ASSOCIATION BETWEEN OPIOID THERAPY TRAJECTORIES AND POTENTIAL OPIOID-RELATED ADVERSE HEALTH EVENTS

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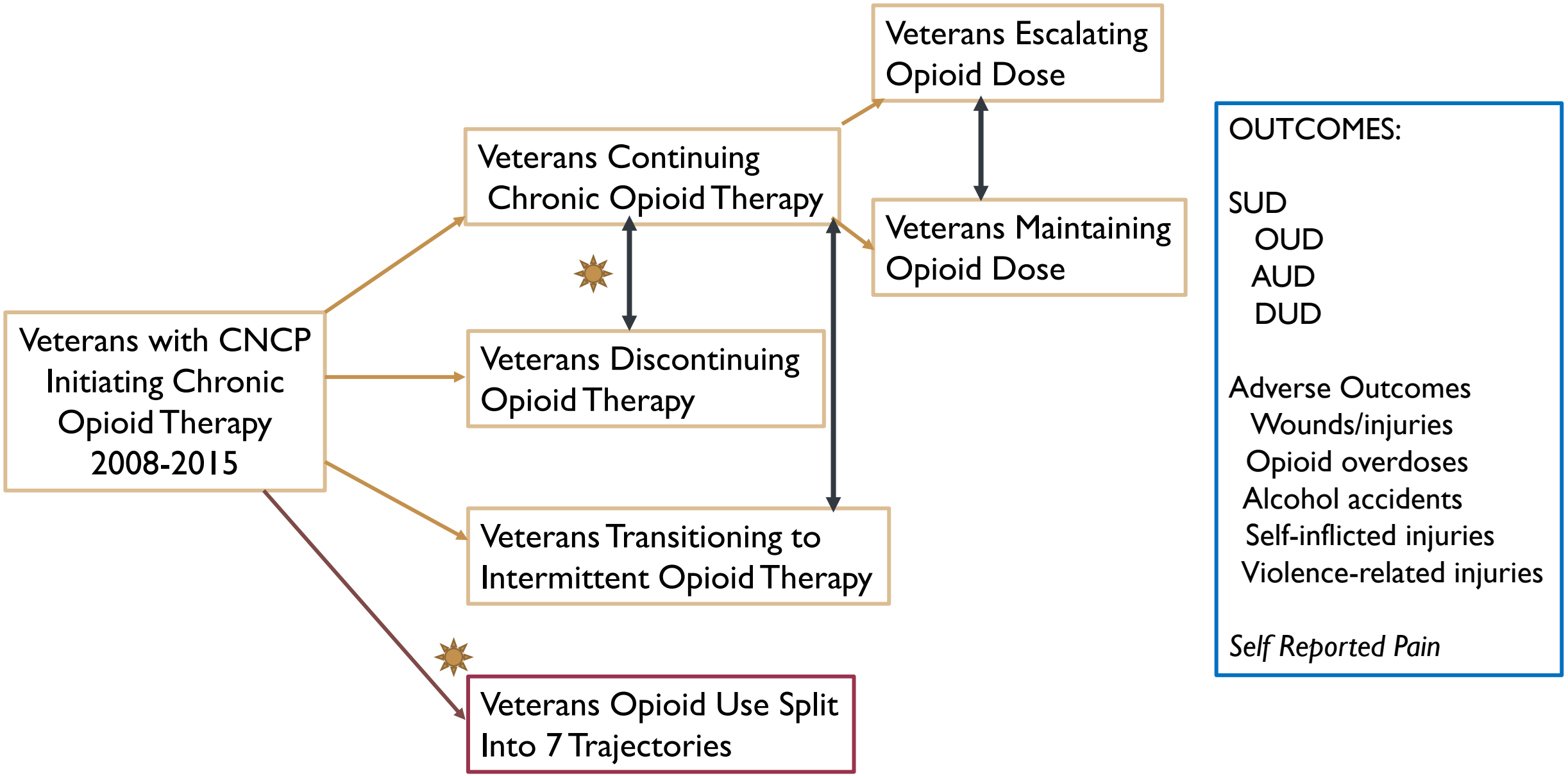
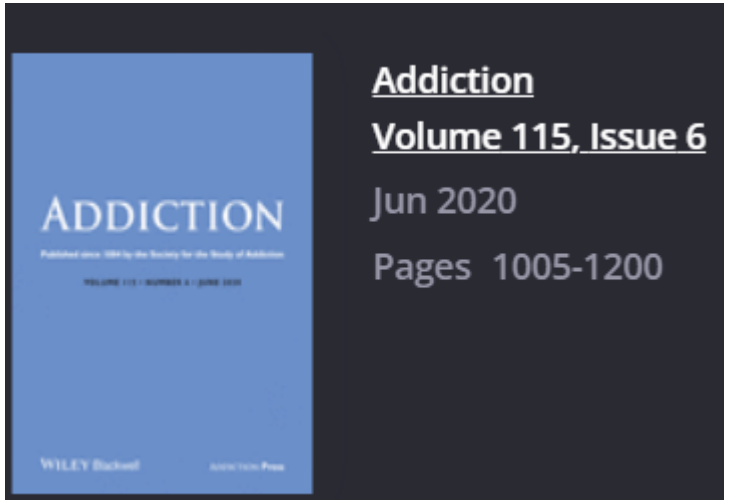

