

Synthetic opioids, (primarily fentanyl and its analogues) continue to push the mortality rate higher

Opioid Epidemic

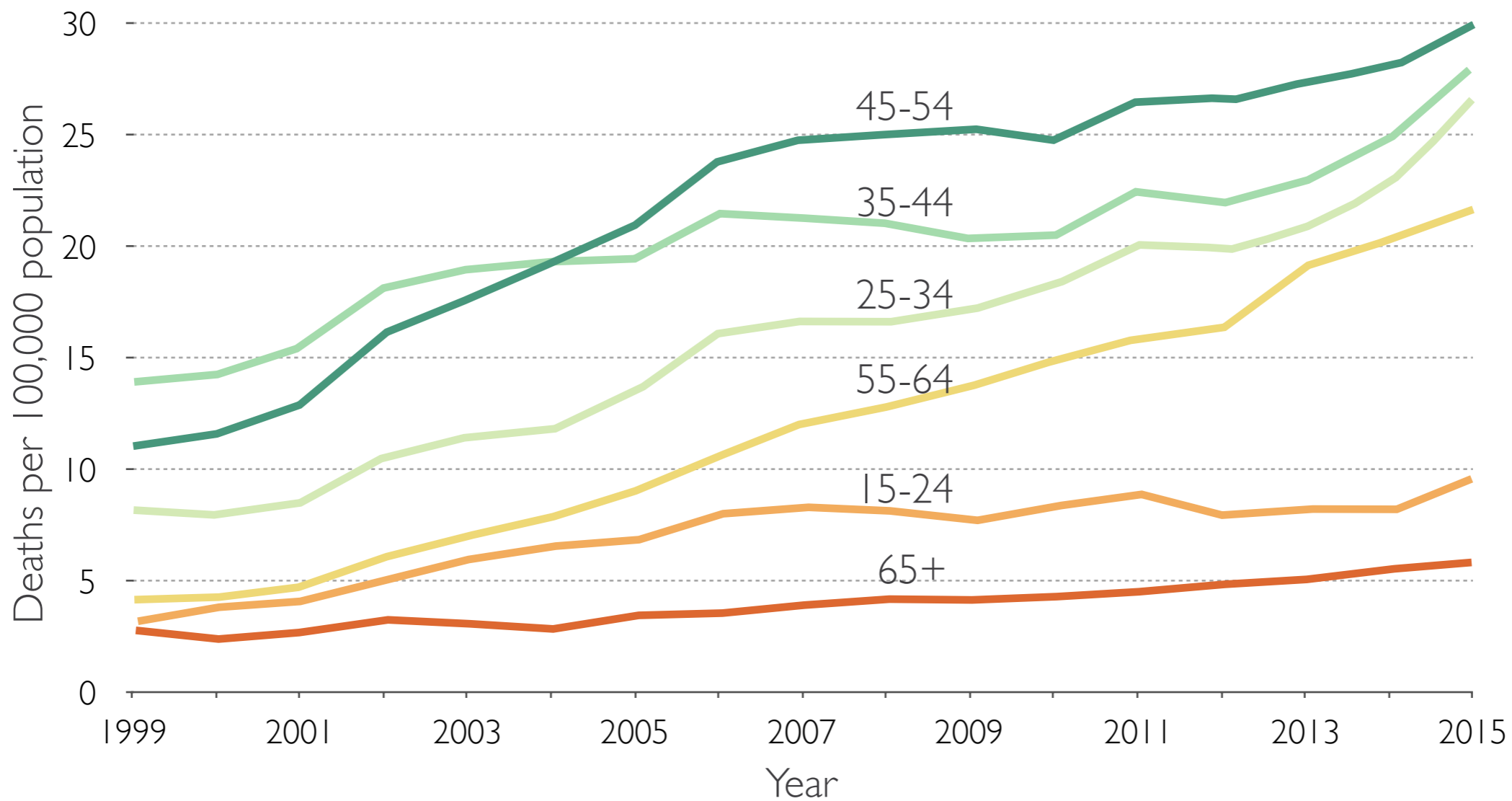
Overdose Death by Opioid Type



Source: CDC/NHCS, National Vital Statistics System, Mortality. US Dept of Health and Human Services

Opioid Epidemic

Age Distribution of Overdose Deaths



- 2012 -2015 shows significant upswing of 25 -44 year olds

Source: CDC

The Opioid Epidemic

What is the Cause ?

Opioid Epidemic Causes

What is Causing the Opioid Epidemic ?

- Narcotics are commonly prescribed by physicians
 - Intended to be used “appropriately”
 - Compton W et al NEJM (2016) described 10.3 million using Rx opioids non medically/not prescribed.
- National Health and Nutrition Examination Survey
 - 1999-2006: % adults using Rx opioid last 30d 5.0% → 6.9%
 - 1999-2012: % adults using Rx opioid >> morphine 17.0% → 37.0%
 - 1999-2010: Rx opioid sold ↑4x over 11 yrs

Source: D Goldberg, 2017 “Impact of the Opioid Epidemic on Organ Donation”

Opioid Epidemic Causes

Why is Heroin Commonly Abused ?

- Δ in M.D. prescribing habits have led to under-Rx after initial over-Rx opioids

- Cost: Heroin vs oral opioids

Oxycodone: \$30 for 30mg oxycodone tab

\$20 for 2x10mg/325mg Percocent tab

Heroin: \$5-10 for bag of heroin (1-5 bags per day)

Street Price

- Onset of Action: Rapid

IV: Peak onset 20 s Duration: 4 hrs

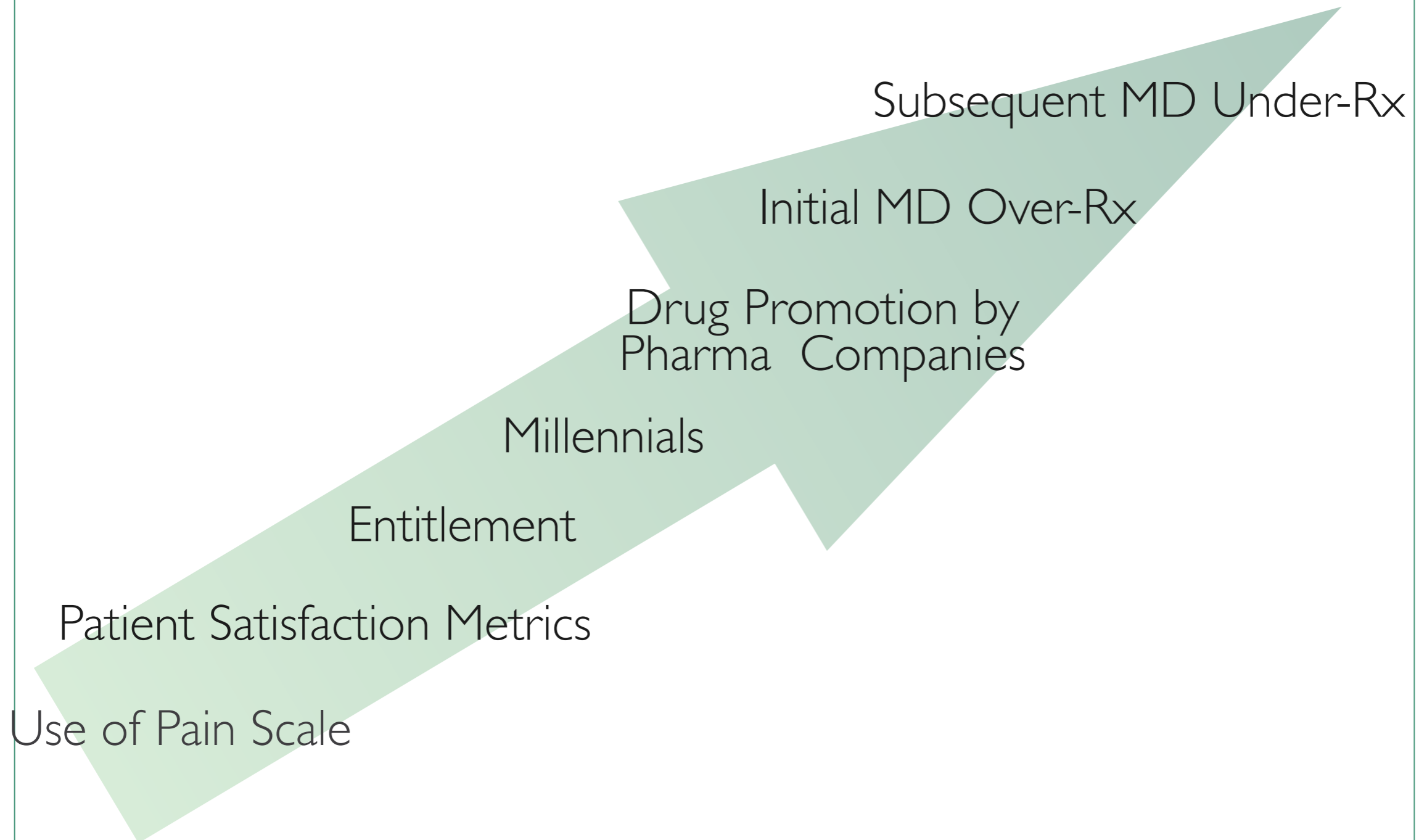
Smoking: Peak onset 10 min Duration: 5 hrs

Snorting: Peak onset 30 min Duration: 3-5 hrs

Source: D Goldberg, 2017 "Impact of the Opioid Epidemic on Organ Donation"

Opioid Epidemic

Reasons for the Opioid Epidemic



The Opioid Epidemic

Where is This Occurring ?

Opioid Epidemic

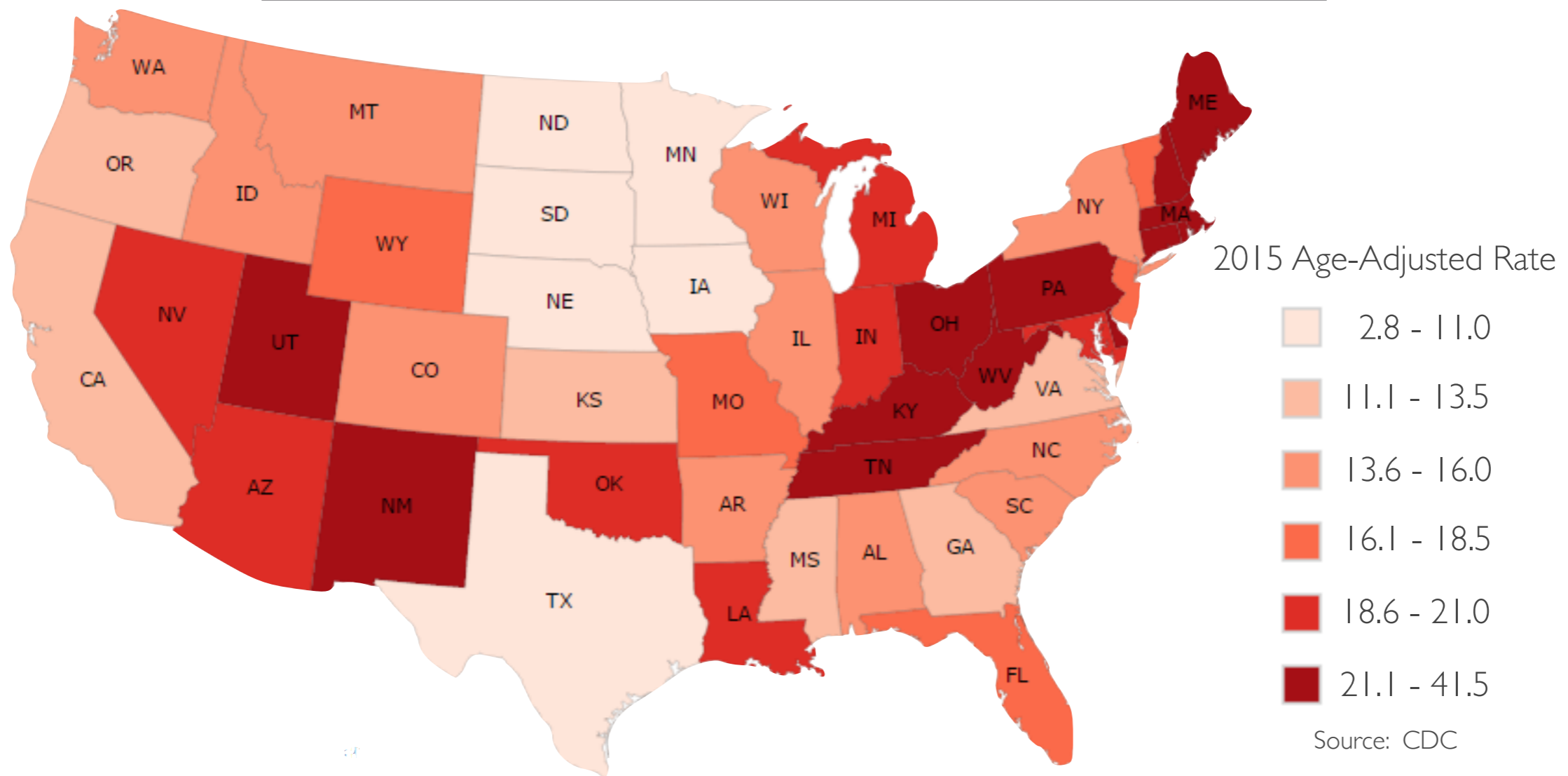
Geographic Impact

- The opioid epidemic does not appear to be affecting all of the US equally
- The most frequent geographic location is related to the demographics of the opiate abuser
- Locations are places where rural, white populations predominate

Opioid Epidemic

Geographic Impact

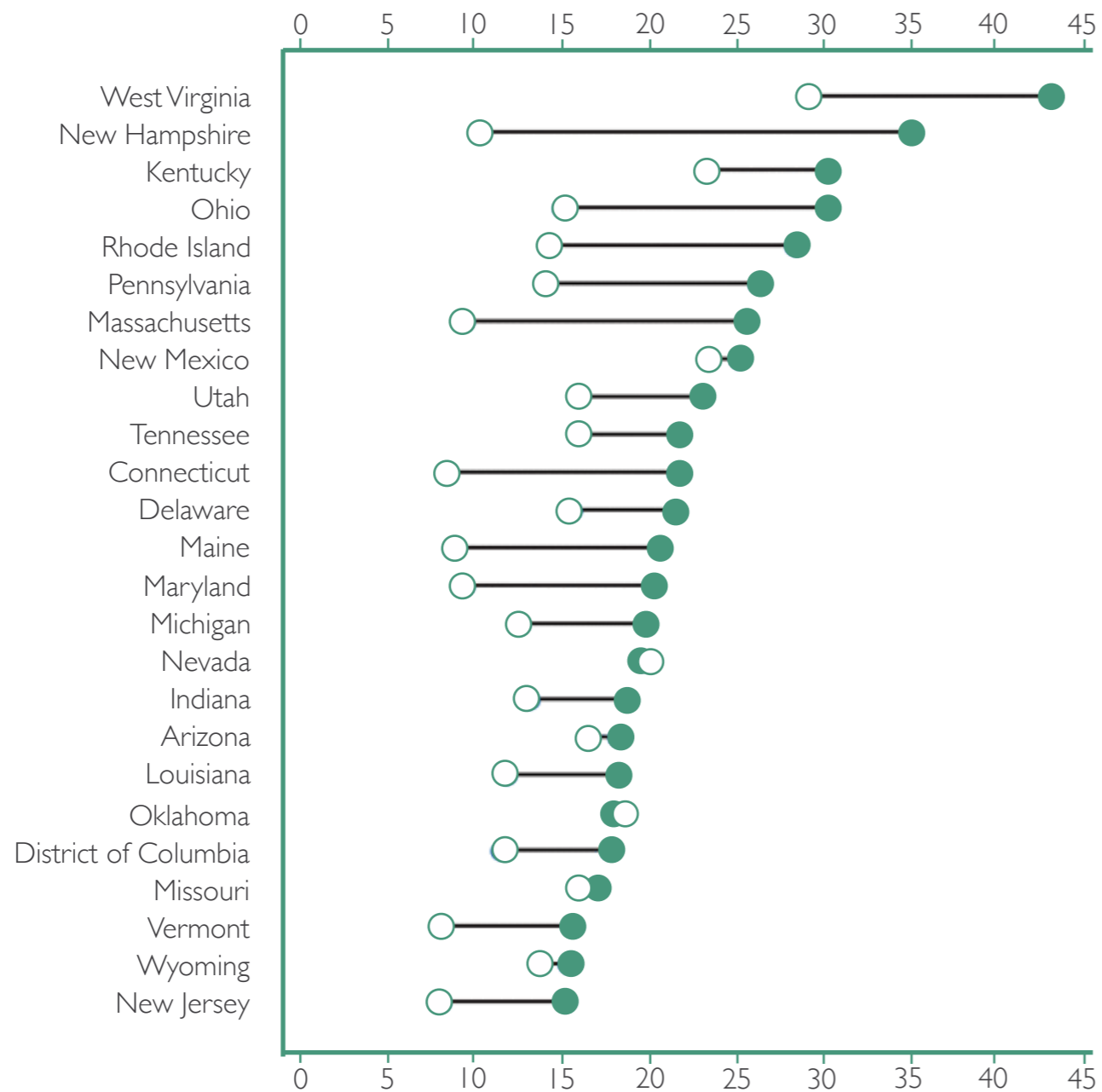
Age- Adjusted Rates of Overdose Deaths Per State



