Does opioid tapering cause harm in patients with chronic pain?

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38TH ANNUAL MEETING

My background

Epidemiologist

Areas: opioid use, pain, mental health

Causal inference

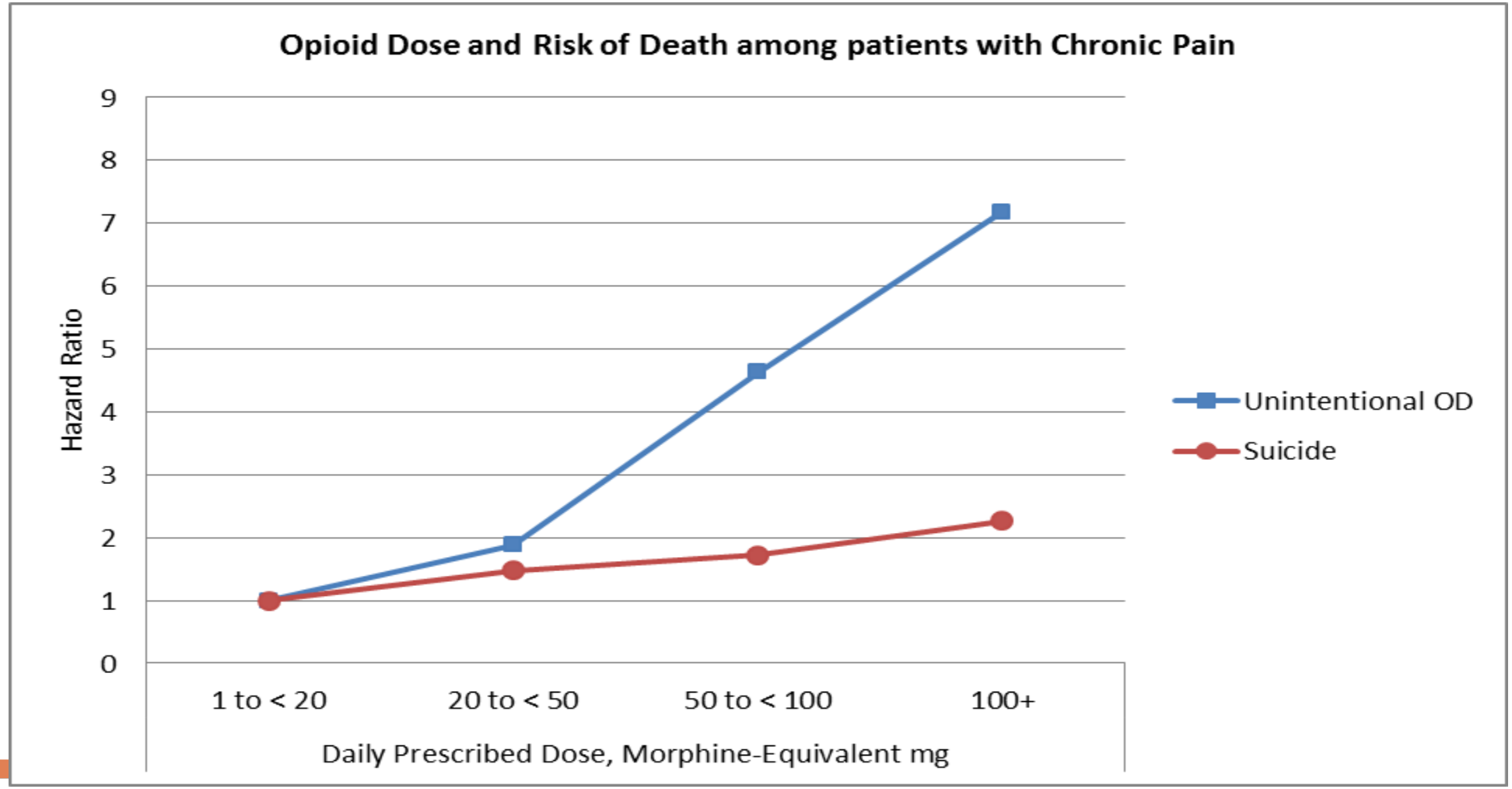
Non-clinician

Disclosures: Funding from NIH, VA, SAMHSA, CDC, Blue Cross Blue Shield of Michigan

Objectives

- Describe scientific rationale for opioid tapering
- Summarize studies of opioid tapering outcomes
- Explain biases and problems with making causal claims from existing studies of tapering outcomes
- Describe findings of an emulated clinical trial of opioid tapering and suicide/overdose and implications for practice

Harms of High Dose Opioids



Ilgen MA, Bohnert AS, Ganoczy D, Bair MJ, McCarthy JF, Blow FC. Opioid Dose and Risk of Suicide. *Pain*. 2016

Bohnert, Valenstein, Bair, Ganoczy, McCarthy, Ilgen, Blow, *JAMA*. 2011.

Opioid Tapering and Pain Outcomes

Annals of Internal Medicine REVIEW

Patient Outcomes in Dose Reduction or Discontinuation of Long-Term Opioid Therapy

A Systematic Review

Joseph W. Frank, MD, MPH; Travis I. Lovejoy, PhD, MPH; William C. Becker, MD; Benjamin J. Morasco, PhD; Christopher J. Koenig, PhD; Lilian Hoffecker, PhD, MLS; Hannah R. Dischinger, BS; Steven K. Dobscha, MD; and Erin E. Krebs, MD, MPH

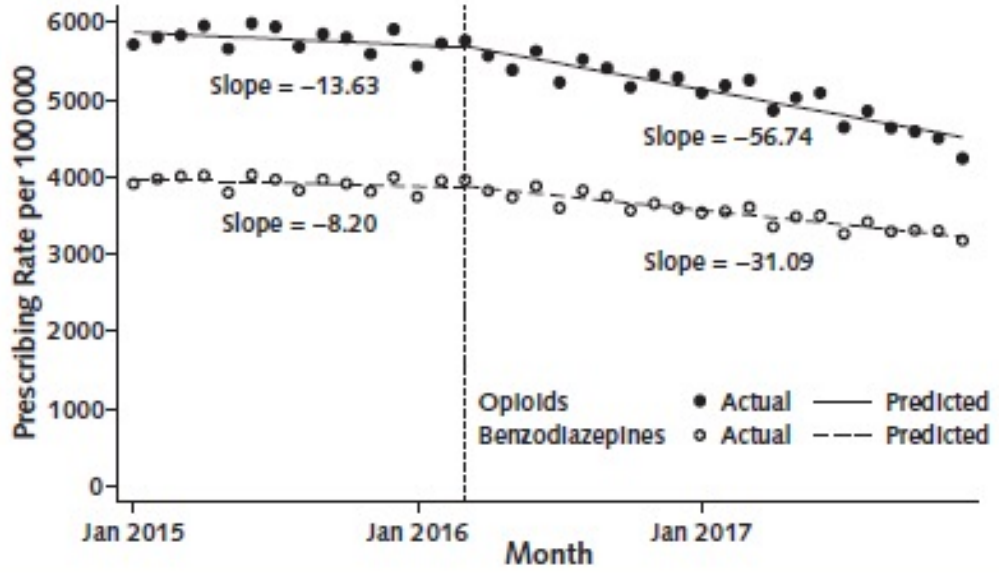
Conclusion: Very low quality evidence suggests that several types of interventions may be effective to reduce or discontinue LTOT and that pain, function, and quality of life may improve with opioid dose reduction.