Veterans Escalating Opioid Dose
Veterans Continuing Chronic Opioid Therapy
Veterans Maintaining Opioid Dose
Veterans with CNCP Initiating Chronic Opioid Therapy 2008-2015
Veterans Discontinuing Opioid Therapy
Veterans Transitioning to Intermittent Opioid Therapy
Veterans Opioid Use Split Into 7 Trajectories
OUTCOMES:
SUD
OUD
AUD
DUD
Adverse Outcomes
Wounds/injuries
Opioid overdoses
Alcohol accidents
Self-inflicted injuries
Violence-related injuries
Self Reported Pain



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ORIGINAL RESEARCH

Trajectories of Opioid Coverage After Long-Term Opioid Therapy Initiation Among a National Cohort of US Veterans

ELSEVIER
The Journal of Pain
Volume 22, Issue 12, December 2021, Pages 1709-1721

Original Reports

Association Between Pain Intensity and Discontinuing Opioid Therapy or Transitioning to Intermittent Opioid Therapy After Initial Long-Term Opioid Therapy: A Retrospective Cohort Study

ELSEVIER
Drug and Alcohol Dependence
Volume 231, 1 February 2022, 109236

Impact of transitioning from long-term to intermittent opioid therapy on the development of opioid-related adverse outcomes: A retrospective cohort study

PAIN®

Impact of opioid dose escalation on pain intensity: a retrospective cohort study

Hayes, Corey J.[a,b]; Krebs, Erin E.[c,d]; Hudson, Teresa[a,b]; Brown, Joshua[e]; Li, Chenghui[f]; Martin, Bradley C.[f,*]

TODAY WE WILL FOCUS ON TWO STUDIES

ADDICTION SSA SOCIETY FOR THE STUDY OF ADDICTION

RESEARCH REPORT | Full Access

Association between discontinuing chronic opioid therapy and newly diagnosed substance use disorders, accidents, self-inflicted injuries and drug overdoses within the prescribers' health care system: a retrospective cohort study

Corey J. Hayes, Erin E. Krebs, Chenghui Li, Joshua Brown, Teresa Hudson, Bradley C. Martin

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ORIGINAL ARTICLE | Full Access

Association between opioid therapy trajectories and potential opioid-related adverse health events

Corey J. Hayes, Ruston M. Koonce, Laura Elisabeth Gressler, Bo Hu, James Silas Williams, Bradley C. Martin

DATA SOURCE

- VHA Corporate Data Warehouse
  - Fiscal Years: 2008 to 2015
  - Consisted of Data from:
    - Healthcare Visit to VA or paid for by VA
      - Inpatient
      - Outpatient
    - Outpatient VA Pharmacy
    - Demographics
    - Vital Signs
    - Vital Status

STUDY DESIGN AND COHORT

Veterans with at least one diagnosis for chronic non-cancer pain

- Arthritis
- Back Pain
- Neck Pain
- Neuropathic Pain
- Headaches/Migraines

Initiating long-term opioid therapy

- 90 days covered of non-parental opioids in a 180 day period without a 30 day gap

Ambulatory with adequate follow up

- Not in palliative care / hospice nor had CA Dx
- Alive at least 180 days after first chronic opioid use period

STUDY OUTCOMES

Potentially Opioid-related Adverse Outcomes

- Wounds/Injuries
- Opioid-related accidents and overdoses
- Alcohol and non-opioid, drug-related accidents and overdoses
- Self-Inflicted Injuries
- Violence-related Injuries

Substance Use Disorder

- Opioid Use Disorder (OUD)
- Non-Opioid Drug Use Disorder (DUD: e.g., stimulants, benzodiazepines, cannabis)
- Alcohol Use Disorder (AUD)

COVARIATES

- Demographic Covariates:
  - Age
  - Race
  - Gender
  - Marital Status
  - Index Date Year
  - Rural/Urban Classification
- Clinical Covariates:
  - Enhanced Charlson Comorbidity Index
  - Mental health conditions
  - Chronic, non-cancer pain conditions
- Pain Scores:
  - Average
  - First Pain Score
  - Change in Pain Score
- Medication Classes:
  - Benzodiazepines
  - Hypnotics/Other non-benzodiazepine sedatives
  - Skeletal muscle relaxants
  - Antidepressants
  - Non-opioid analgesics
- Opioid Medication Characteristics:
  - Schedule
  - Duration of Action
  - Mean Dose
  - Days Covered
- Prior Healthcare Utilization:
  - Physical Therapy
  - Pain Clinic
  - Chiropractic
  - Primary Care
  - ER
  - Mental Healthcare