Predominance of deaths in the Appalachian region, Southwest and industrial heartland

Opioid Epidemic

Geographic Impact



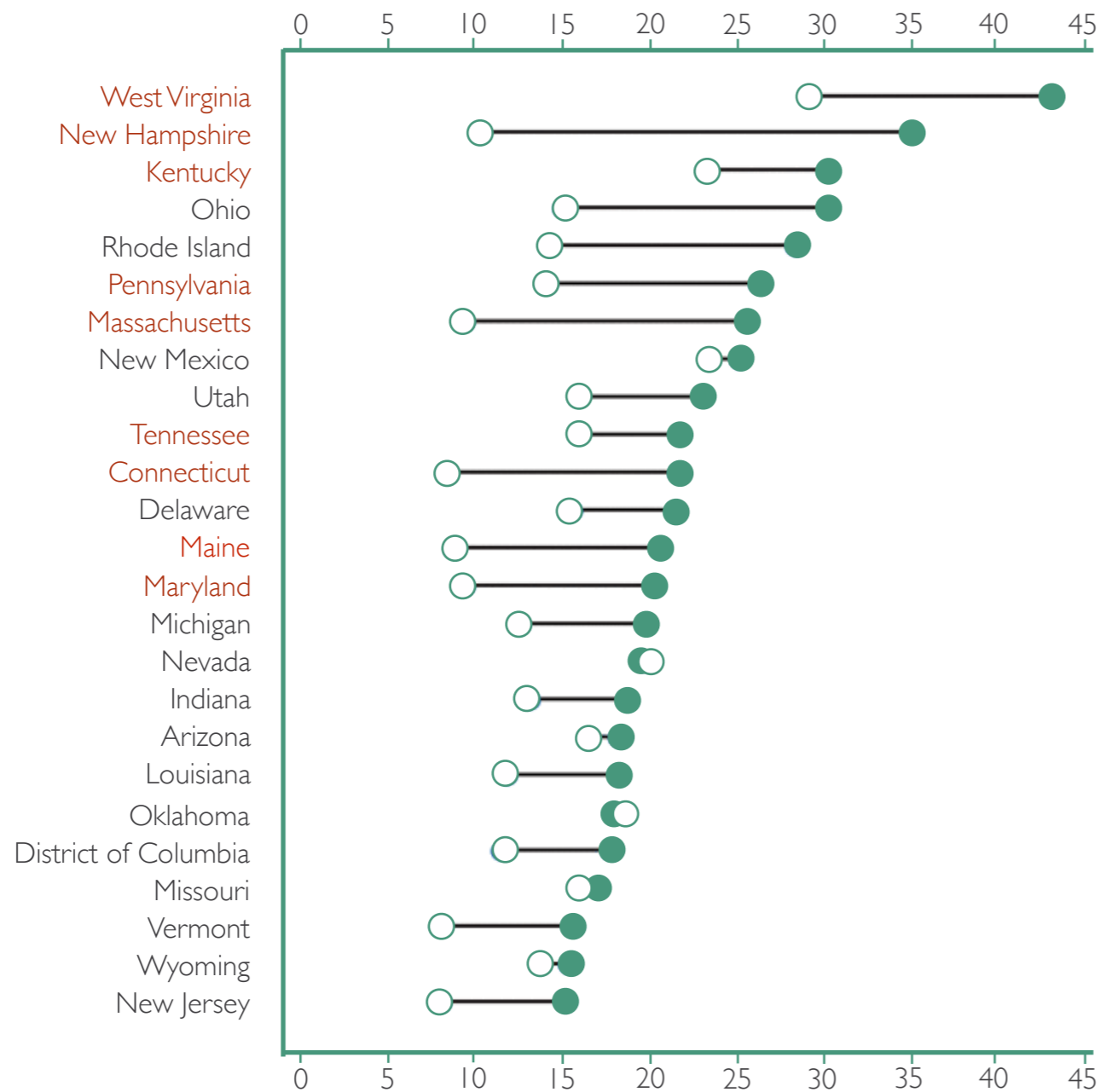
Age-Adjusted Rate of Drug Overdose Deaths by State

- 2010
- 2015

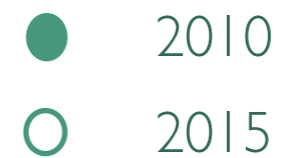
Predominance of Overdose Deaths Occur in the:

- Appalachian States
- Northeast States
- Southwest States
- Industrial Heartland

Opioid Epidemic Geographic Impact



Age-Adjusted Rate of Drug Overdose Deaths by State

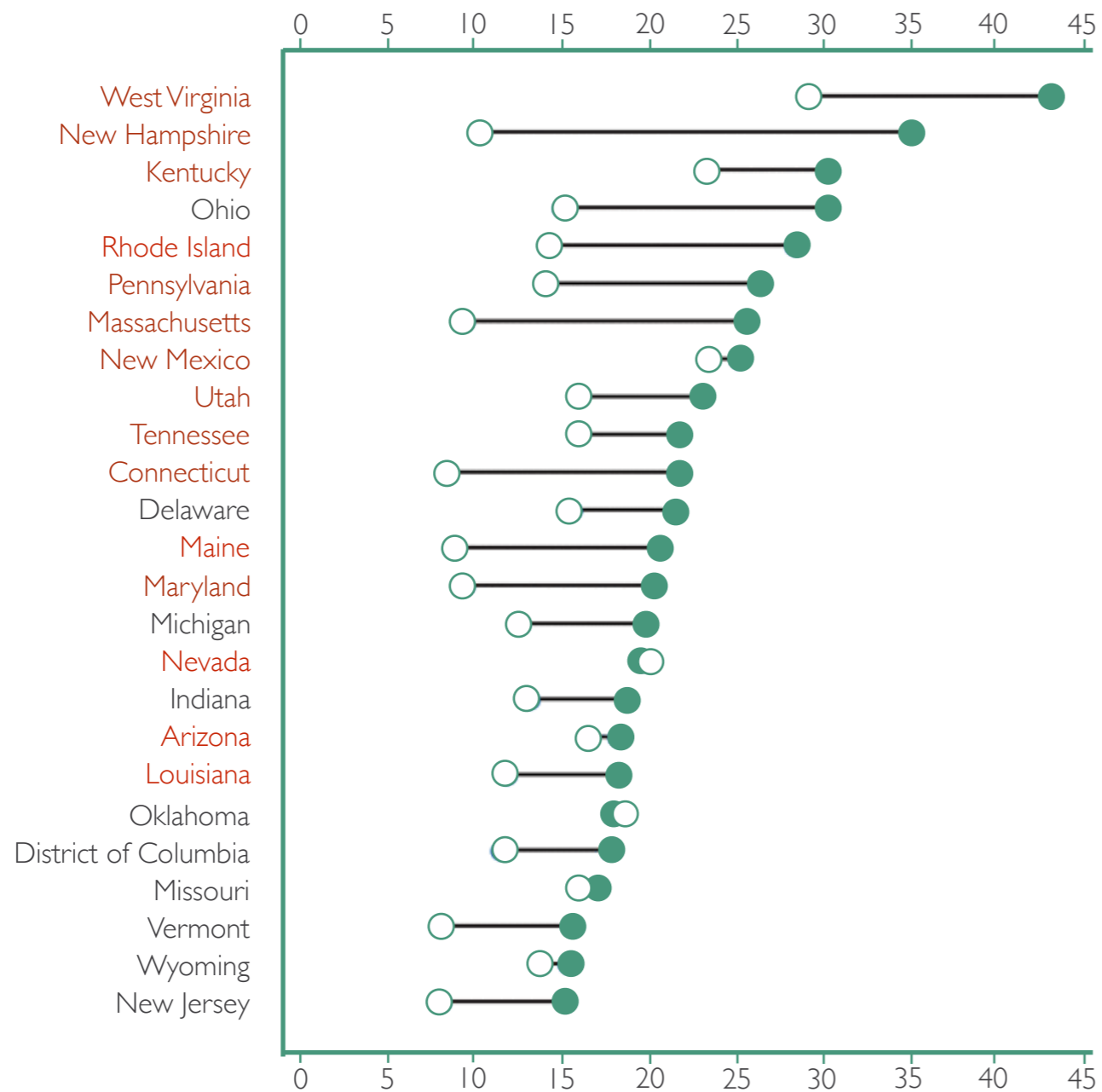


Predominance of Overdose Deaths Occur in the:

- Appalachian States
- Northeast States
- Southwest States
- Industrial Heartland

Opioid Epidemic

Geographic Impact



Age-Adjusted Rate of Drug Overdose Deaths by State

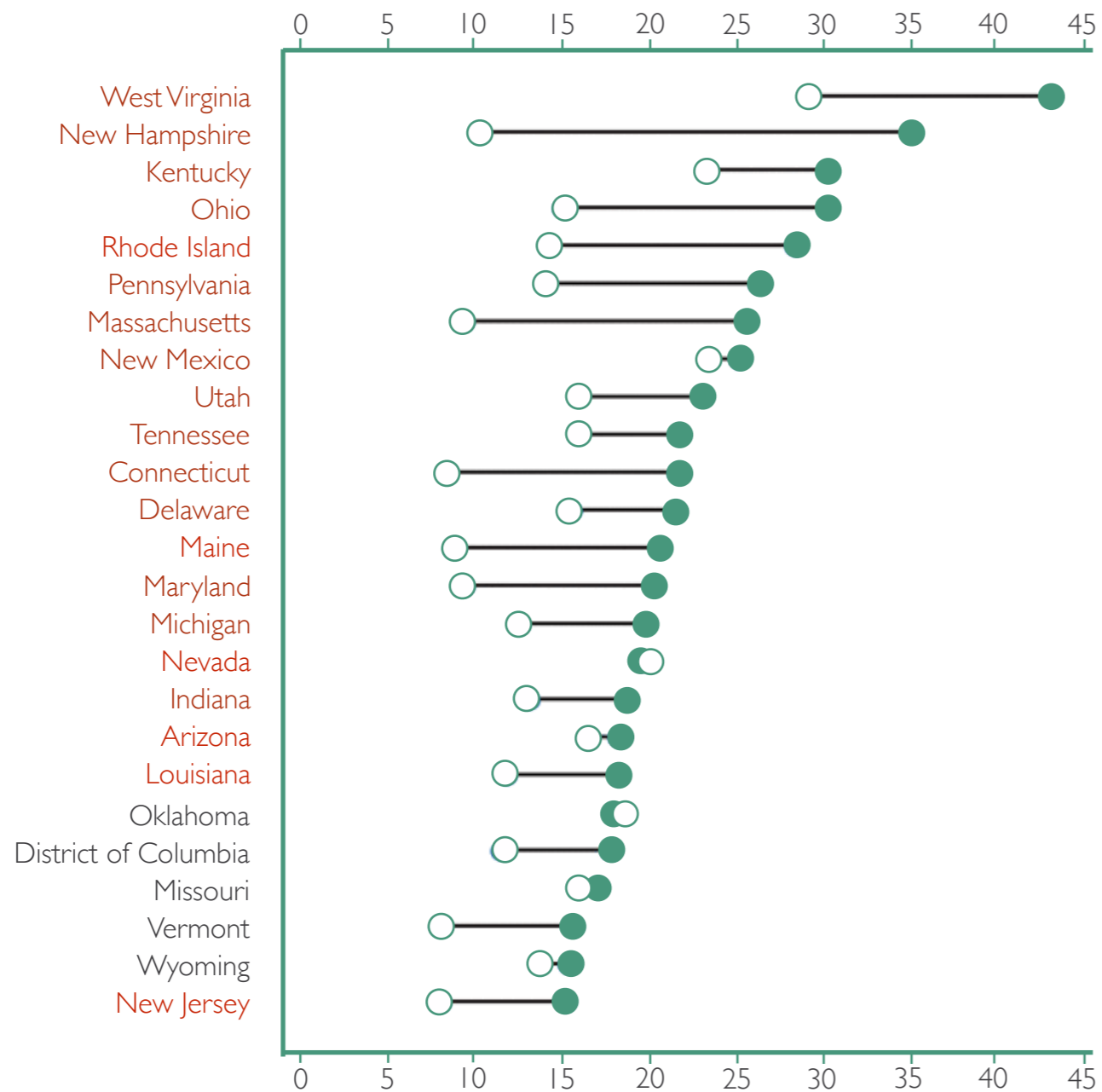
- 2010
- 2015

Predominance of Overdose Deaths Occur in the:

- Appalachian States
- Northeast States
- Southwest States
- Industrial Heartland

Opioid Epidemic

Geographic Impact



Age-Adjusted Rate of Drug Overdose Deaths by State

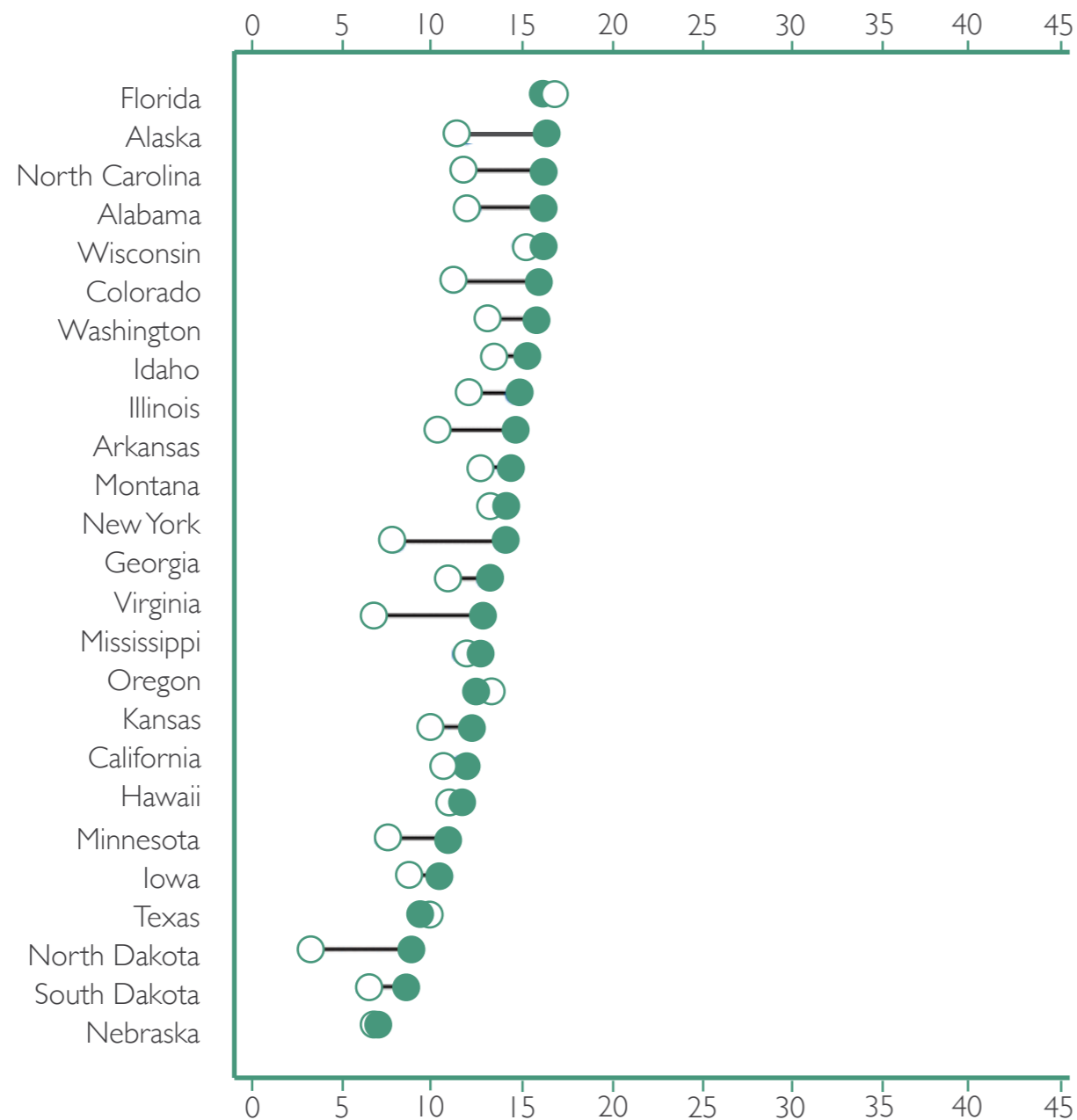
- 2010
- 2015

Predominance of Overdose Deaths Occur in the:

- Appalachian States
- Northeast States
- Southwest States
- Industrial Heartland

Opioid Epidemic

Geographic Impact



Age-Adjusted Rate of Drug Overdose Deaths by State

- 2010
- 2015

Predominance of Overdose Deaths Occur in the:

- Appalachian States
- Northeast States
- Southwest States
- Industrial Heartland