Annals of Internal Medicine ORIGINAL RESEARCH

Opioid Prescribing in the United States Before and After the Centers for Disease Control and Prevention's 2016 Opioid Guideline

Amy S.B. Bohnert, PhD, MHS; Gery P. Guy Jr., PhD, MPH; and Jan L. Losby, PhD, MSW

Appendix Figure 2. Count of prescriptions dispensed per month, per 100 000 persons, for opioid and benzodiazepine medications before and after release of the CDC's *Guideline for Prescribing Opioids for Chronic Pain* in March 2016.



Dashed vertical line represents the month of CDC guideline implementation (March 2016). CDC = Centers for Disease Control and Prevention.

The New York Times

What the Opioid Crisis Took From People in Pain

March 7, 2022

Jeremy Leung

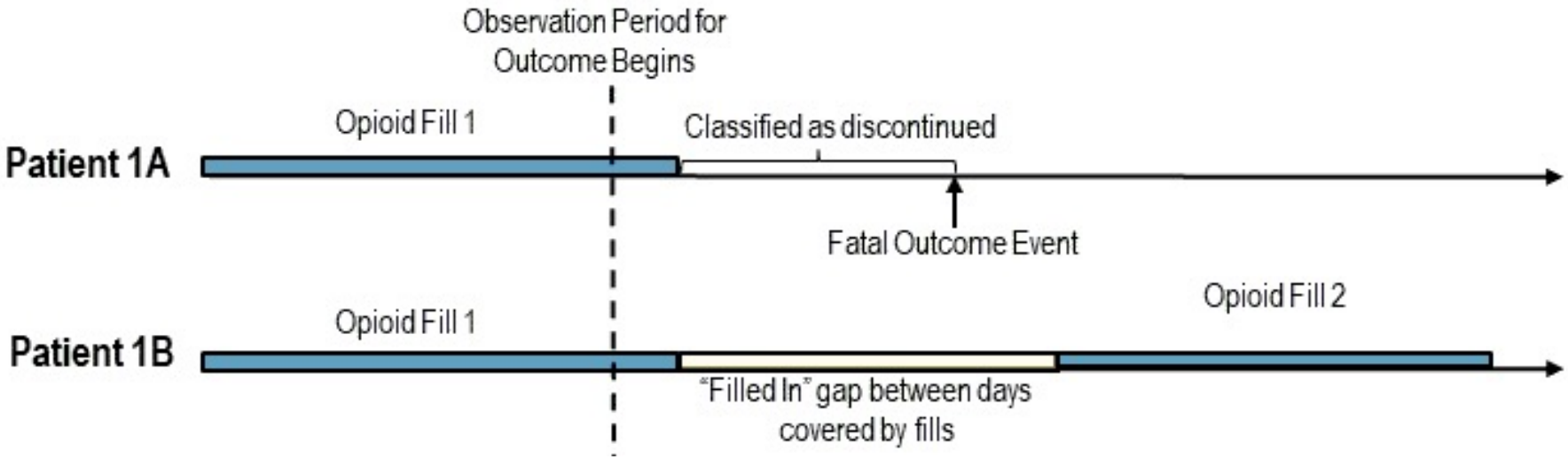
For people with chronic pain, research is only beginning to show how widespread the damage from opioid prescription cuts is. One study examined the medical records of nearly 15,000 Medicaid patients in Oregon who were taking long-term, high doses of opioids. Those whose medications were stopped were three and a half to four and a half times as likely to die by suicide compared to those whose doses were stable or increased. Another study, which included the medical records of over 100,000 people, found that drastically reducing a patient's opioid dosage increased the risk of overdose by 28 percent and increased the risk of mental health crisis requiring hospitalization by 78 percent.

Why Randomized Trials are better than Observational Studies

- Avoid imbalance/confounding

- Alignment of time anchors
  - Eligibility
  - Group assignment
  - Follow-up

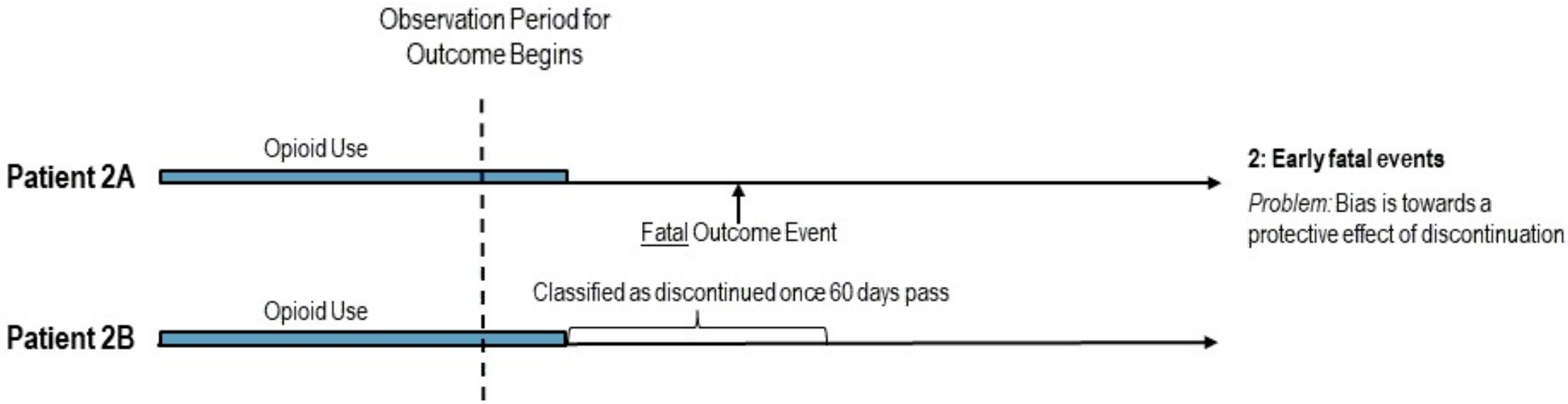
Time Anchor Problem 1



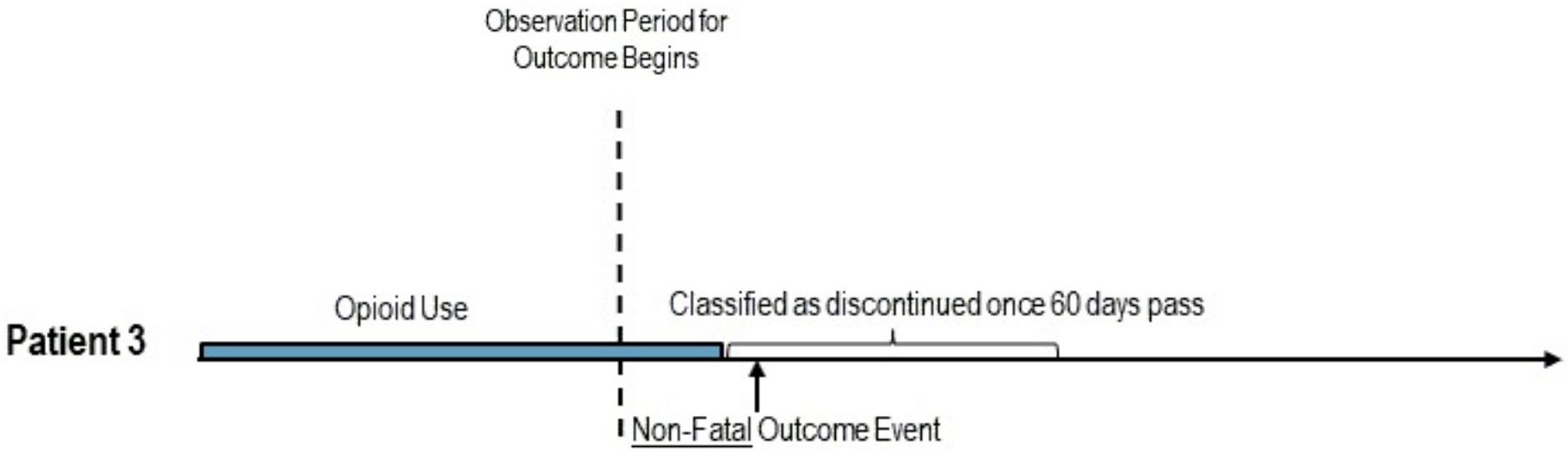
1: "Filling in" treatment gaps

Problem: Bias is towards a harmful effect of discontinuation.

Time Anchor Problem 2



Time Anchor Problem 3



3: Early non-fatal events

Problem: Reverse causation.

Where to learn more on time anchors

Journal of Clinical Epidemiology 79 (2016) 70–75

Journal of Clinical Epidemiology

Specifying a target trial prevents immortal time bias and other self-inflicted injuries in observational analyses

Miguel A. Hernán[a,b,c,*], Brian C. Sauer[d], Sonia Hernández-Díaz[a], Robert Platt[e,f,g], Ian Shrier[g]

AnnalsATS Volume 18 Number 5 | May 2021

Timing Is Everything

The Importance of Alignment of Time Anchors for Observational Causal Inference Research

Stephanie Parks Taylor[1], Marc A. Kowalkowski[2], and Andrew J. Admon[3]

VA study of sensitivity to measurement

VHA patients receiving opioids, FY2013-FY2016

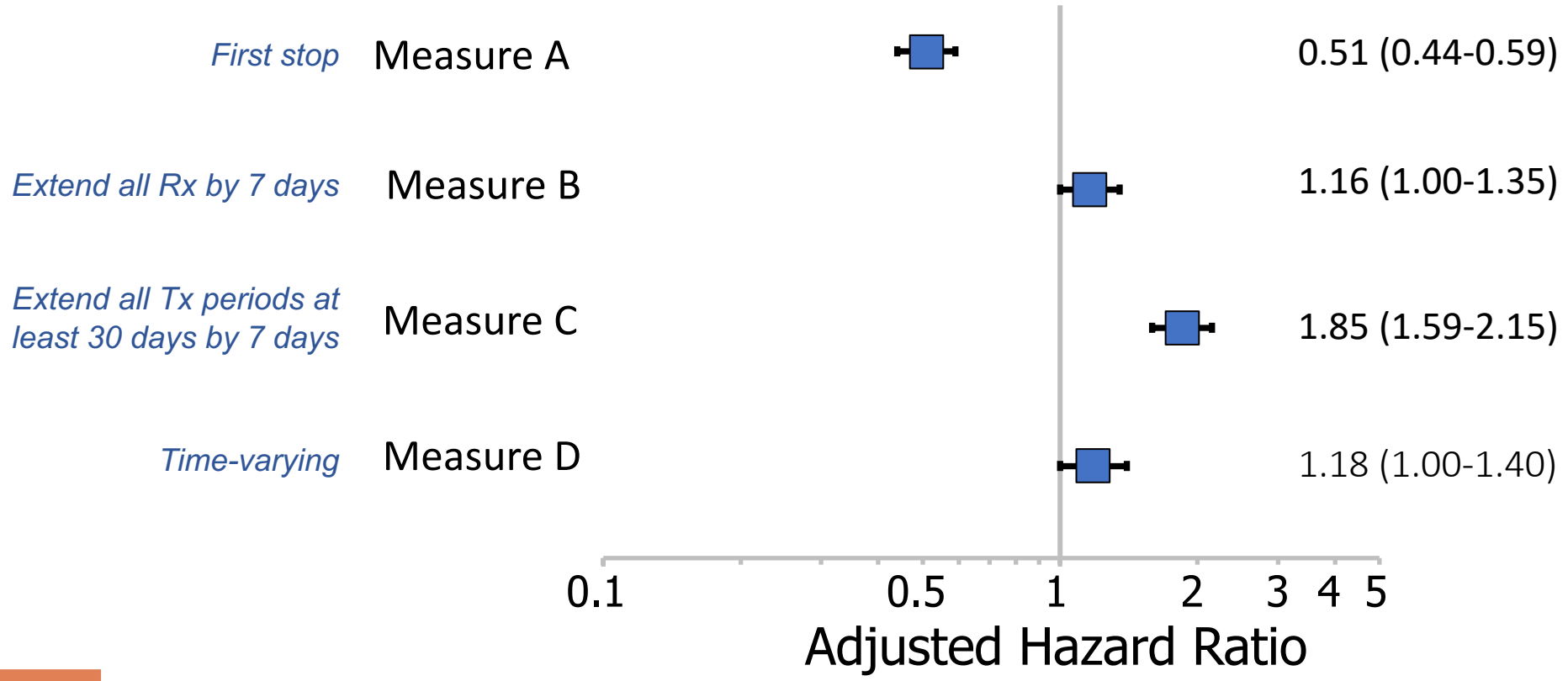
Design: prospective cohort

Outcome: suicide or overdose death

Purpose: compare models using different measures of discontinuation

Adjusted hazard for overdose/suicide mortality

By measure of opioid discontinuation



Conclusion

- Findings highly sensitive to how discontinuation is measured
- Can we emulate a clinical trial to get a more accurate estimate of the causal effect?

An emulated trial of opioid tapering and abrupt discontinuation

Study Objective and Motivation

- Conduct an emulated trial in a large claims database:
  - **Population**: patients on stable long-term opioid therapy
  - **Interventions**: opioid tapering, abrupt discontinuation
  - **Comparator**: stable opioid therapy
  - **Outcome**: opioid overdose or suicidal ideation