The Opioid Epidemic

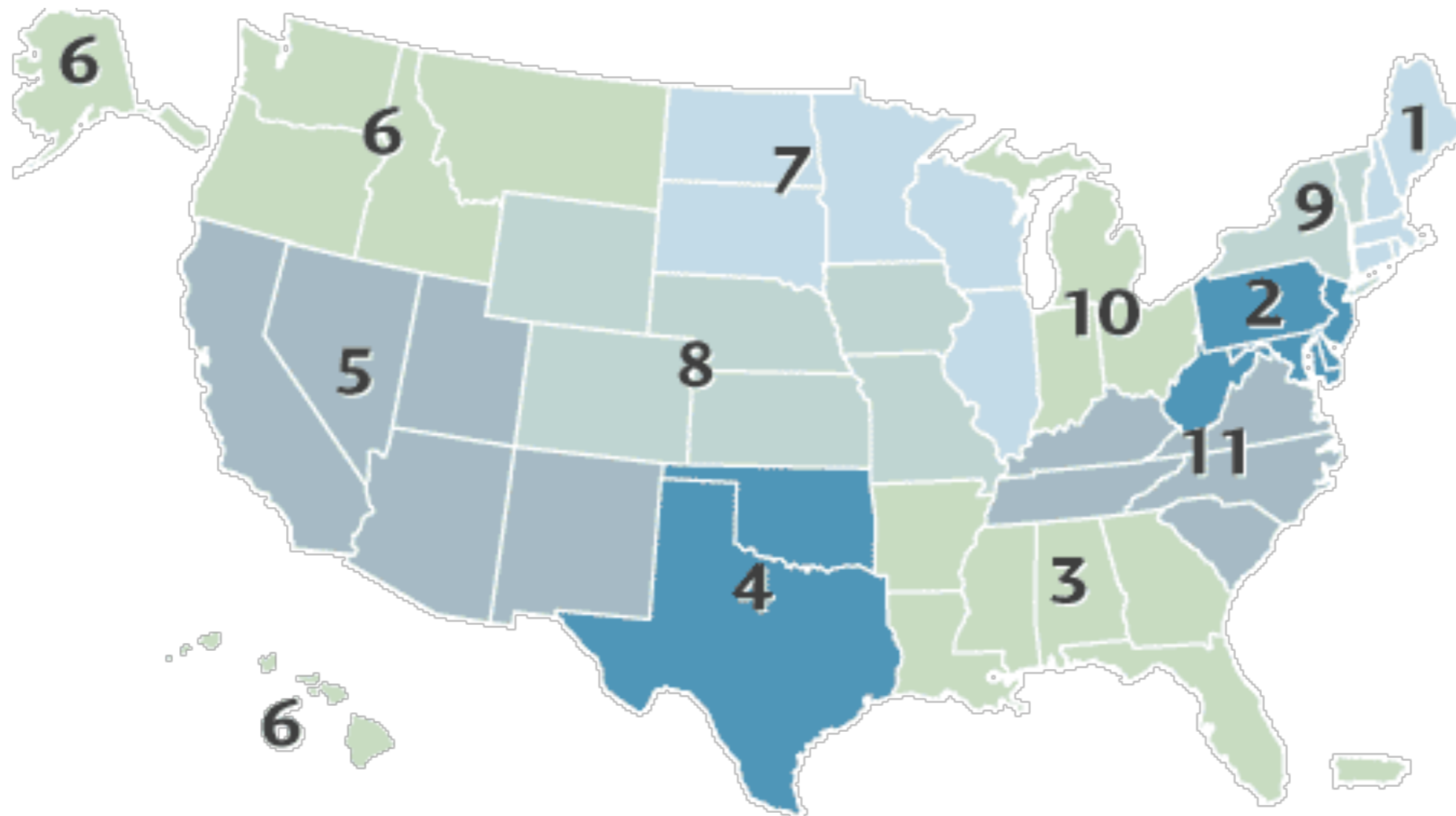
Does this Geographical Specificity Impact
Organ Donation ?

The Opioid Epidemic

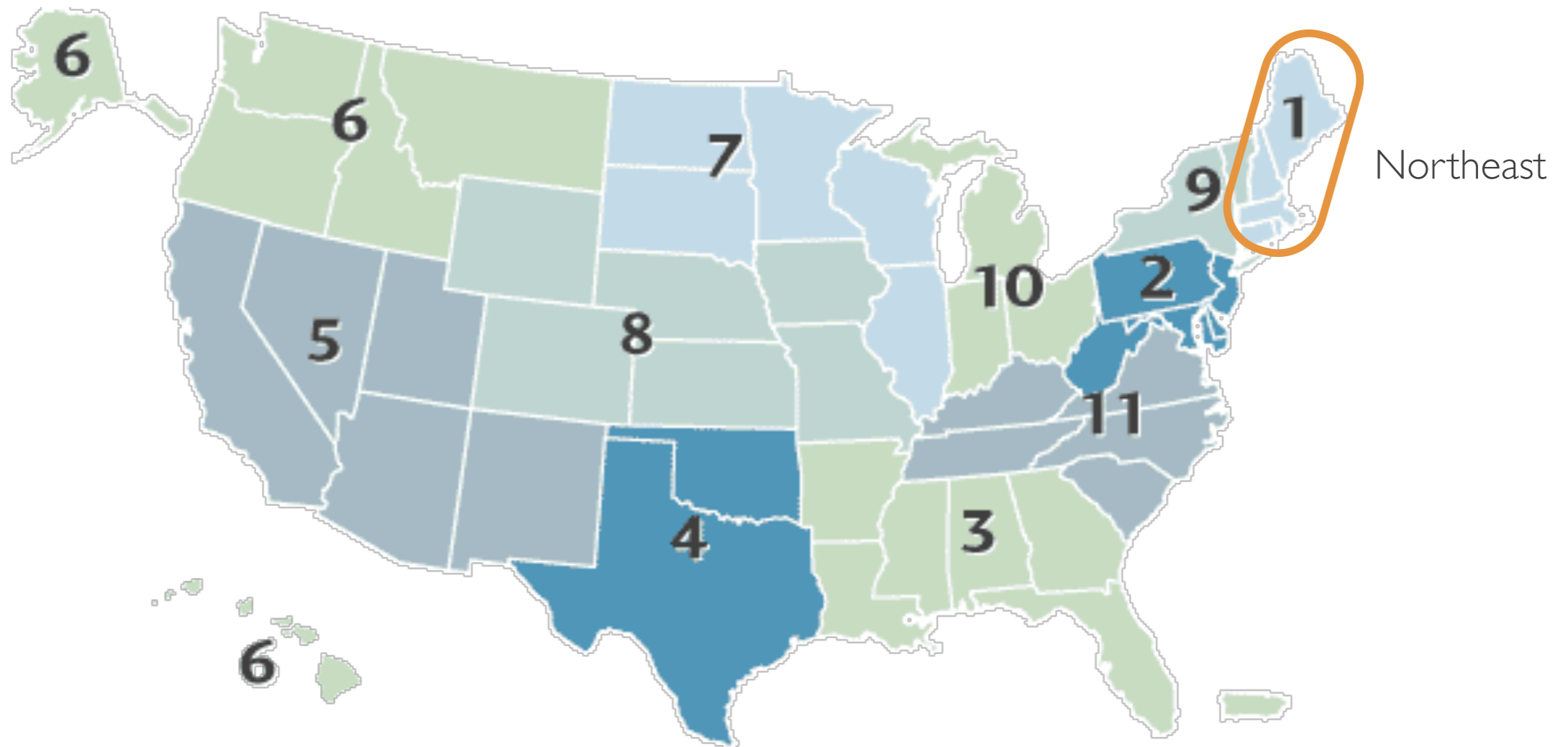
Does this Geographical Specificity Impact
Organ Donation ?

Yes

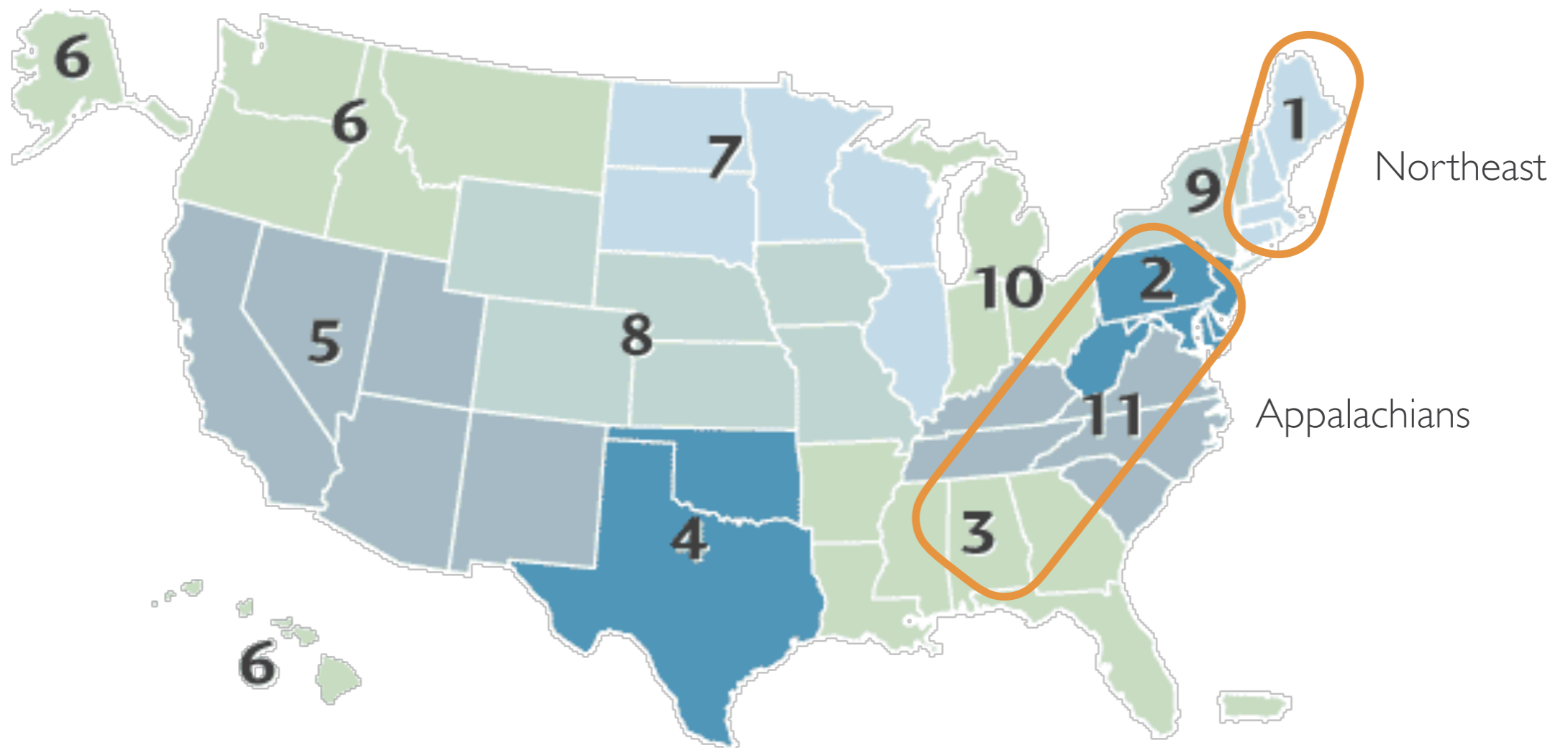
Opioid Epidemic Impact on Transplant per Region



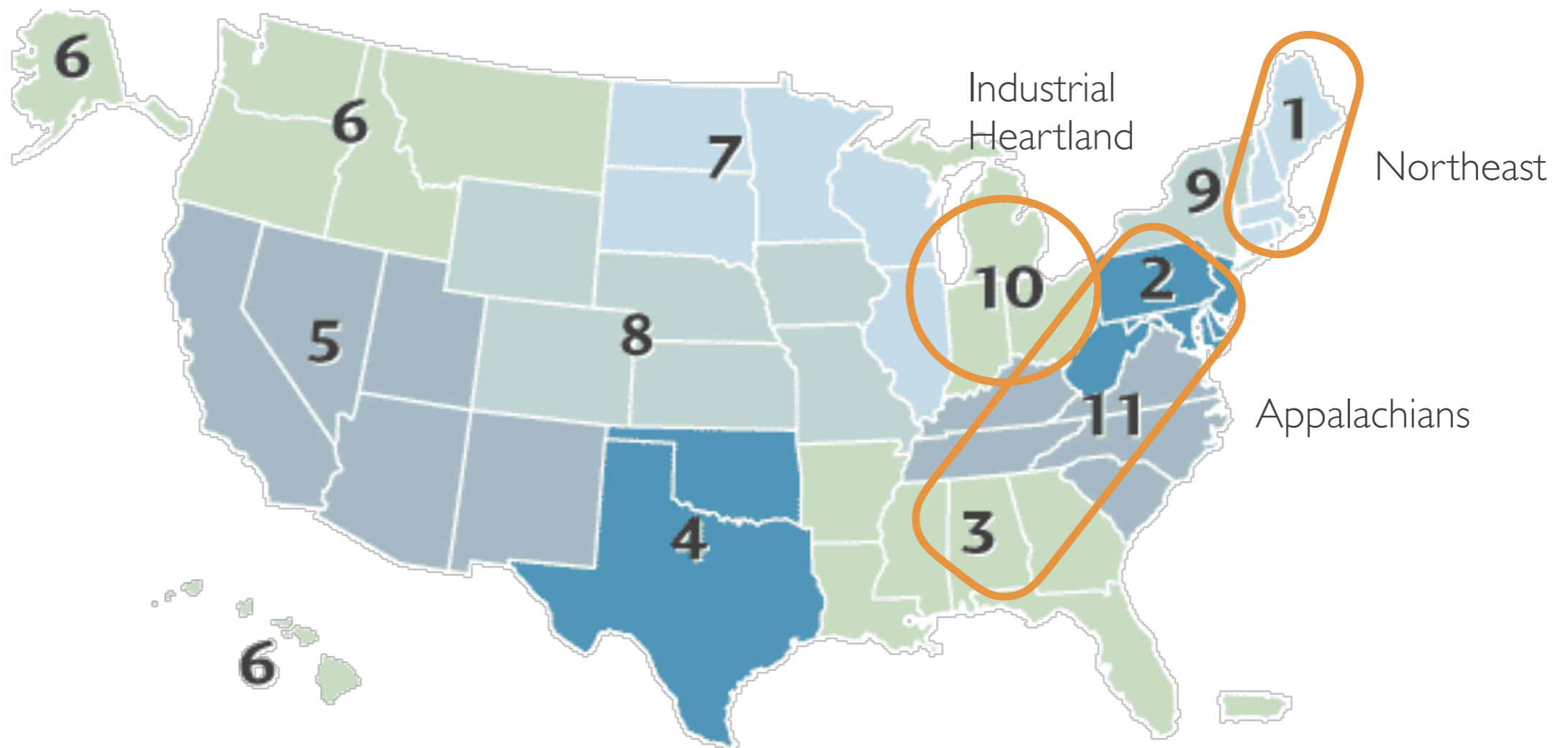
Opioid Epidemic Impact on Transplant per Region



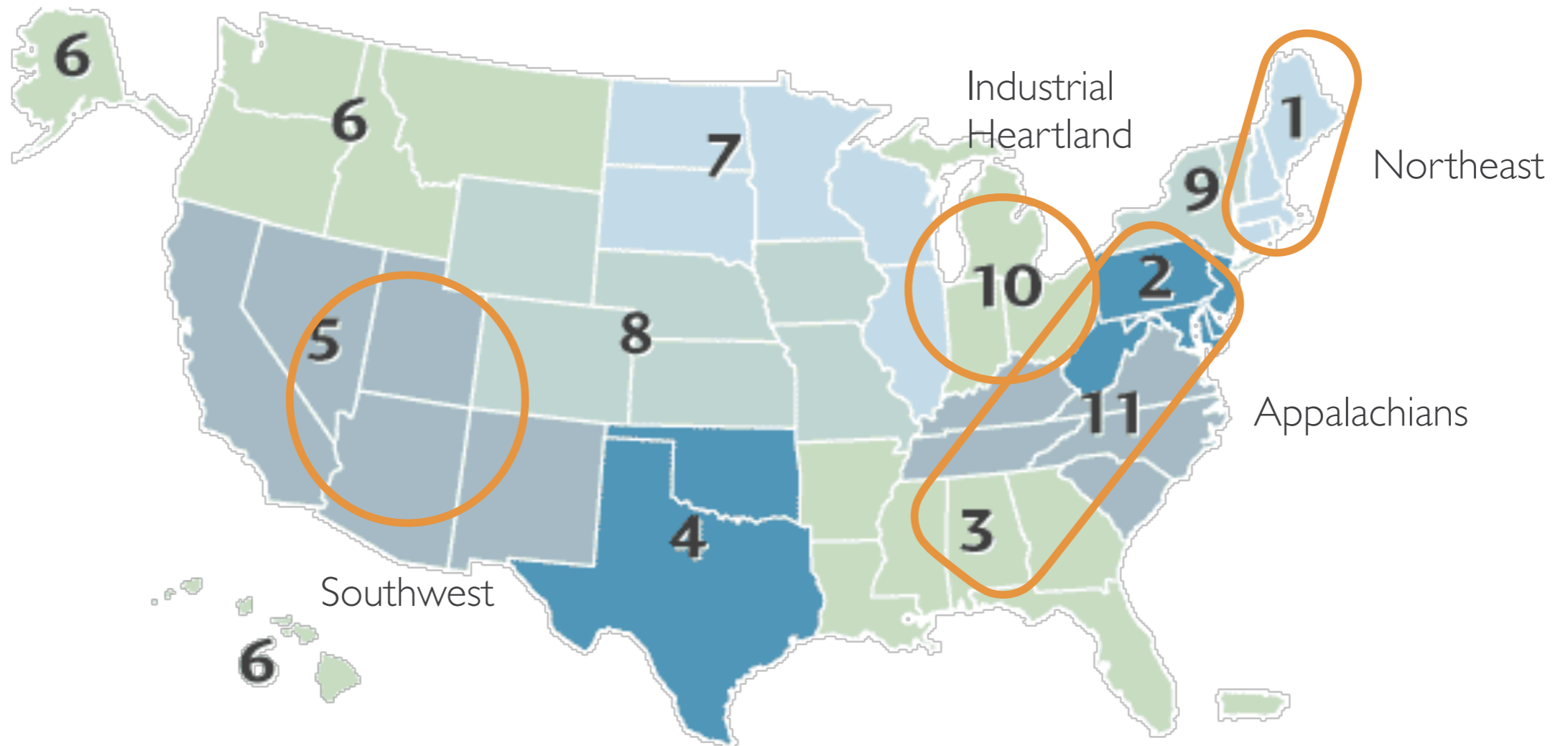
Opioid Epidemic Impact on Transplant per Region