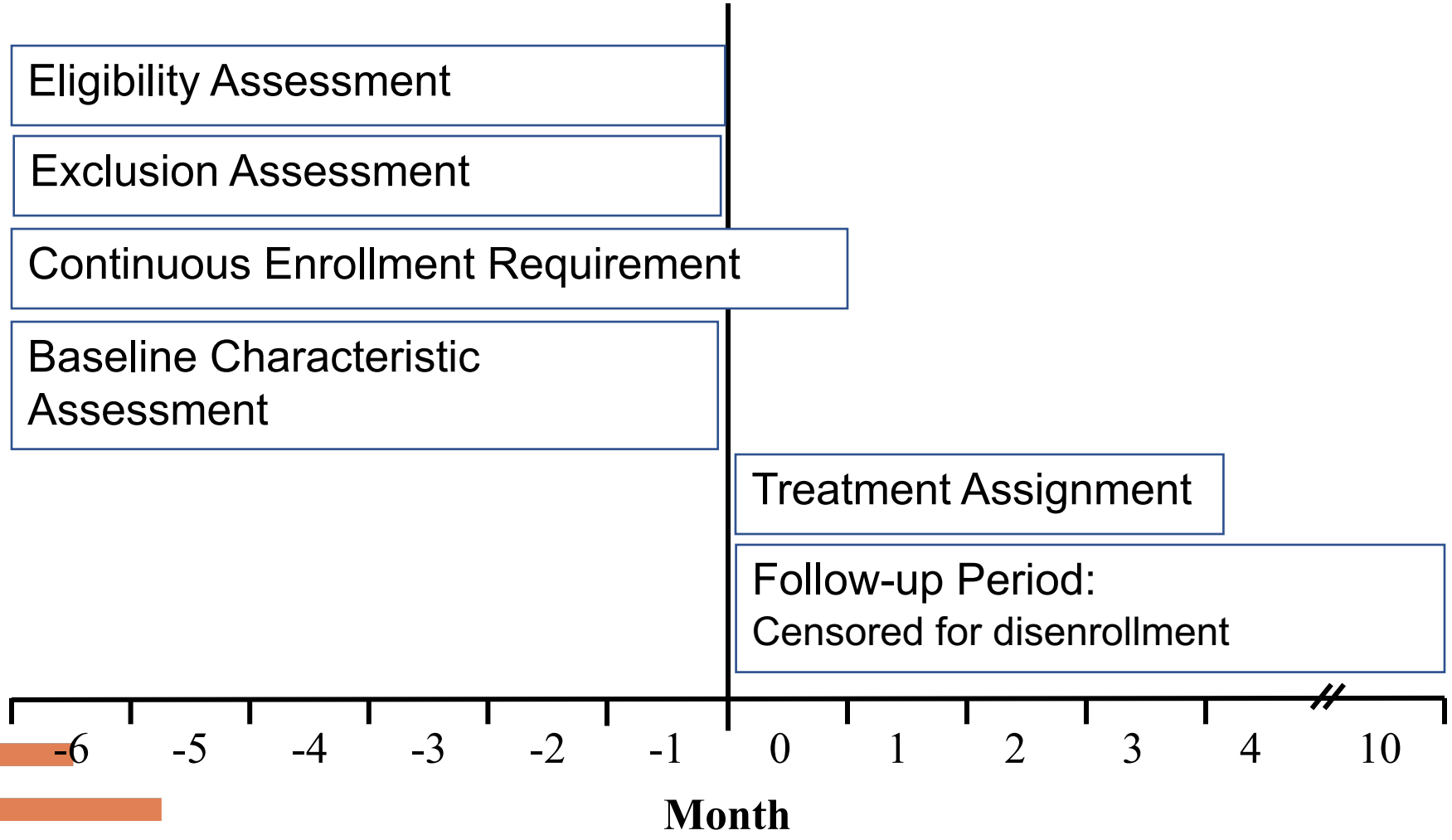
- Attempt to address (some) limitations from prior studies:
  - Restricting to cohort to patients without evidence of OUD or opioid misuse
  - Align time 0/start of follow-up

Methods – Design and Data Source

- Optum de-identified Clinformatics® Data Mart
  - Commercial or Medicare Advantage in 50 states, DC and Puerto Rico
  - Pharmacy, outpatient, and inpatient medical claims
  - Data from January 2010-2018

- Adapted emulated trial protocol proposed to study opioid tapering published by the National Academies of Sciences, Engineering, and Medicine 2019.

Methods – Overview of Study Timeframe



Methods – Eligibility Criteria

Stable long-term opioid therapy:

1. 6 months of continuous opioid therapy (≥ 90% of days covered)
2. Mean MME ≥ 50 mg per day in each month
3. Mean MME for each month within 15% of 6 month average

Individuals could contribute up to 1 episode per year.

Exclusion criteria:

- Cancer or receipt of hospice
- > 3 opioid prescribers or
- ≥ 2 early refills
- Substance use diagnosis
- Indicator of OUD (medication for OUD, opioid overdose, detoxification)
- Indicator of injection drug use (injection-related infection, Hepatitis C)

Methods – Treatment Assignment

Identified during 4-month treatment assignment period:

1. Tapering – 2 consecutive months with MME reduction of ≥ 15% compared to baseline

2. Abrupt Discontinuation – Meets tapering criteria and MME is 0 MME in 2nd month

3. Stable – not meeting tapering or abrupt discontinuation (increases allowed)

Methods – Causal Contrast and Analysis

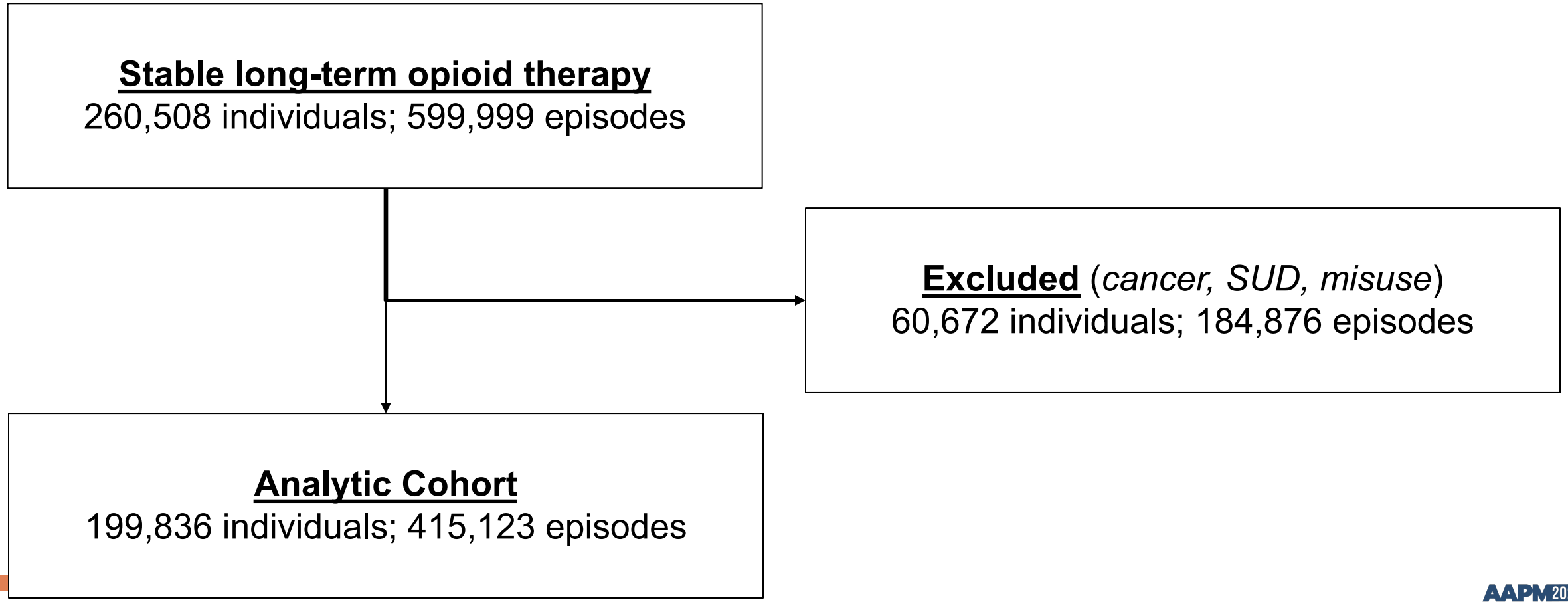
- Causal Contrast:
  - Intent-to-treat – treatment does not change after assignment
  - Per protocol – censor for lack of adherence