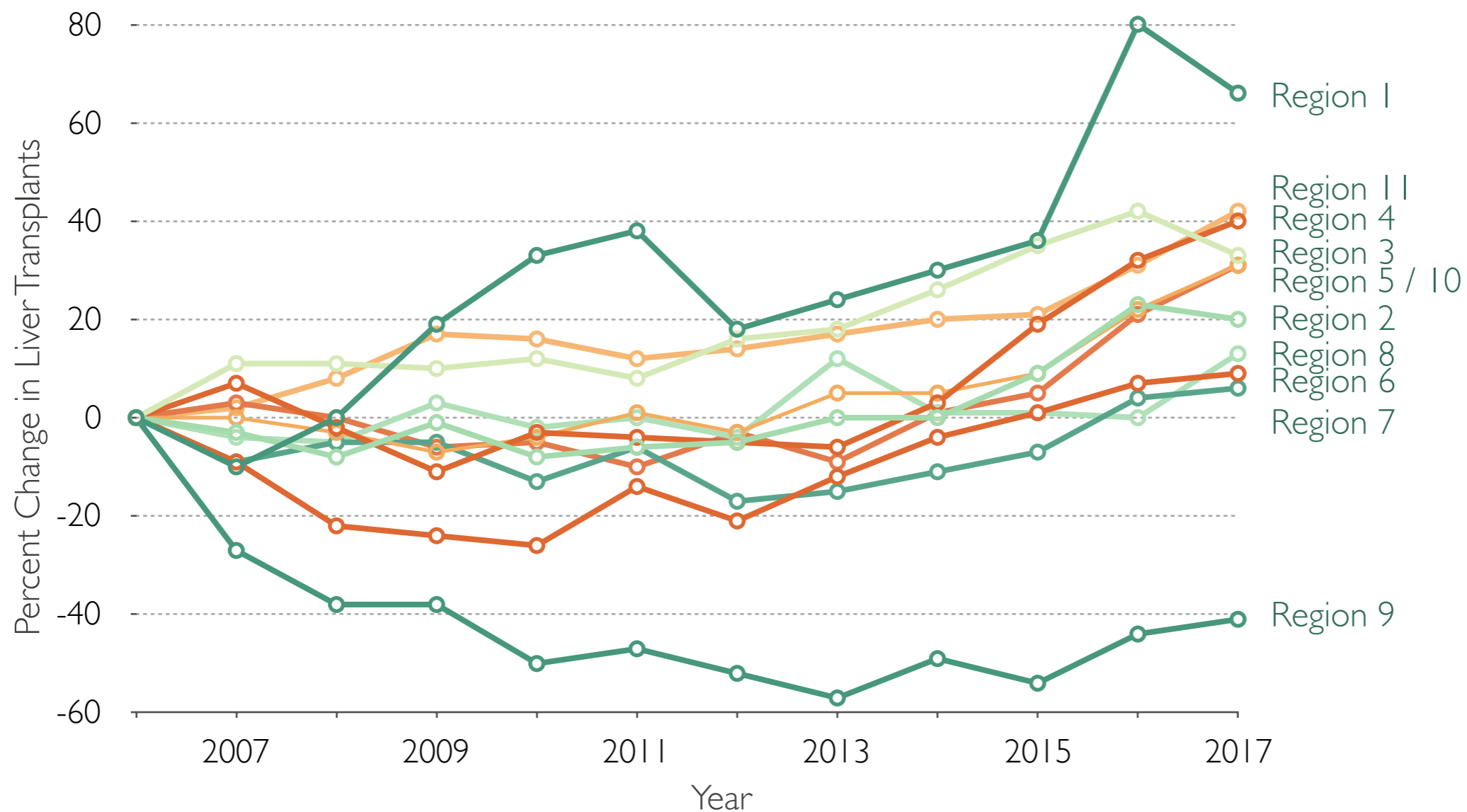
Opioid Epidemic Impact on Transplant per Region



Opioid Epidemic Impact on Transplant per Region

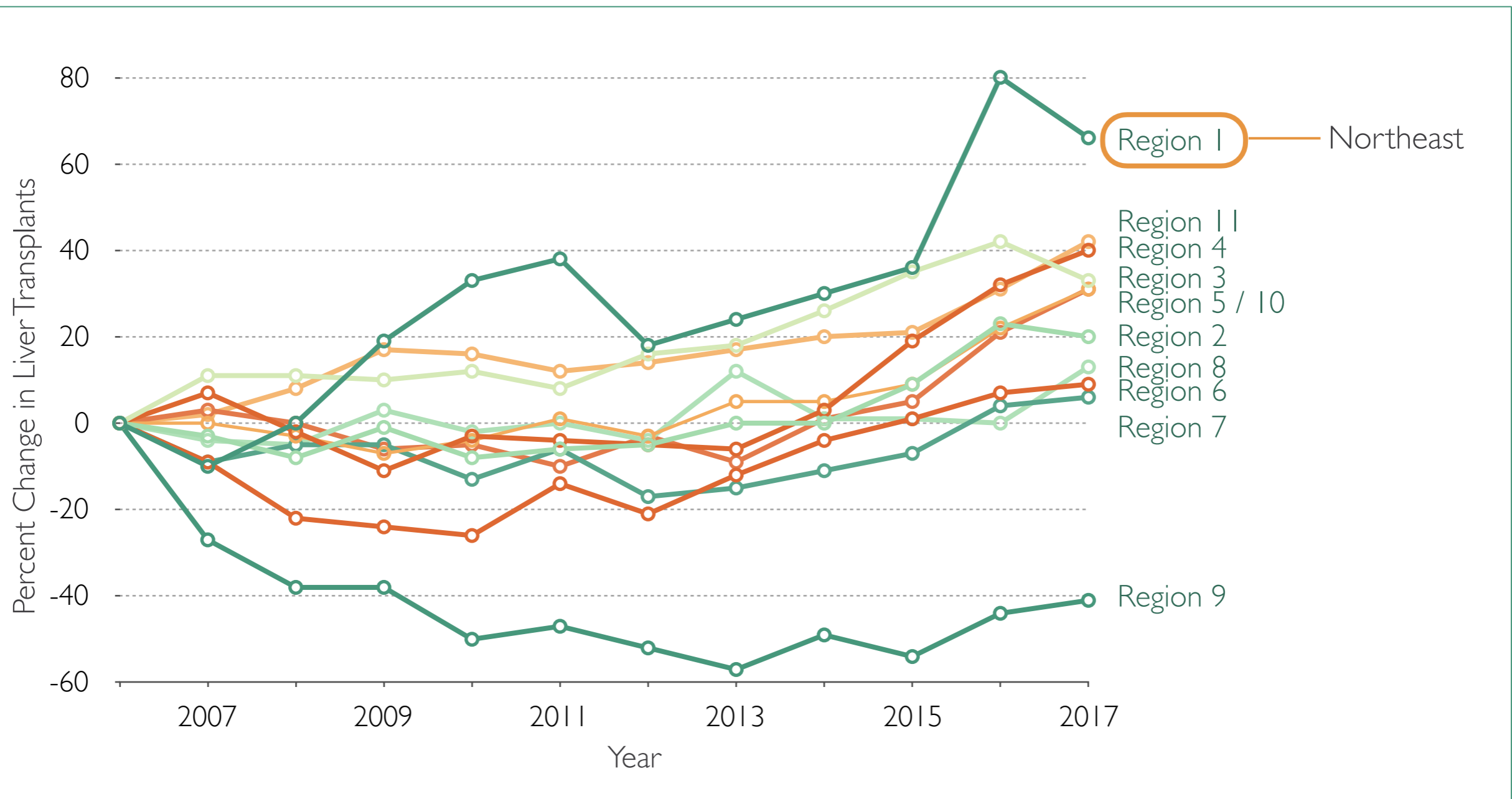


Opioid Epidemic Impact on Liver Transplants per Region



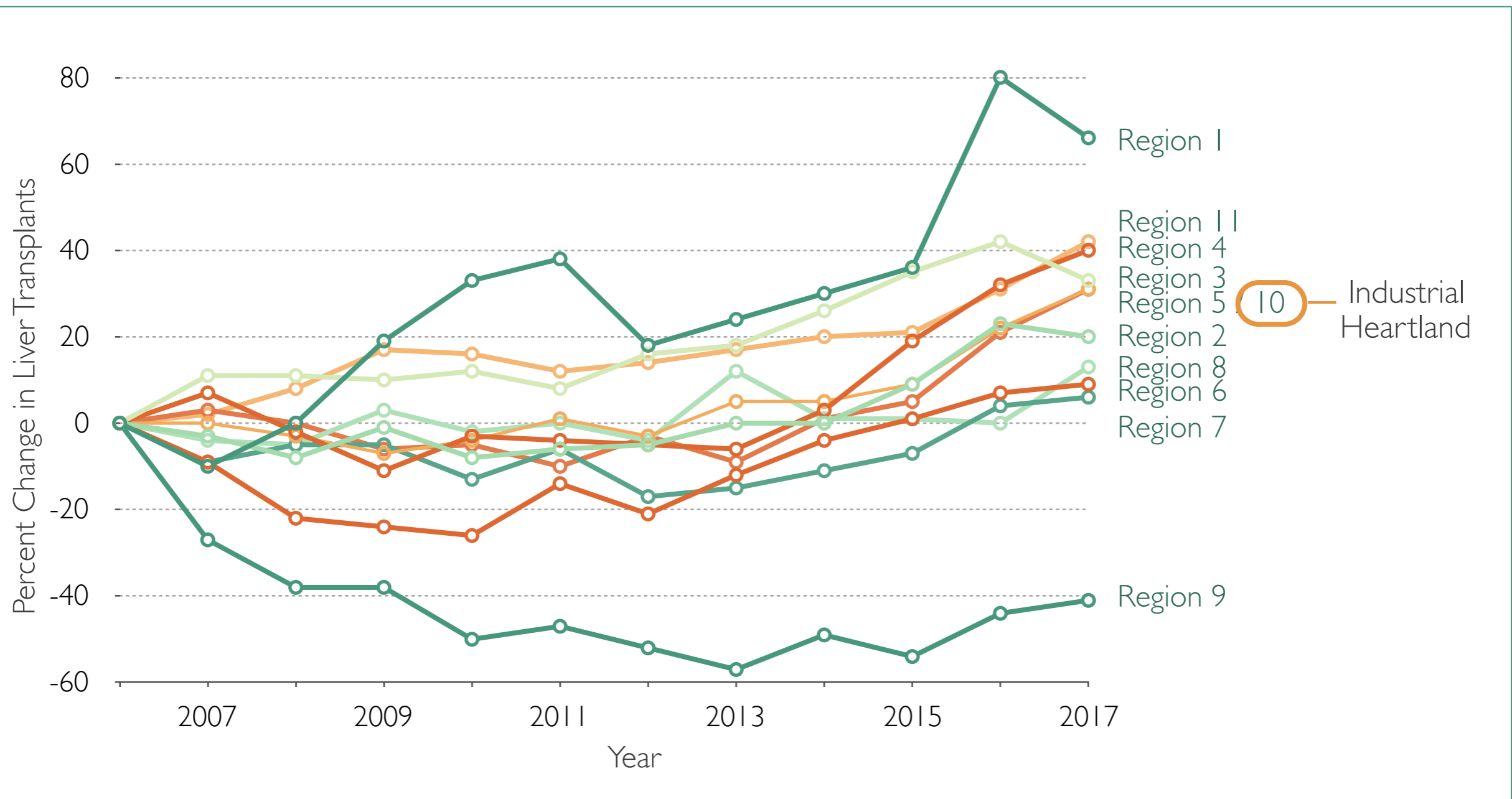
Opioid Epidemic

Impact on Liver Transplants per Region



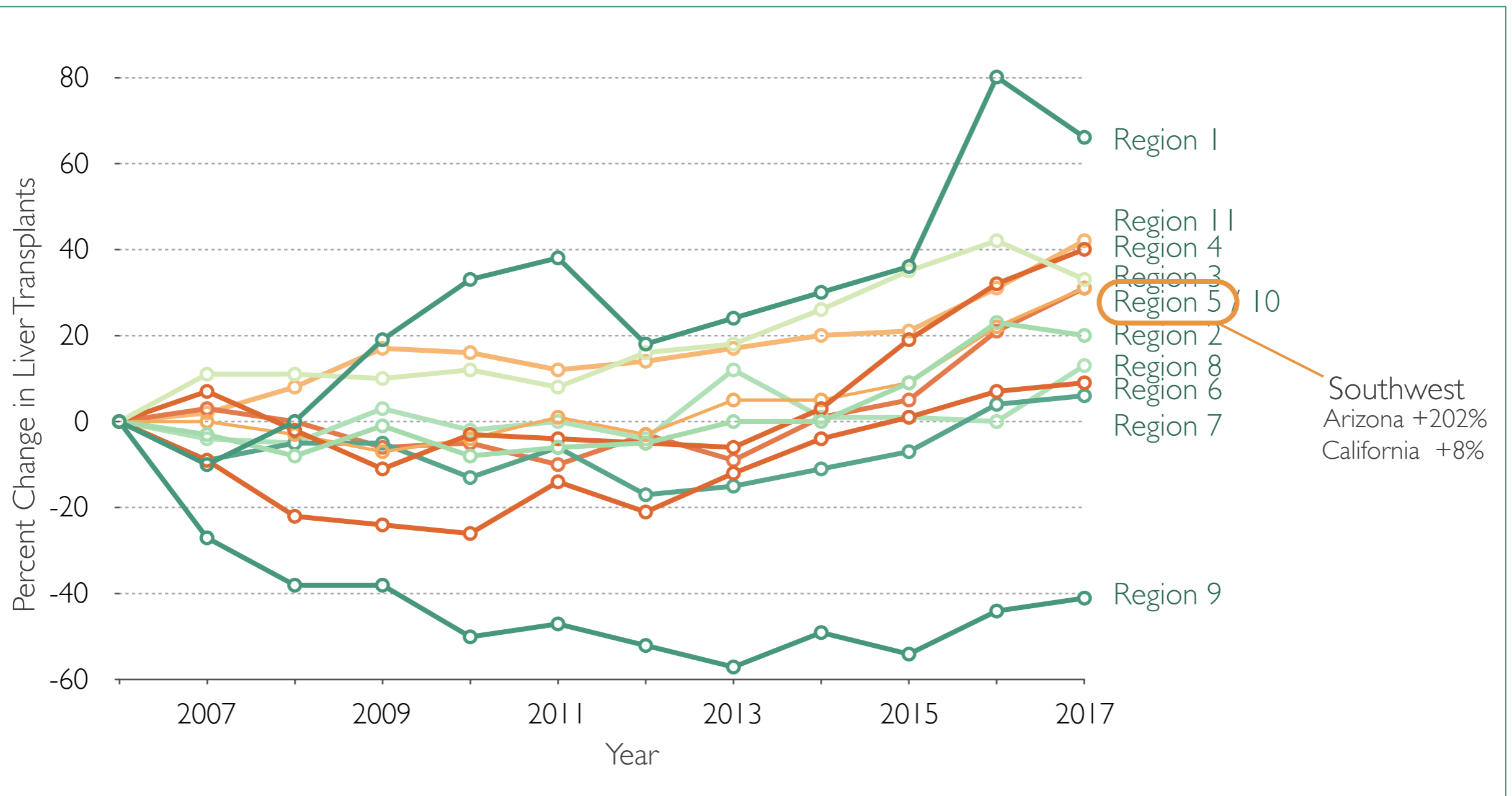
Opioid Epidemic

Impact on Liver Transplants per Region



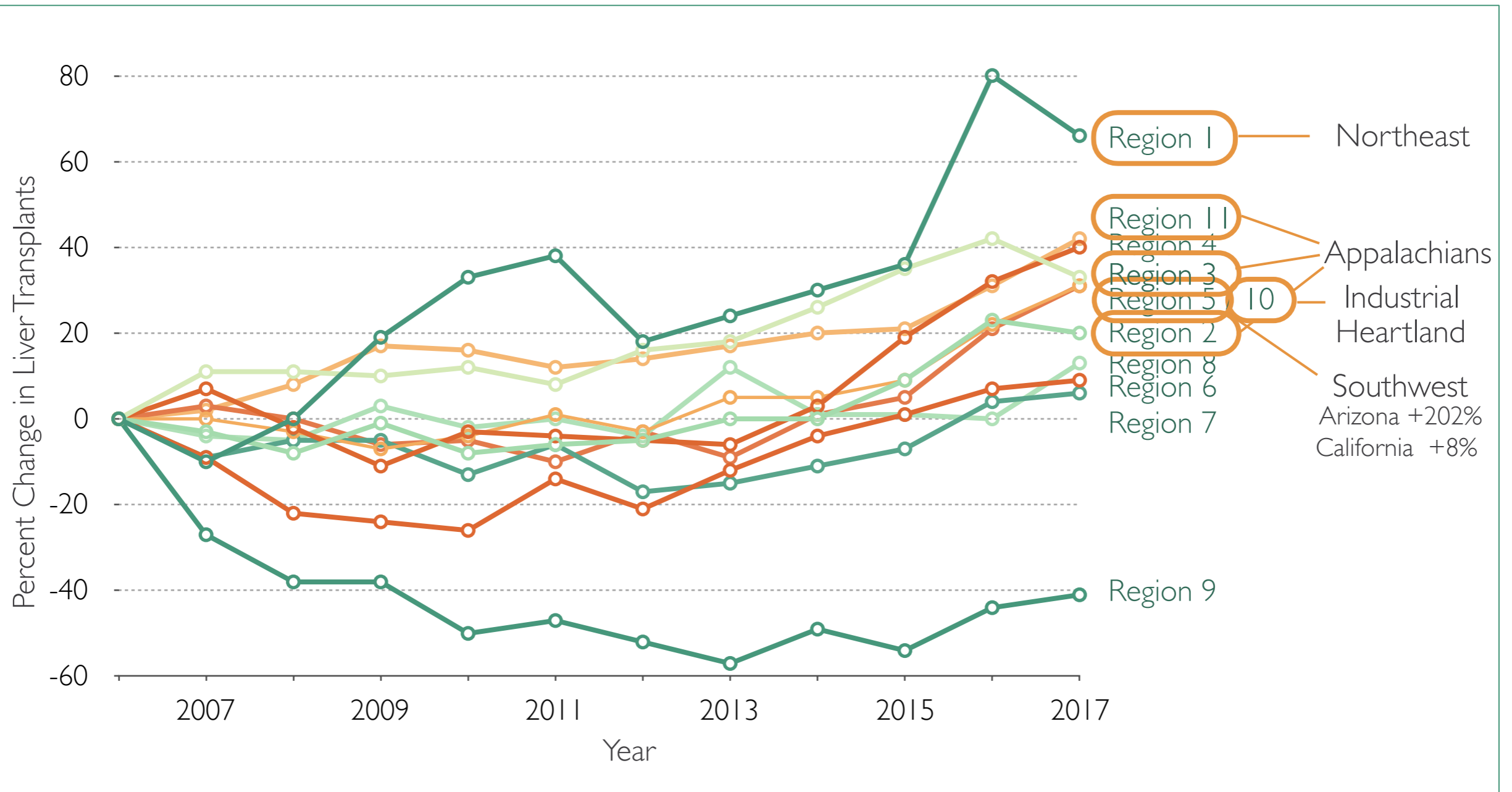
Opioid Epidemic

Impact on Liver Transplants per Region



Opioid Epidemic

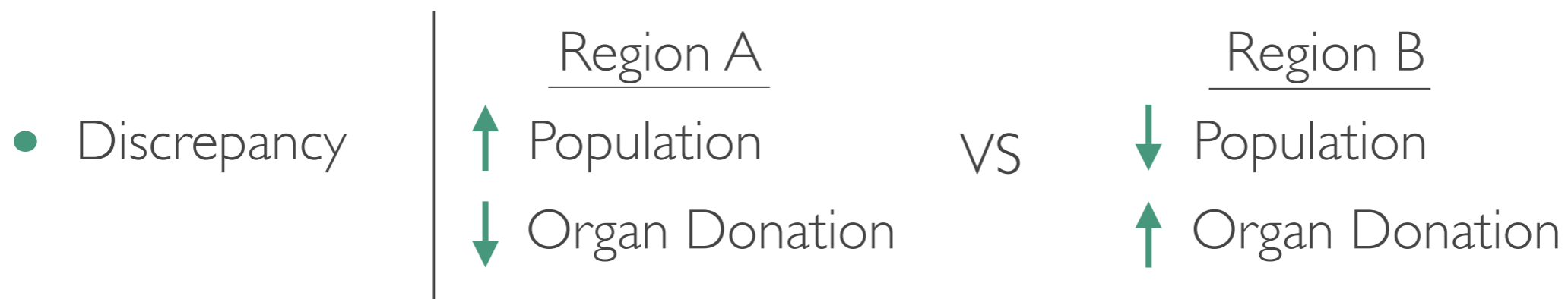
Impact on Liver Transplants per Region



Opioid Epidemic

Impact on Liver Transplants per Region

- Organ allocation has been one of the most contentious issues in liver transplantation for the last 5 years

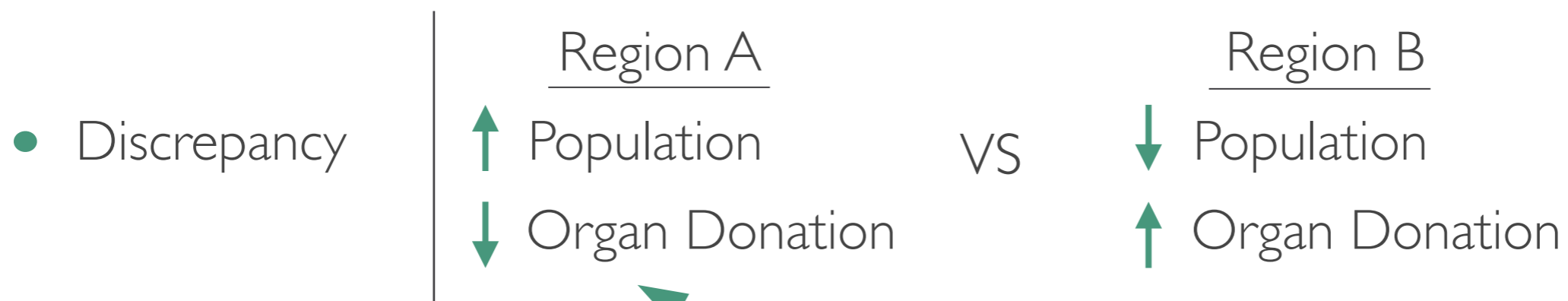


- Political pressure for redistricting → Change organ allocation rules

Opioid Epidemic

Impact on Liver Transplants per Region

- Organ allocation has been one of the most contentious issues in liver transplantation for the last 5 years



- Political pressure for redistricting → Change organ allocation rules

Opioid Epidemic

Impact on Liver Transplants per Region

- The UNOS regions and OPOs with ↑ organ donation now roughly correspond to those areas where the opioid epidemic predominates.
- Fixed decisions regarding organ allocation are being considered in which calculations are being made from the variable opioid epidemic.
- Aggressive strategies that might reduce the opioid epidemic, would also quickly alter the organ donation calculation.
 - ↳ Subsequent re-redistricting would not be as rapid

Opioid Epidemic and Transplant

First Summary

- Opioids have quickly become the leading cause of death in < 50 yr
- The opioid epidemic predominantly impacts rural young white males in:
 - 1) Northeast US
 - 2) Appalachians
 - 3) Industrial Heartland
 - 4) Southwest US
- The opioid epidemic has dramatically ↑ the number of organ donors
- The increase in US donor organs is not homogenous and is clustered in the UNOS Regions where the epidemic predominates
- Decisions on future redistricting and organ allocation need to consider the variable impact of opioid epidemic

Opioids and Organ Donation

HCV+ Donors

Opioids and Organ Donation

HCV+ Donors

Change in Incidence of HCV — Impact of Opioid Epidemic

- Recent abrupt rise in incidence of acute HCV
- Acute HCV incidence has ↑ 3x over last few years.
- Timing of ↑ HCV incidence parallels the opioid epidemic
- The ↑ acute HCV matches the demographics and geography of the opioid epidemic

Opioids and Organ Donation

HCV+ Donors

Change in Incidence of HCV — Impact of Opioid Epidemic

- Recent abrupt rise in incidence of acute HCV
- Acute HCV incidence has ↑ 3x over last few years.



- Timing of ↑ HCV incidence parallels the opioid epidemic
- The ↑ acute HCV matches the demographics and geography of the opioid epidemic

Opioids and Organ Donation

HCV+ Donors

Change in Incidence of HCV — Impact of Opioid Epidemic

↑ Opioids/Heroin → ↑ Overdose Deaths → ↑ Organ Donors

Opioids and Organ Donation

HCV+ Donors

Change in Incidence of HCV — Impact of Opioid Epidemic

↑ Opioids/Heroin → ↑ Overdose Deaths → ↑ Organ Donors

+

↑ Opioids/Heroin → ↑ HCV Transmission → ↑ Acute HCV+

Opioids and Organ Donation

HCV+ Donors

Change in Incidence of HCV — Impact of Opioid Epidemic

↑ Opioids/Heroin → ↑ Overdose Deaths → ↑ Organ Donors

+

↑ Opioids/Heroin → ↑ HCV Transmission → ↑ Acute HCV+

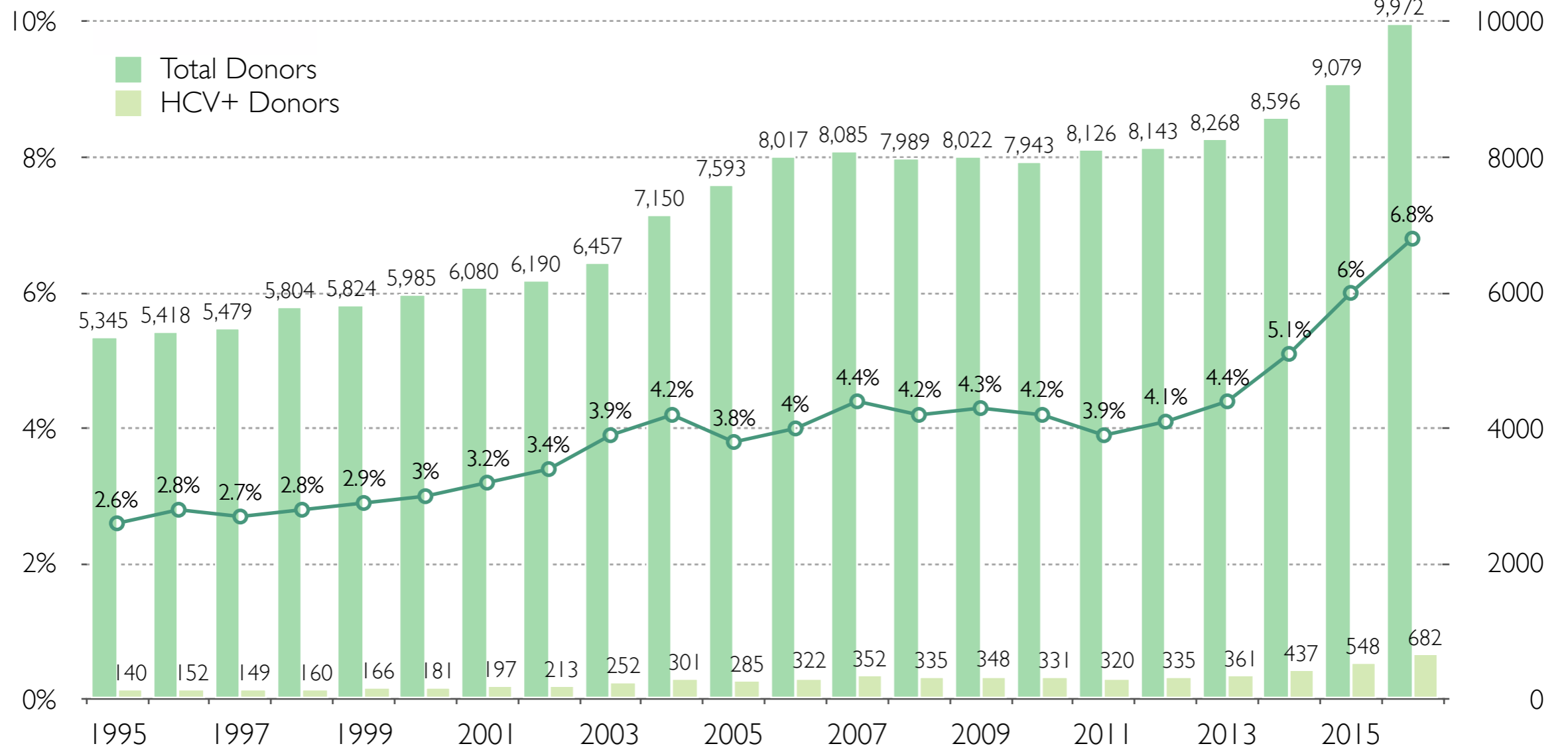
=

↑ HCV+ Organ Donors

Opioids and Organ Donation

HCV+ Donors

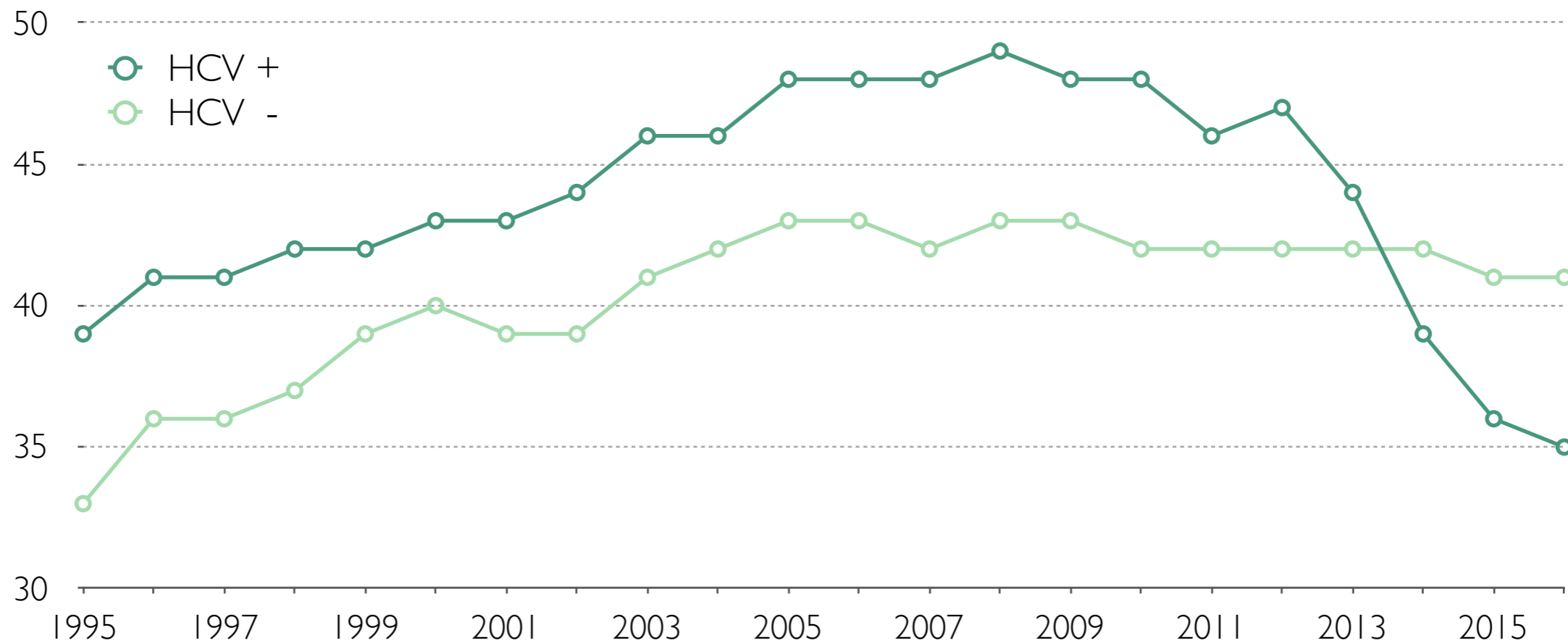
Change in Incidence of HCV+ Organ Donors