- Analysis:
  - To avoid immortal time bias during treatment assignment, episodes were cloned
  - Estimates adjusted for baseline characteristics using inverse probability weighting, calculating weights for:
    - Informative censoring of clones during treatment assignment
    - Loss to follow-up
    - Censoring due to lack of treatment adherence

Methods – Clones and Treatment Assignment

		Baseline Period	Treatment Assignment Period				Follow-up Period					
	Month:	-1	0	1	2	3	4	5	6	7	8	9
Example 1: Stable.												
		100%	100%	90%	95%	105%	95%	105%	95%	100%	95%	110%
CLONES	Stable		1	1	1	1	1	1	1	1	1	1
	Taper		1	1	0	0	0	0	0	0	0	0
	Abrupt Discontinuation		1	1	0	0	0	0	0	0	0	0
Example 2: Abrupt Discontinuation												
		100%	100%	80%	0%	0%	0%	0%	0%	0%	0%	0%
CLONES	Stable		1	1	0	0	0	0	0	0	0	0
	Taper		1	1	0	0	0	0	0	0	0	0
	Abrupt Discontinuation		1	1	1	1	1	1	1	1	1	1
Example 3: Taper												
		100%	84%	70%	65%	60%	50%	50%	95%	100%	95%	110%
CLONES	Stable		1	0	0	0	0	0	0	0	0	0
	Taper		1	1	1	1	1	1	1	1	1	1
	Abrupt Discontinuation		1	0	0	0	0	0	0	0	0	0

Consort Diagram



Selected Baseline Characteristics

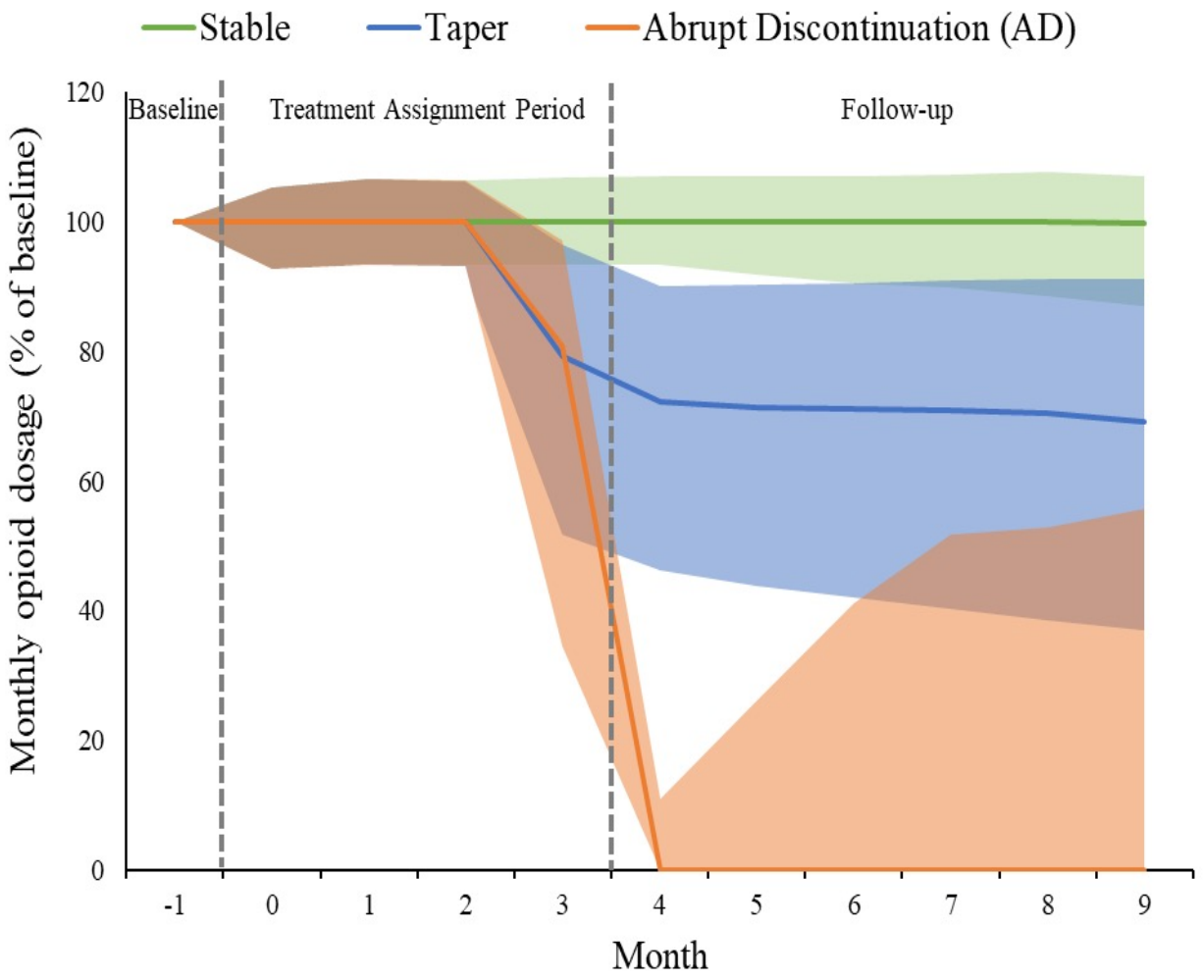
Characteristic	Stable (n=332,121)	Taper (n=42,246)	Abrupt Discontinuation (n=6,886)
Male	46%	43%	49%
Age			
18-44 years	12%	13%	16%
45-64 years	59%	57%	53%
65+ years	28%	30%	31%
Race/Ethnicity			
Non-Hispanic White	73%	72%	71%
Non-Hispanic Black	10%	11%	11%
Hispanic	6%	6%	6%
Asian	1%	1%	1%
Unknown	10%	10%	12%