Opioids and Organ Donation

HCV+ Donors

Median Deceased Donor Age By HCV Status



- Median age of HCV+ donor: 47 yr in 2012 → 35 yr in 2016 (↓12 yr over 5 yr)

Opioids and Organ Donation Utilizing HCV+ Donors

- We have been transplanting HCV+ donor liver allografts into HCV+ recipients for almost 20 years with acceptable outcomes

*American Journal of Transplantation 2003; 3: 1167–1172
Blackwell Munksgaard*

Copyright © Blackwell Munksgaard 2003

ISSN 1600-6135

Hepatitis C Positive Grafts may be used in Orthotopic Liver Transplantation: A Matched Analysis

Sammy Saab^{a,b,*}, Rafik M. Ghobrial^b, Ayman B. Ibrahim^c, Gregg Kunder^b, Francisco Durazo^{a,b}, Steven Han^{a,b}, Douglas G. Farmer^b, Hasan Yersiz^b, Leonard I. Goldstein^b and Ronald W. Busuttil^b

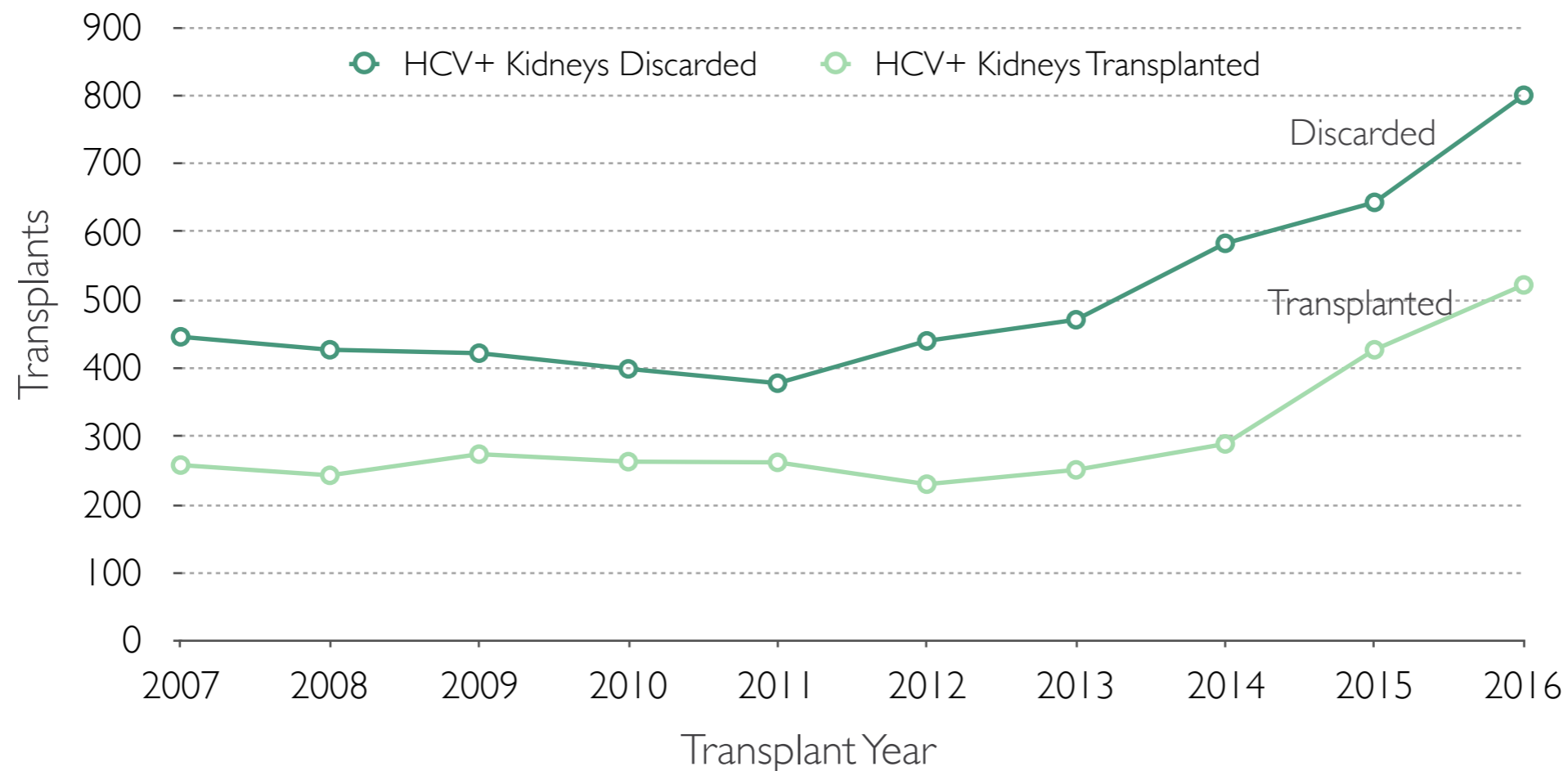
Orthotopic liver transplantation (OLT) is a definitive treatment for decompensated liver disease. Whereas the 1-year survival for patients with decompensated cirrhosis is less than 60%, orthotopic liver transplantation achieves overall 5-year survival rates of greater than 60–70% (2–5). Currently, the leading indication for liver transplantation is

- Many centers are very comfortable using HCV+ donor livers

Opioids and Organ Donation

Utilizing HCV+ Donors

- Many HCV+ kidney donor allografts have gone untransplanted however.



- 2/3 of kidneys from HCV+ donors are discarded

Source: D Goldberg, 2017

Opioids and Organ Donation

HCV+ Donors

Change in Incidence of HCV — Impact of HCV - DAA Therapy

- The landscape of HCV has changed dramatically over the last few years
- Key has been the HCV Direct Acting Antiviral Agents (HCV - DAA)

HCV - DAA → SVR in 98 - 99% pts

↳ - Across multiple genotypes
- Previous unresponsive to Rx

- Mild side effect profile has made staying on Rx easy
- Last decade saw a impressive ↓ in HCV infection
- Nearly all listed transplant patients have had their HCV treated

Opioids and Organ Donation

HCV+ Donors

The **NEW ENGLAND**
JOURNAL *of* **MEDICINE**

ESTABLISHED IN 1812

DECEMBER 31, 2015

VOL. 373 NO. 27

Sofosbuvir and Velpatasvir for HCV Genotype 1, 2, 4, 5,
and 6 Infection



Table 2. Response during and after Treatment.*

Response	Sofosbuvir–Velpatasvir (N = 624)
HCV RNA <15 IU/ml	
During treatment period — no. (%)	
At wk 2	355 (57)
At wk 4	564 (90)
At 12 wk after treatment period — no./total no. (%)	
Any genotype	618/624 (99)
1a	206/210 (98)
1b	117/118 (99)
2	104/104 (100)
4	116/116 (100)
5	34/35 (97)
6	41/41 (100)
Virologic failure — no. (%)	
During treatment	0
After treatment	2 (<1)
Other reason for classification as failure — no. (%)	
Loss to follow-up	2 (<1)
Withdrawal of consent	1 (<1)
Death	1 (<1)

12 week therapy

1 tablet daily

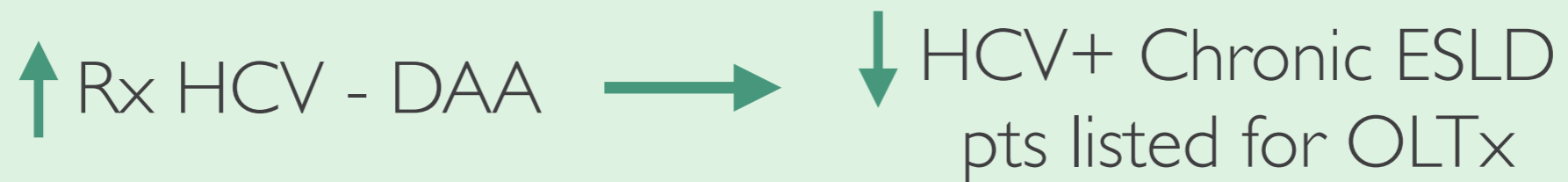
Cure Rate = 99.7%

622/624 pts

Opioids and Organ Donation

HCV+ Donors

Change in Incidence of HCV — Impact of HCV - DAA Therapy



Opioids and Organ Donation

Utilizing HCV+ Donors

- Because of the opioid epidemic, there are significantly **↑** HCV+ donors

335 HCV+ donors
(2012)



682 HCV+ donors
(2016)

2x more HCV+ donor
allografts over last 4 yrs

- HCV+ allografts are youngest of the last 20 years, and are younger than HCV- allografts. The **↓** age means improved allograft quality.
- Because of Rx HCV - DAA , there are significantly **↓** HCV+ ESLD pts.
- It has become harder to find a recipient for HCV+ livers, so otherwise suitable organs have been discarded

Opioids and Organ Donation

HCV+ Donors into HCV - Recipients

Opportunities

- 1) Use of organs that were previously discarded
- 2) ↓ waiting time for recipient
- 3) ↓ wait list mortality
- 4) No Δ posttransplant survival — Often young donors
- 5) Opportunity for some recipients who might not get a donor

Opioids and Organ Donation

HCV+ Donors into HCV - Recipients

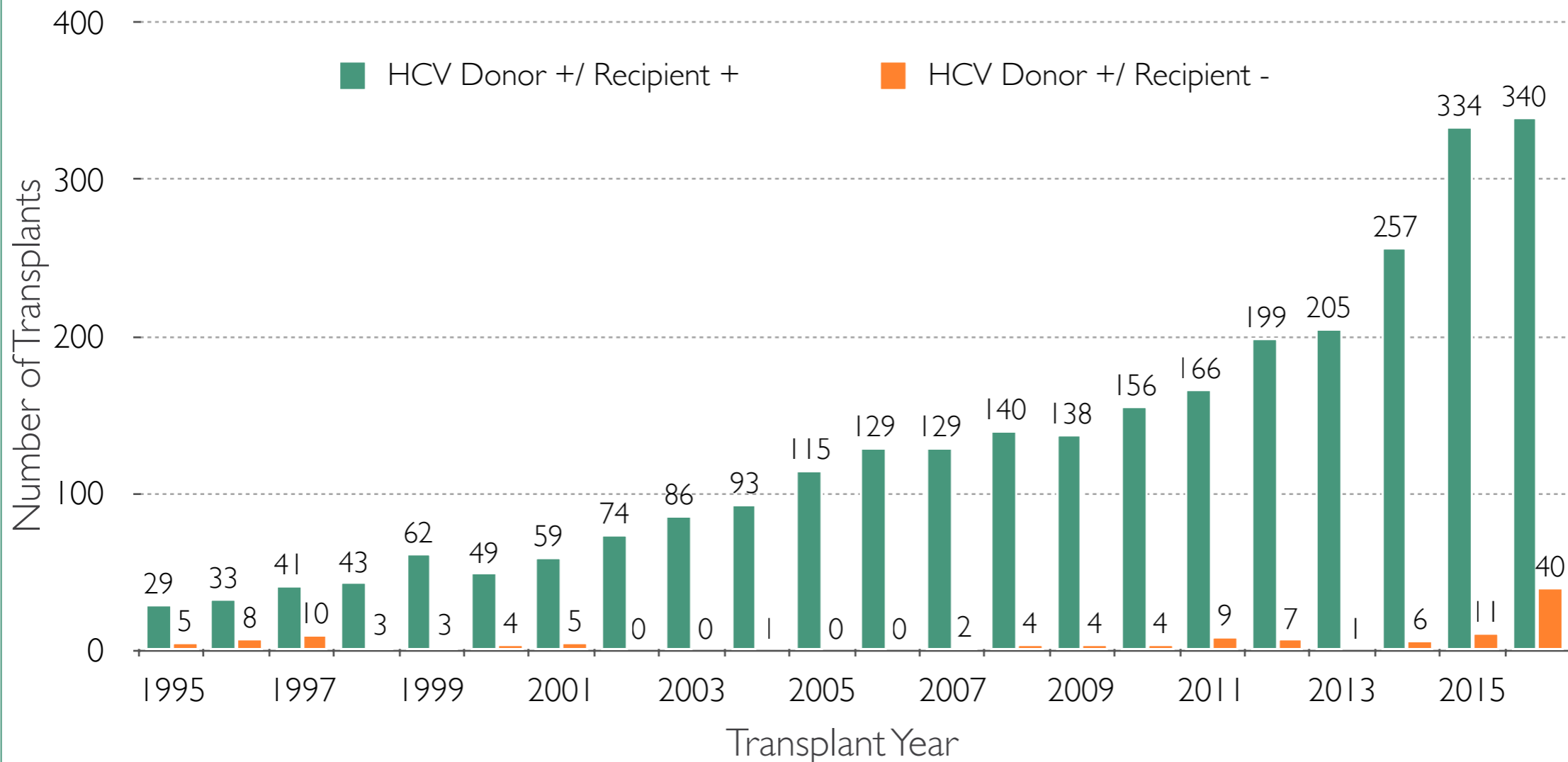
Pitfalls

- 1) Infecting patient with potentially lethal virus
- 2) HCV - DAA Rx is expensive (Who is the payor?)
- 3) HCV - DAA Rx not indicated for treating acute HCV
- 4) HCV - DAA Rx are paid for after willfully infecting patient.

Opioids and Organ Donation

HCV+ Donors into HCV - Liver Recipients

HCV+ Deceased Donor Liver Transplants by Recipient HCV Status at Time of OLTx

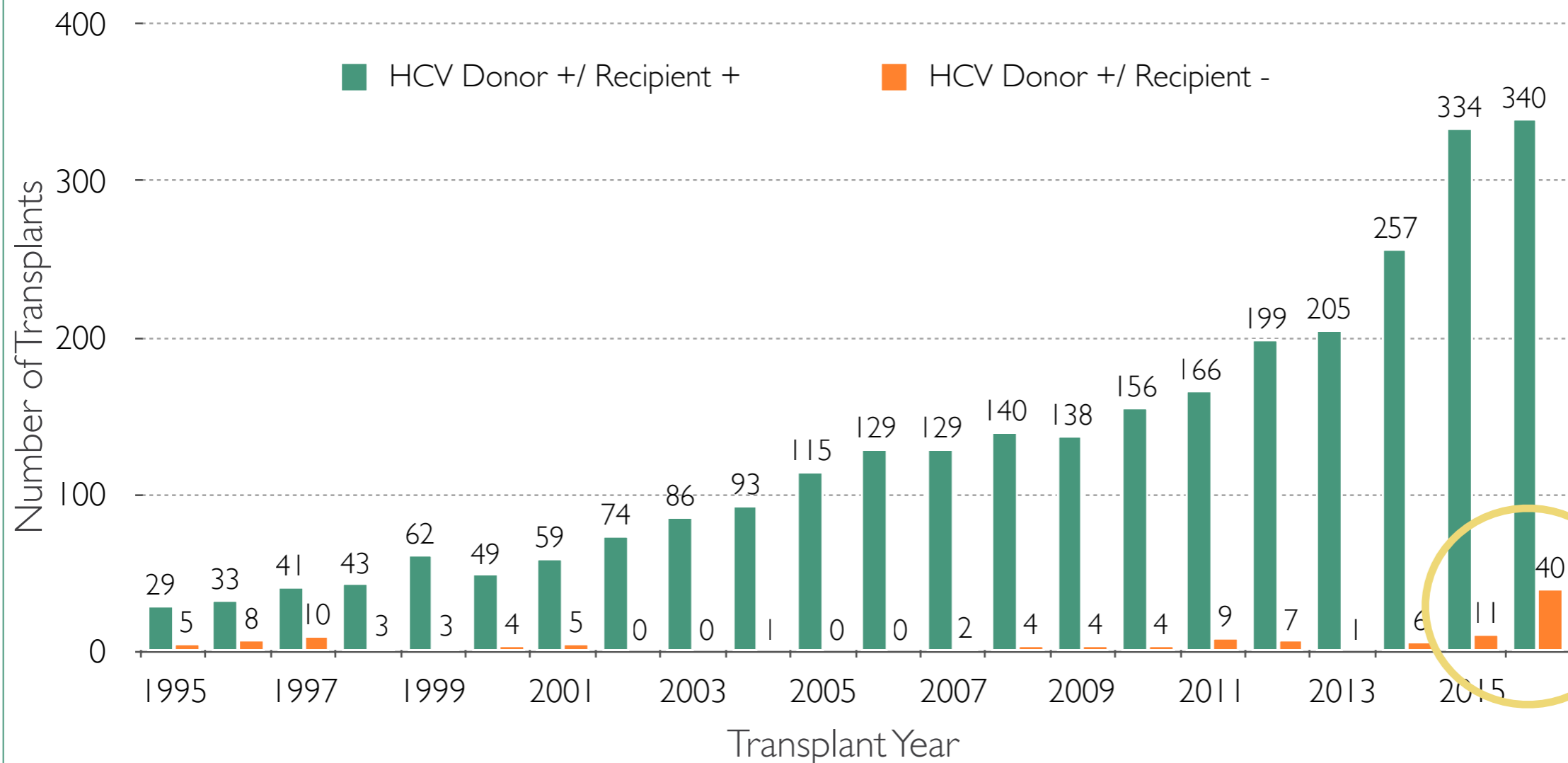


Source: Stewart, unpublished analysis 2017

Opioids and Organ Donation

HCV+ Donors into HCV - Liver Recipients

HCV+ Deceased Donor Liver Transplants by Recipient HCV Status at Time of OLTx

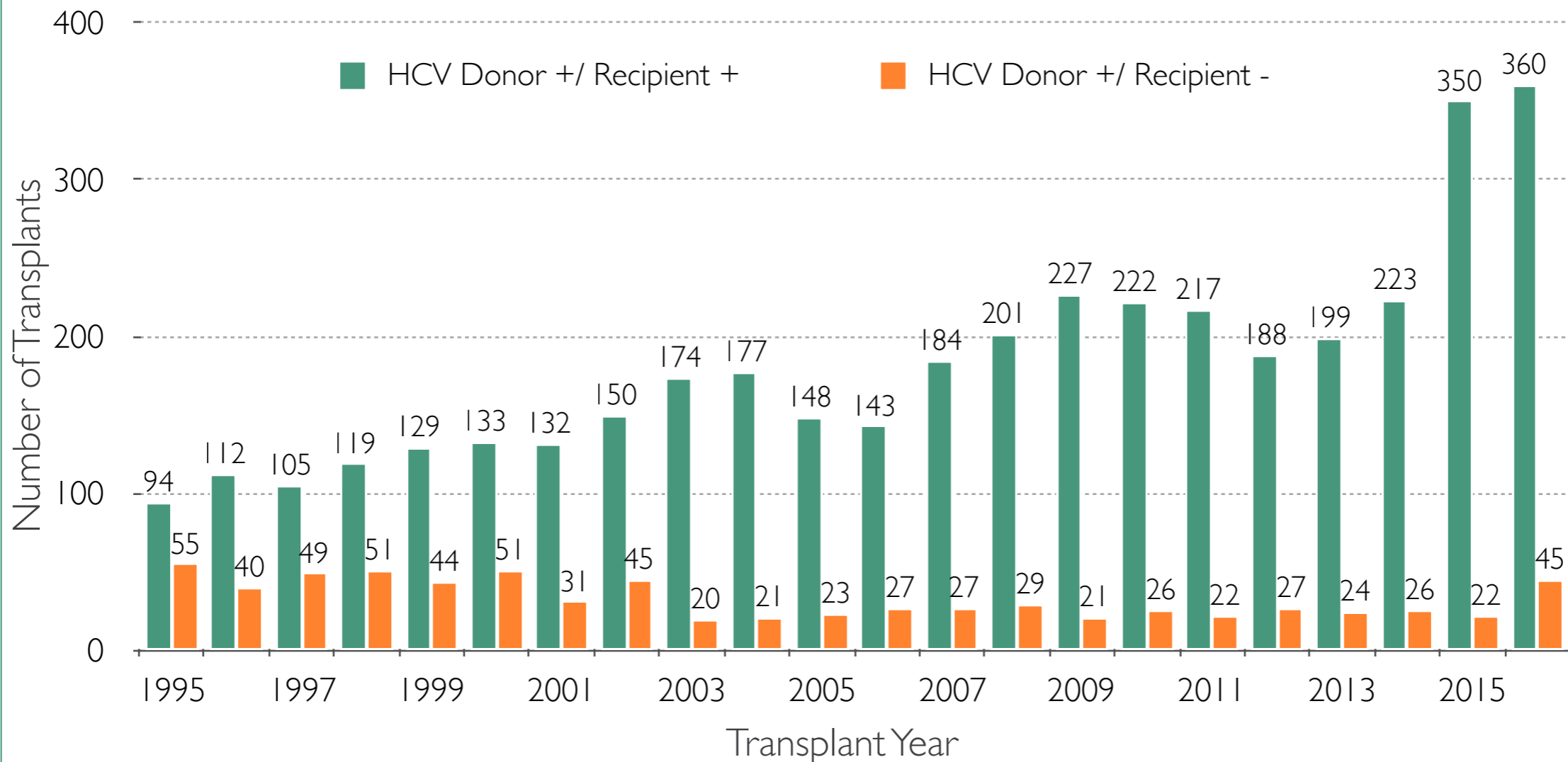


Source: Stewart, unpublished analysis 2017

Opioids and Organ Donation

HCV+ Donors into HCV - Kidney Recipients

HCV+ Deceased Donor Kidney Transplants by Recipient HCV Status at Time of OLTx

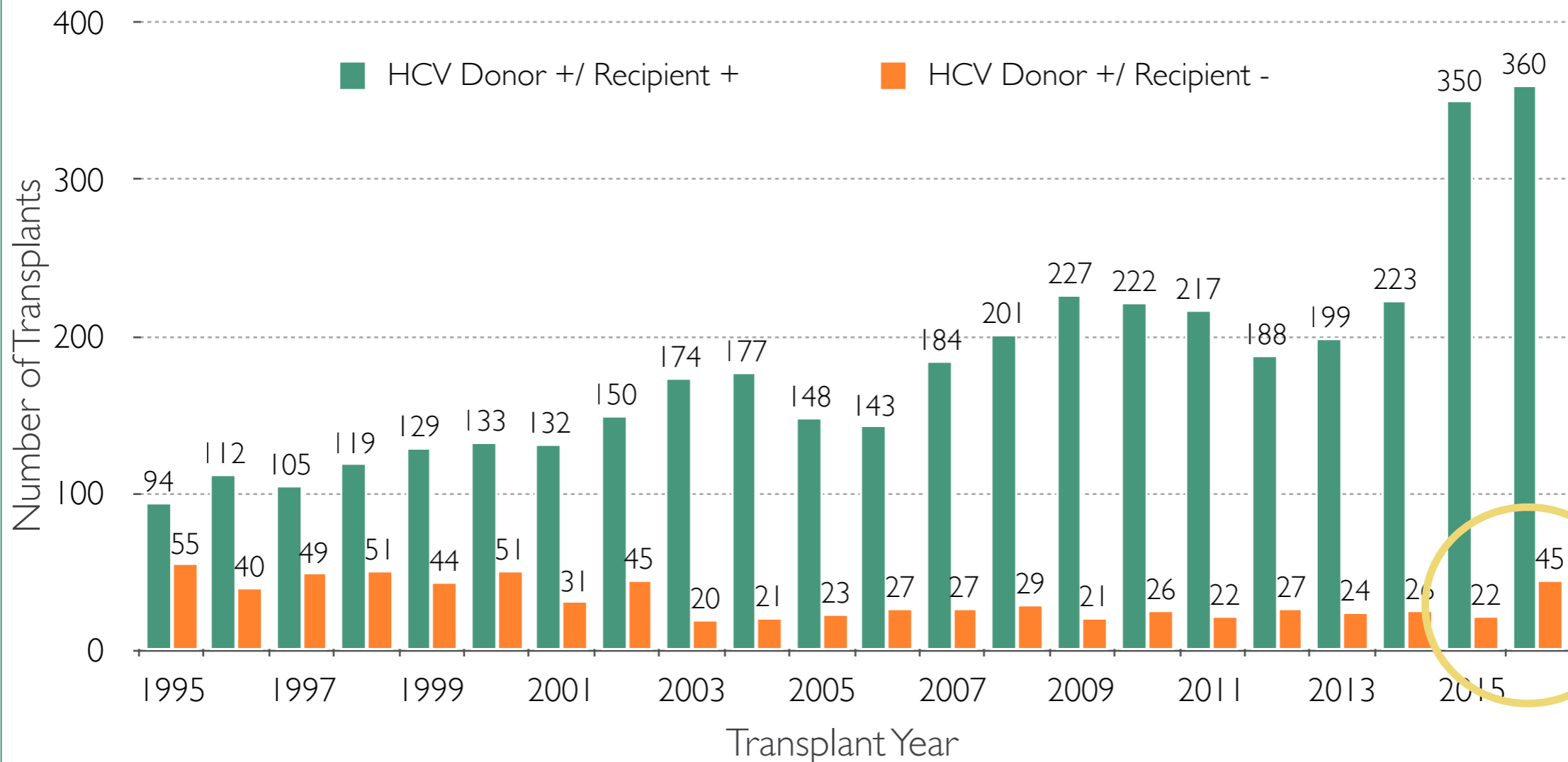


Source: Stewart, unpublished analysis 2017

Opioids and Organ Donation

HCV+ Donors into HCV - Kidney Recipients

HCV+ Deceased Donor Kidney Transplants by Recipient HCV Status at Time of OLTx

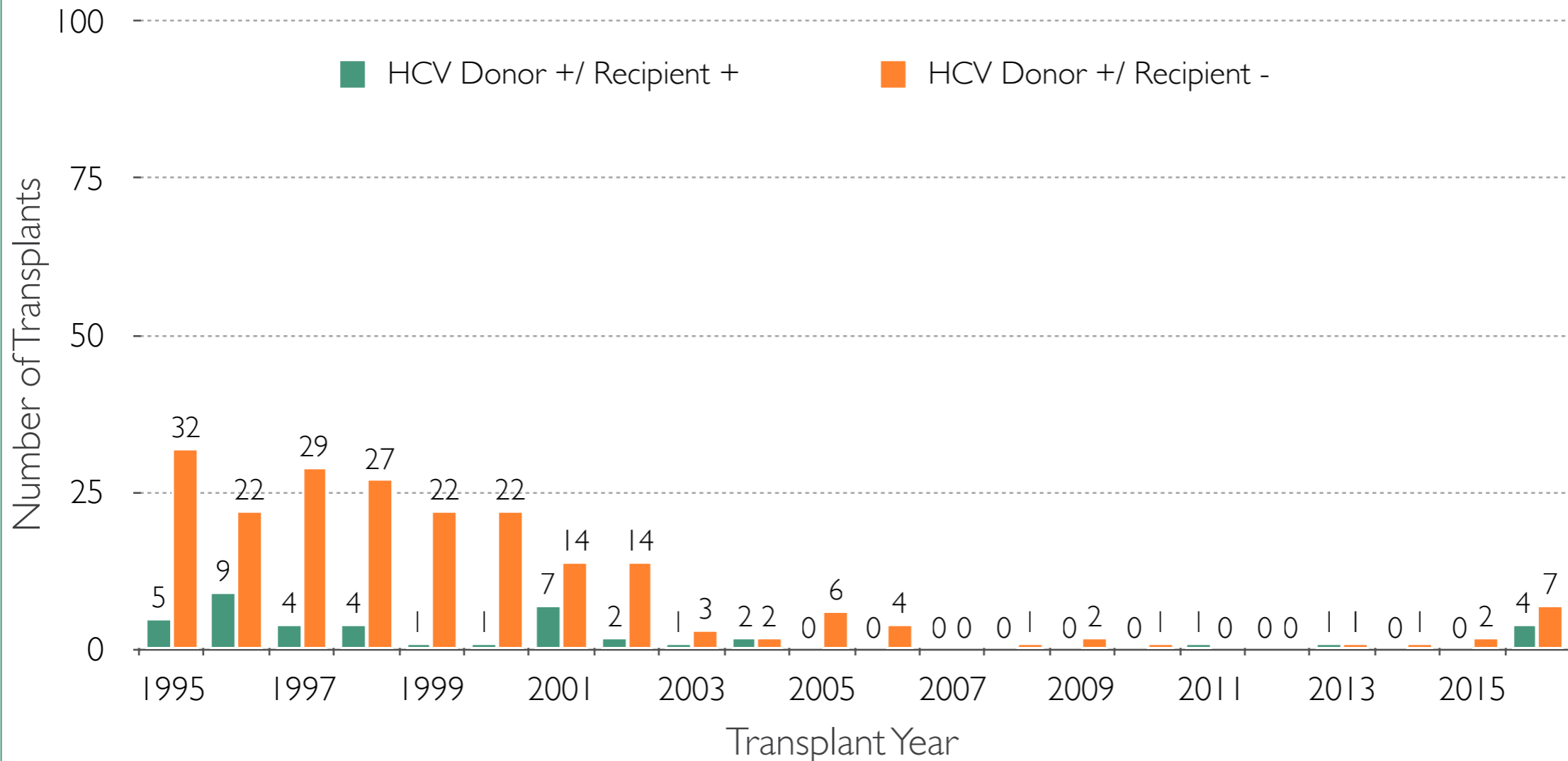


Source: Stewart, unpublished analysis 2017

Opioids and Organ Donation

HCV+ Donors into HCV - Heart Recipients

HCV+ Deceased Donor Heart Transplants by Recipient HCV Status at Time of OLTx

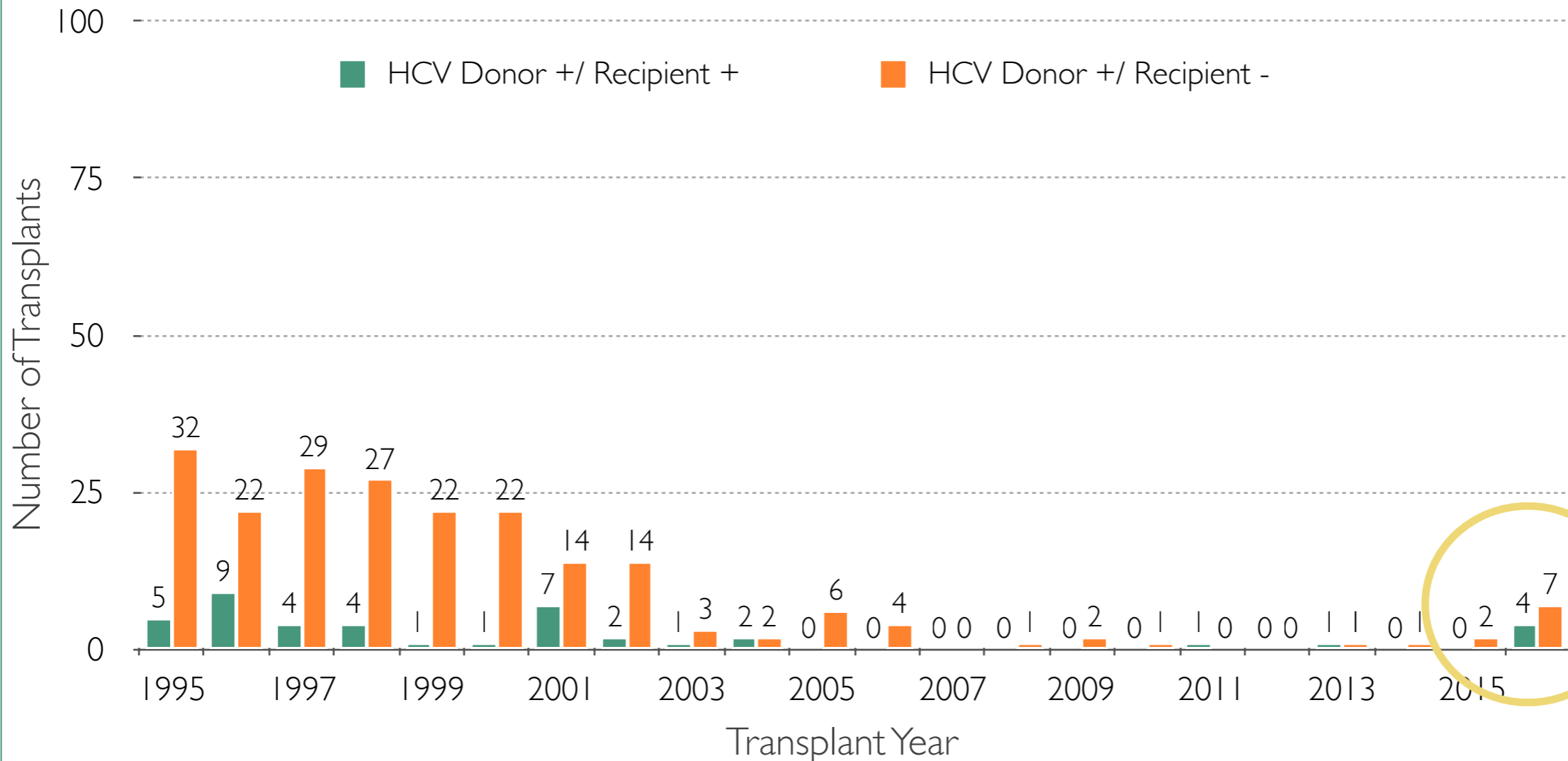


Source: Stewart, unpublished analysis 2017

Opioids and Organ Donation

HCV+ Donors into HCV - Heart Recipients

HCV+ Deceased Donor Heart Transplants by Recipient HCV Status at Time of OLTx



Source: Stewart, unpublished analysis 2017

Opioids and Organ Donation

HCV+ Donors into HCV - Recipients

THINKER Trial — Kidney Transplant Trial

T ransplanting
H epatitis C Kidneys
I nto
N egative
K idnEy
R ecipients

- Pilot trial for transplanting HCV+ donors into HCV - recipients
 - 10 HCV - kidney recipients consented
 - Mean waiting time 58 d
 - Kidney from HCV+ donor
 - Recipient viremic by POD 3
 - Rx with elbasvir-grazoprevir* for 12 wks
 - 100% cured of HCV

*Can be used at any level of renal function, no cardiotoxicity

Opioids and Organ Donation

HCV+ Donors into HCV - Recipients

USHER Trial — Heart Transplant Trial

USing

HCV+ Hearts for

negative

Recipients

- Pilot trial for transplanting HCV+ donors into HCV - recipients
 - 10 HCV - heart recipients transplanted
 - Heart from HCV+ donor
 - Rx with elbasvir-grazoprevir* for 12 wks
 - 100% cured of HCV

*Can be used at any level of renal function, no cardiotoxicity, no amiodarone interaction

Opioids and Organ Donation

HCV+ Donors into HCV - Recipients

Logistics for Any Transplants Using HCV+ Donor / HCV - Recipient

- 1) 100% assurance every single pt can be treated after transplant
- 2) Pts have to be educated early about the potential benefits and risks
- 3) Issues with treating patients early posttransplant
 - Not all become viremic
 - ↑immune = ? ↓drug efficacy
 - ↑contraindications/drug interactions
 - Transplant complications ↓Rx success
 - Drugs not stocked in hospital pharmacy
- 4) Cost of therapy — Impact on transplant contract
 - \$ 100,000 for Rx course
 - ? Treat with the first 90 d

Opioids and Organ Donation

HCV+ Donors into HCV - Recipients

Logistics for Any Transplants Using HCV+ Donor / HCV - Recipient

Liver / Kidney Transplant

Baylor Dallas is one of few centers in the US approved for Gilead trial of 30 HCV+ donors/HCV- recipient liver and kidney transplants.