Selected Baseline Characteristics

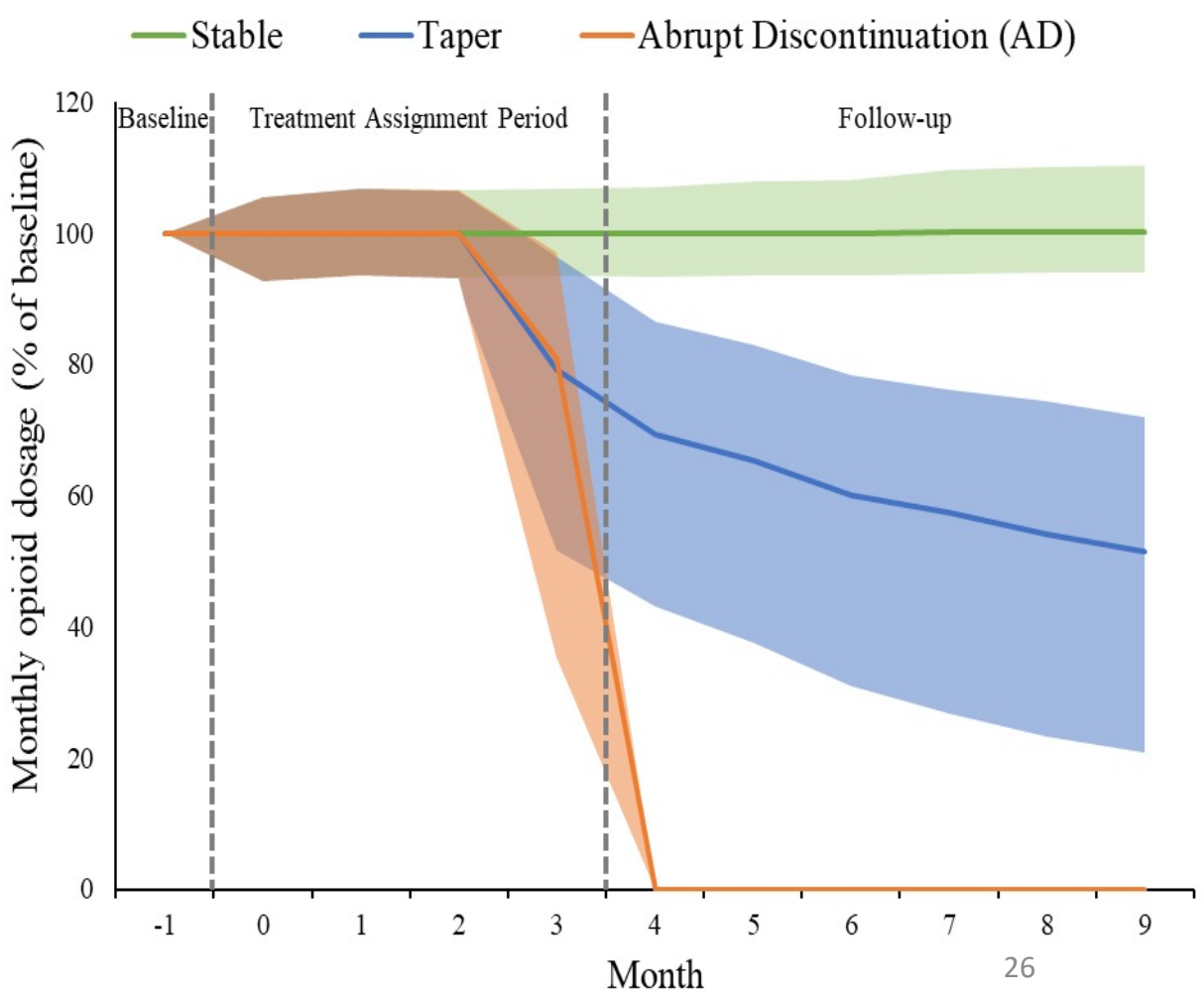
Characteristic	Stable (n=332,121)	Taper (n=42,246)	Abrupt Discontinuation (n=6,886)
Baseline MME			
50-89 mg	38%	32%	43%
90-199 mg	37%	38%	36%
200+ mg	26%	30%	20%
Benzodiazepine rx	35%	37%	36%
Gabapentinoid rx	32%	34%	33%
Depression	19%	21%	20%
Anxiety	18%	19%	20%