Heart Transplant

Baylor Dallas is the pivotal center for HCV+ donor / HCV - recipient heart transplant trial.

Opioid Epidemic and Transplant

Second Summary

- Number of HCV+ donors has doubled in the last 5 yrs
 - Mean donor age of HCV+ donors has ↓ by 12 yrs
 - HCV+ donors are often good quality, young donors
 - Great variation in between liver, kidney, heart re: utilization of HCV+ donor
 - Efficacy of Rx HCV - DAA in curing HCV means fewer recipients for these HCV+ donors
 - Trials underway to use HCV+ donors in HCV - recipients and Rx after with HCV - DAA to eliminate HCV → Expand donor pool
- Directly linked to opioid epidemic

Does the Opioid Epidemic Impact
the Transplant Center and Potential
Recipients ?

Does the Opioid Epidemic Impact
the Transplant Center and Potential
Recipients ?

Yes

Opioids and the Pretransplant Patient

Candidate Listing Practices

Opioids and the Pretransplant Patient Candidate Listing Practices

N Fleming et al. Clinical Transplantation (2017)

- Survey of 61 of 114 Liver Transplant Centers regarding pre-OLT opioid use
- There is no national consensus regarding listing patients on opioid Rx

Transplant Listing Policy

Absolute Contraindication → 1.6% Opioid Use
1.6% Methadone Use

Relative Contraindication → 64% Opioid Use
37% Methadone Use

- Study showed great variability among centers as to practice of listing patients taking opioids

Opioids and the Pretransplant Patient Candidate Listing Practices

N Fleming et al. Clinical Transplantation (2017)

- The majority of transplant centers utilize unreliable screening methods
 - Self reporting
 - Medical records review
- Large reliance on toxicology tests however these have limitations
 - Timing between exposure and test
 - Cross-reactivity of the opiate metabolites and urinary test target
- Most accurate method for opiate screening is the State Prescription Drug Monitoring Program (Operational in 49/50 states)
 - Underutilized by transplant programs

Opioids and the Pretransplant Patient

Pain Management

Opioids and the Pretransplant Patient Pain Management

Pain Management in the Pretransplant Patient

- Opioid use can impact potential transplant recipients
- Many pretransplant recipients suffer from chronic pain
 - Renal → HD causes bone degeneration and pain
 - Liver → Liver inflammation from hepatitis causes RUQ pain
Splenomegaly from portal HTN causes LUQ pain
 - All → Immobility leads to chronic back pain
- Rogal et al 2015: 77% of OLT candidates reported pain as symptom

Opioids and the Pretransplant Patient Pain Management

Pain Management in the Pretransplant Patient

- Many pretransplant patients suffer from chronic pain → Limited options
 - Renal → NSAIDs are avoided in renal disease
 - Liver → Acetaminophen is avoided in liver disease
 - Altered liver metabolism interferes with metabolism of many pain medications
- Lack of standard pain management choices and ↑ sources of pain leads to ↑ prescribing of narcotics
- Patient have Rx opioid analgesia, often before transplant team involved

Opioids and the Pretransplant Patient Pain Management

Pain Management in the Pretransplant Patient

- Wait-list use of opiates varies with the transplant organ population

Renal → 43.1% of transplant recipients received opiates on wait-list

Liver → 9.3% of transplant recipients received opiates on wait-list

3% took the highest level of opiate (Level 3 or Level 4)

↳ 65% of these continued at this level posttransplant

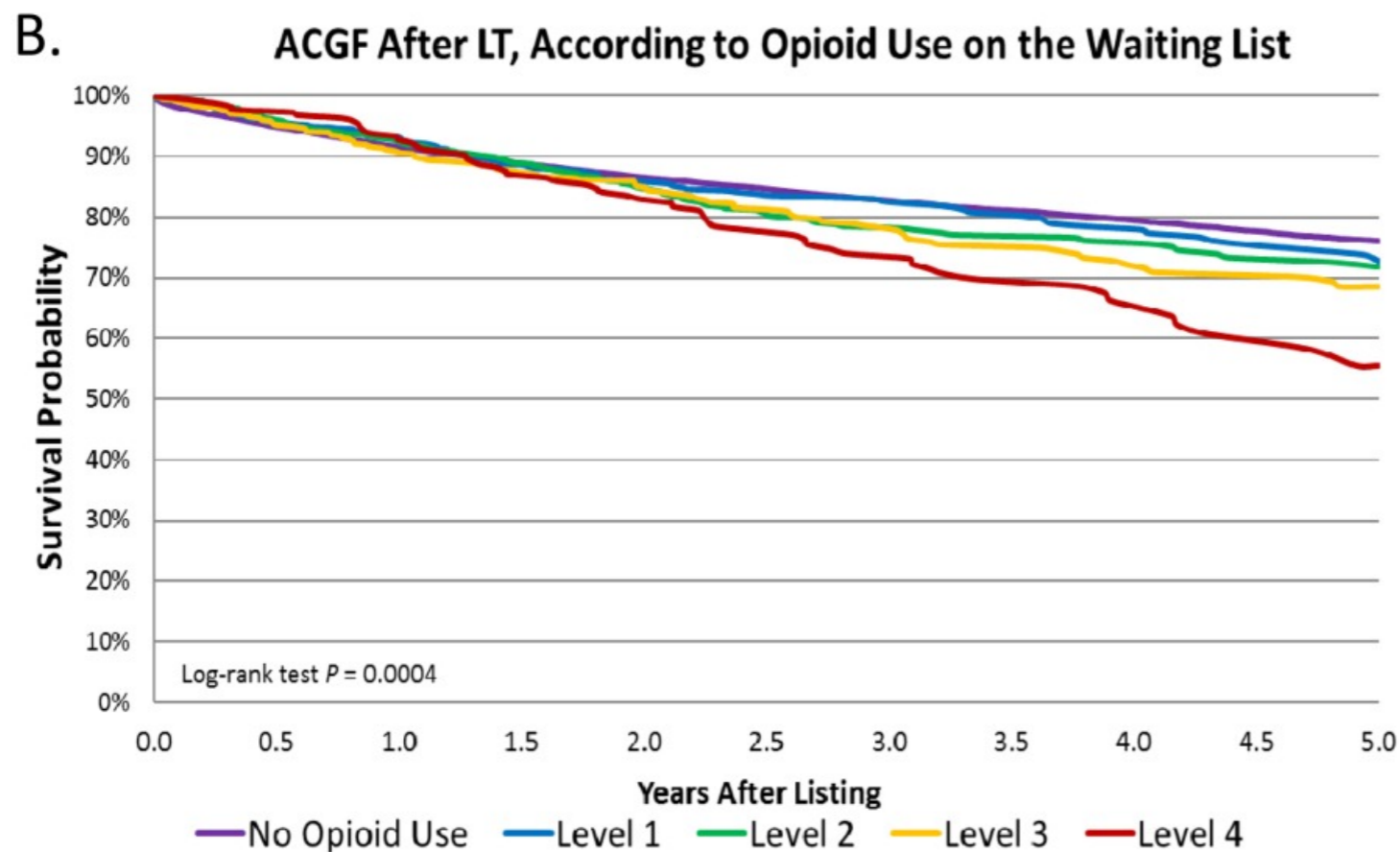
- Wait-list use of opiates should be minimized if possible to impact outcomes

Opioids and the Pretransplant Patient

Outcomes and Survival

Opioids and the Pretransplant Patient Survival Outcomes - Liver

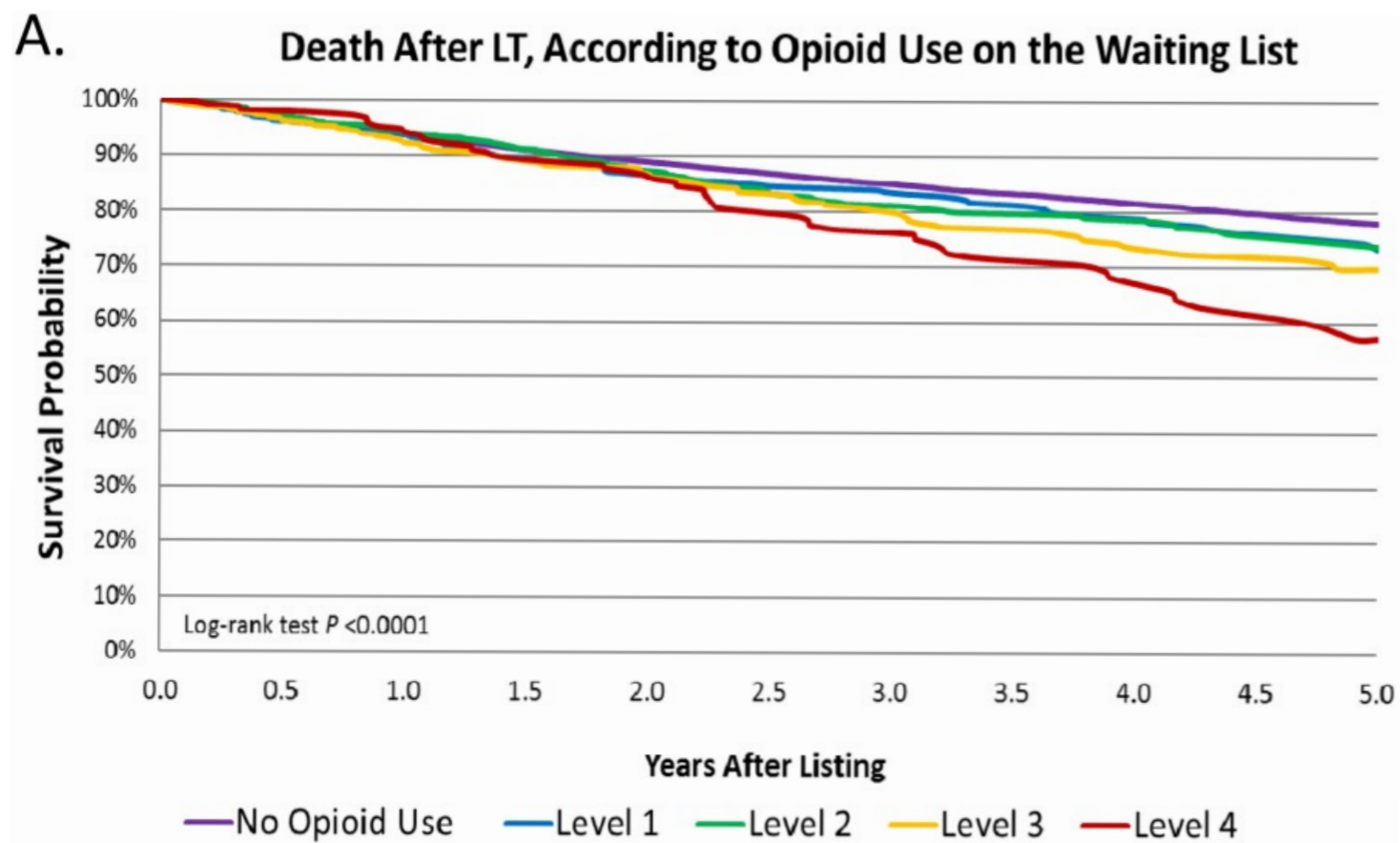
Liver Transplant



Compared with no use of opiates pre-OLT of ME $> 10/d$ was associated with \downarrow graft failure at 5 years post-OLT

Opioids and the Pretransplant Patient Survival Outcomes - Liver

Liver Transplant



Compared with no use of opiates pre-OLT of ME $> 10/d$ was associated with \uparrow mortality at 5 years post-OLT

Opioids and the Pretransplant Patient Survival Outcomes - Kidney

Kidney Transplant

KL Lentine et al AJT 2018

- Patients on pre-transplant opiates were likely to persist posttransplant
- Rx opioid use in the first year after transplant had a strong, graded association of ↑ 2-fold increased risk of death death and graft loss
- Compared with no use, highest level of opiate use (>70 ME/d) predicted:
 - 2x ↑ risk of death
 - 35% ↑ risk of death-censored graft failure
 - 68% ↑ risk of all-cause graft failure

Opioids and the Pretransplant Patient Readmission Rates

Kidney LD Donors

- Presurgical use of opioid analgesics is increasingly recognized as a predictor of post-operative complication and resource utilization
- Living donor kidney donors are the closest approximation of a general surgery patient in transplantation

- Lentine et al AJT 2017

Donors with the highest levels of pre-donation opiate use were more than 2x as likely to be readmitted to hospital

6.8% vs 2.6%

OR: 2.49 (CI 1.74 - 3.58)

Opioid Epidemic and Transplant

Third Summary

- Study showed great variability among centers as to practice of listing patients taking opioids
- Most accurate method for opiate screening is the State Prescription Drug Monitoring Program
- Many pretransplant recipients suffer from chronic pain → Limited options
- Wait-list Rx of opiates predicts posttransplant opiate use
- High pretransplant opiate use significantly ↓ graft survival and ↑ mortality in both liver and kidney transplant patients
- High pre-donation opiate use in LD kidney donor → ↑ readmission rates

Opioids and the Posttransplant Patient

Patient Management

Opioids and the Posttransplant Patient

Pain Management

Pain Management in the Posttransplant Patient

- Post-transplant pain can be significant and options are limited
 - Steroid-sparing IS protocols are compounding pain issues
 - NSAIDs are avoided because of concomitant CNI dosing
- Pretransplant opiate use, particularly if long-term can make it difficult to avoid opiates in the posttransplant setting

Opioids and the Posttransplant Patient Pain Management

Con Rx Opiates post-OLT

- Significant Side effects
(↓ bowel motility, oversedation)
- ↑ risk of graft failure and mortality with high level use
- ↑ risk of hospital readmission with high level use
- ↑ risk of addiction and overdose

Decision to Use Opiates

Pro Rx Opiates post-OLT

- Major traumatic abdominal surgery
(Large incision, heavy retraction)
- Limited options to Rx pain
- Steroid sparing IS protocols lose the antiinflammatory effects of steroids
- Patient satisfaction scores heavily dependent on pain control

Opioids and the Posttransplant Patient Pain Management

Baylor Dallas Pain Management Strategy for Transplant

Intra-operative

1) Subcostal TAP block w/ long acting Exparel or bupivacaine

Immediate Post-op

- 1) Aggressive early mobilization out of bed POD #1
- 2) Minimize all IV opiates → Tylenol#3 PO PRN
- 3) Currently trialing low dose ketamine

Subsequent Post-op

- 1) Acetaminophen 650 mg PO q4h
- 2) Gabapentin 300 mg PO BID
- 3) Tramadol 50 mg PO q4h
- 4) Tylenol#3 PO PRN * (Replace acetaminophen/tramadol)
(* If inadequate analgesia on 1-3)

Opioid Epidemic and Transplant

Fourth Summary

- Pain management can be difficult because of limited options
- Pretransplant opiate use, particularly if high can hinder opiate avoidance in the posttransplant period
- Use all potential strategies including intra-op TAP blocks and post-op gabapentin
- Move to mobilize the patient very early, POD #1 if possible
- Transition from IV opiates to PO very early w/ goal of codeine as opiate
- Outpatient use gabapentin and tramadol to avoid codeine

Summary

Summary

- The opioid epidemic and organ transplantation have a complex and multifaceted connection. It impacts organ supply, quality, allocation and pre-and post- transplant management and outcomes
- It is a national health tragedy that needs urgent attention and aggressive intervention by the medical community
- The opioid epidemic has had a profound impact on organ supply and organ allocation.
- It has necessitated new paradigms for transplantation and donation, and further understanding of circumstance may yield further benefits