Dosage Trajectories

a) Intent-to-treat

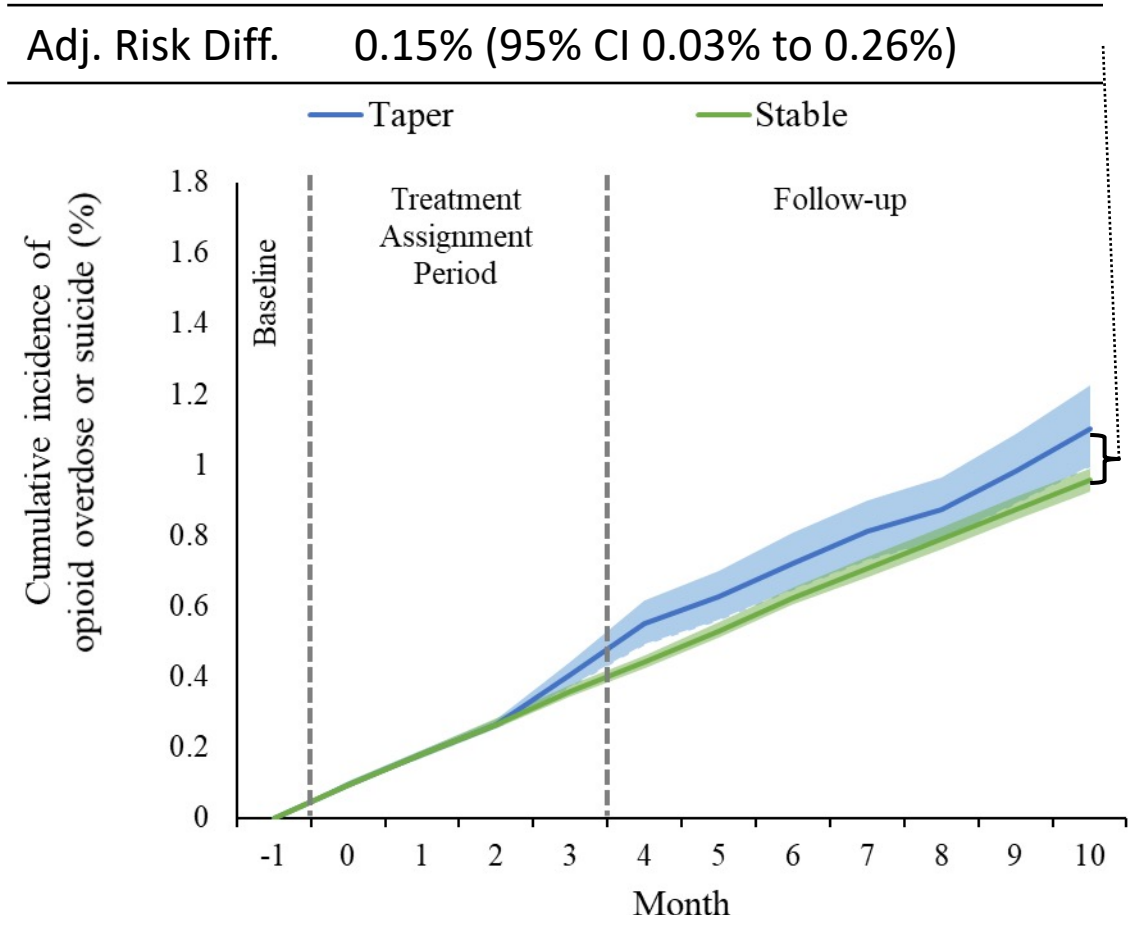


b) Per protocol

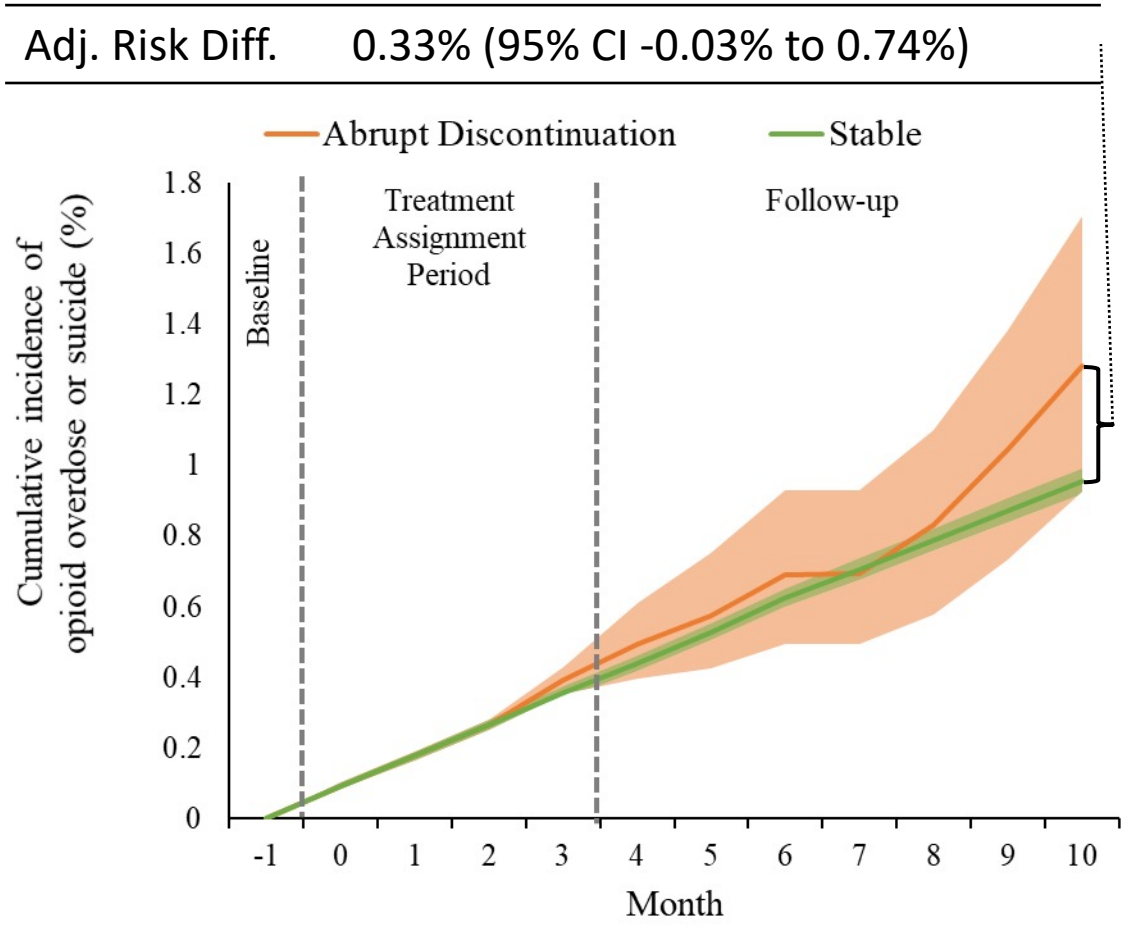


Adjusted Cumulative Incidence of Opioid OD or Suicide Event: Intent-to-treat

a) Taper vs Stable



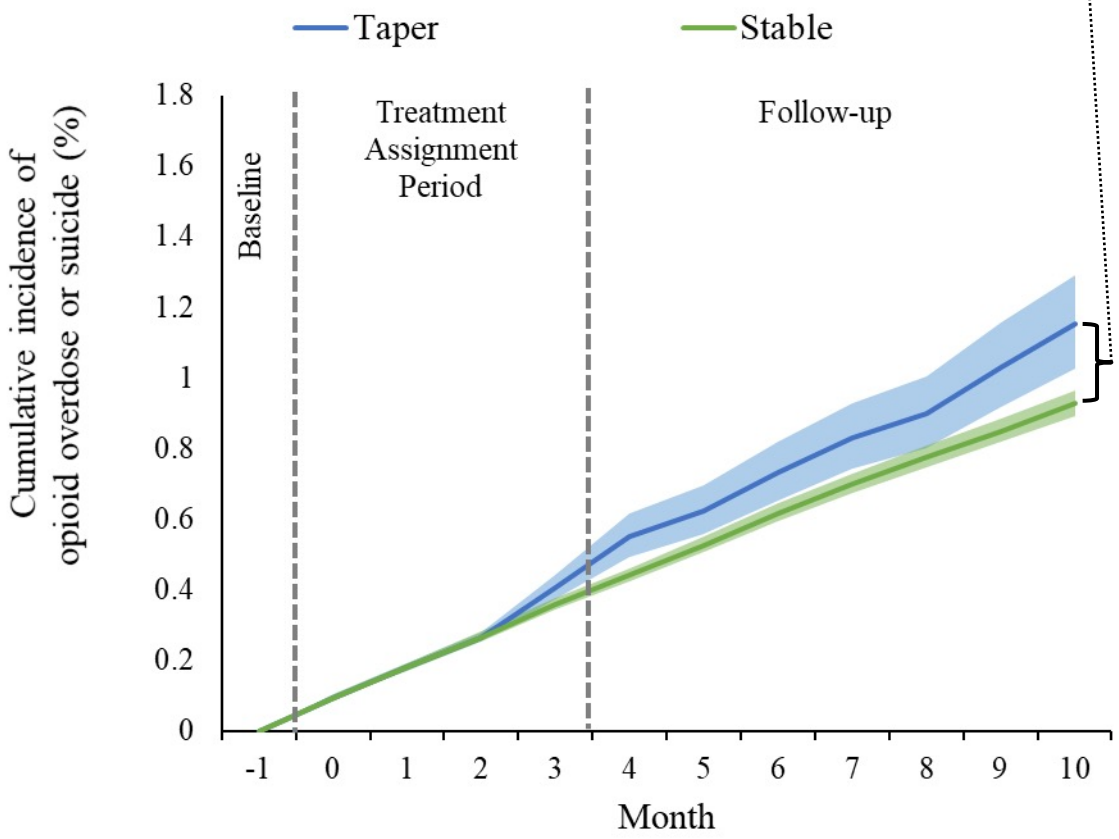
b) Abrupt Discontinuation vs Stable



Adjusted Cumulative Incidence of Opioid OD or Suicide Event: Per Protocol

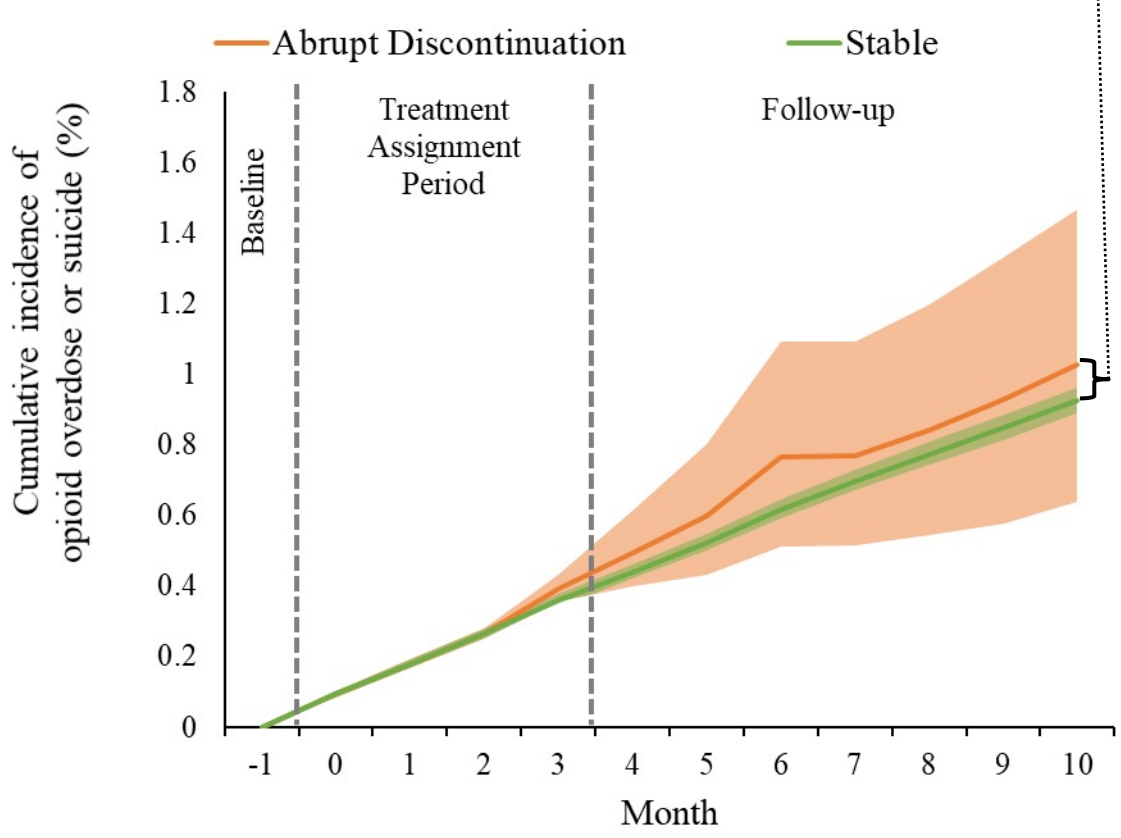
a) Taper vs Stable

Adj. Risk Diff. 0.22% (95% CI 0.10% to 0.36%)



b) Abrupt Discontinuation vs Stable

Adj. Risk Diff. 0.10% (95% CI -0.29% to 0.53%)



Methods and Results Comparison with Agnoli et al JAMA 2021

	Agnoli et al.	**Our analysis**
Result	Adj. Risk Diff*: 3.8 (3.0-4.6) aIRR, 1.68 (1.53-1.85)	Adj. Risk Diff: 0.15% (0.03%-0.26%) aRR 1.14 [95% CI, 1.04-1.27]
Data Source	Optum	Optum
Eligibility	Stable long-term opioid therapy	Stable long-term opioid therapy
Exclusion	Cancer or buprenorphine	Cancer, evidence of opioid misuse or other SUD
Treatment Assignment	Time-varying over follow-up	4-month assignment window
Outcome	Overdose or withdrawal	Overdose, suicide event
Analysis	Incidence rate (multiple events)	Time-to-event (censored after first event)

* Per 100 person-years of follow-up

Conclusions

- Opioid tapering was associated with a small (0.15%) absolute increase in the risk of overdose or suicide over 11 months of follow-up
- Emulated trial approach may be reducing bias
- Findings data do not support policies of mandatory opioid dosage limits or tapering practices for the purpose of reducing opioid-related harm

Summary - what do we know now?

- Unclear causality
- No evidence of a ***benefit*** of discontinuation for the outcome (overdose) that spurred increase in tapering
- Consensus that discontinuation should be done with caution, slowly
- Likely that some patients benefit, and some are destabilized

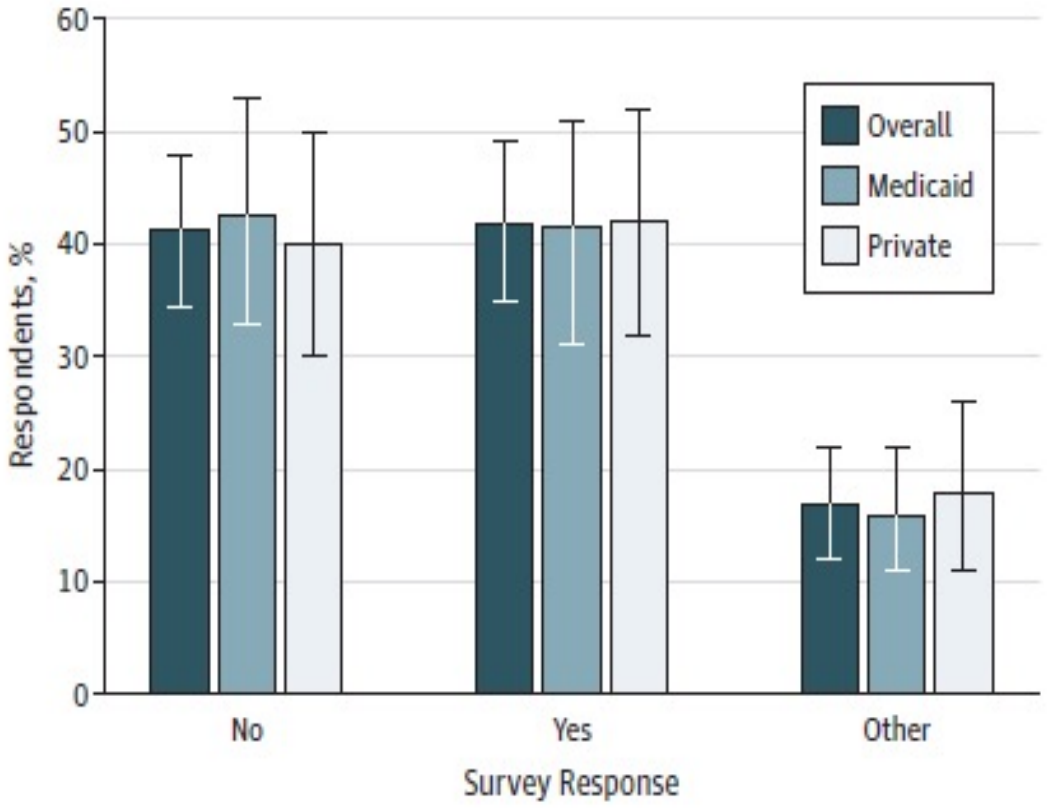
JAMA Network | Open

Original Investigation | Substance Use and Addiction

Access to Primary Care Clinics for Patients With Chronic Pain Receiving Opioids

Pooja A. Lagisetty, MD, MSc; Nathaniel Healy, BS; Claire Garpestad, BS; Mary Jannausch, MS; Renuka Tipirneni, MD, MSc; Amy S. B. Bohnert, PhD, MHS

Figure 2. Percentage of 194 Clinics Accepting New Patients Currently Taking Opioids



"Opioid Refugees"

- Fractured patient-provider relationships
- Precipitated withdrawal

Collaborators

- Sara Lodi, PhD
- Shapei Yan, MPH
- Barbara A. Clothier, MS, MA
- Elizabeth S. Goldsmith, MD, MS
- Marc Larochelle, MD, MPH
- Pooja Lagisetty, MD
- Allison Lewei Lin, MD
- Dara Ganoczy, MPH
- Erin Krebs, MD
- William Becker, MD