ADDICTION

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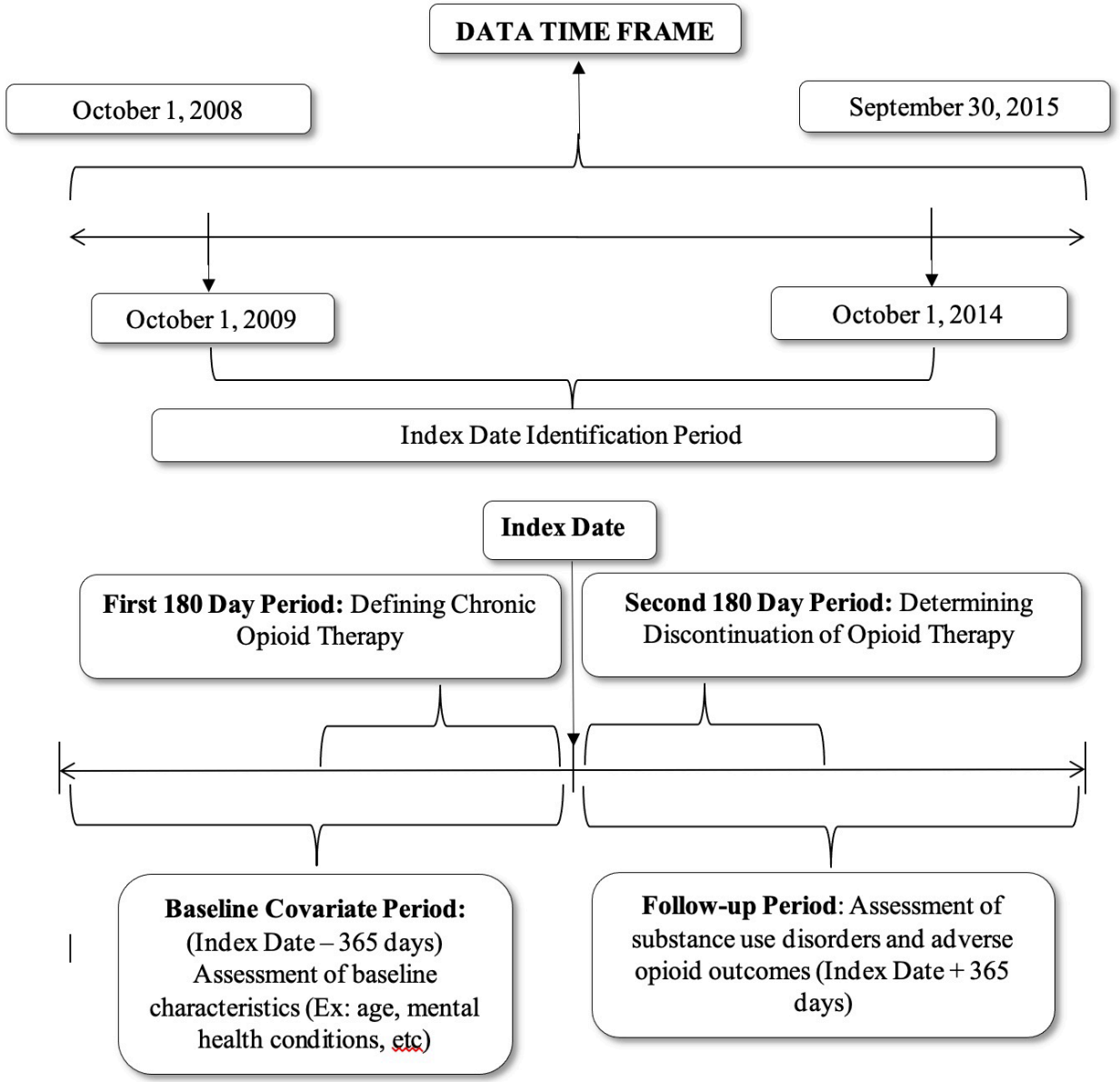
COMPARISON

VETERANS CONTINUING CHRONIC OPIOID THERAPY

VETERANS DISCONTINUING CHRONIC OPIOID THERAPY



Analyses: Adverse Opioid Outcomes and Substance Use Disorders

<table>
<tr><td rowspan="4">Unadjusted Logistic Regression</td><td rowspan="4">Adjusted Logistic Regression</td><td rowspan="4">Logistic Regression among the Propensity Score Matched Sample—Primary Analysis</td><td rowspan="4">Logistic Regression among the Entire Sample using SIPTW</td><td>Post-Hoc: Instrumental Variable Models—Percent Discontinuers per VAMC</td></tr>
<tr><td>Wald Estimator</td></tr>
<tr><td>Two-Stage Least Squares Models</td></tr>
<tr><td>Biprobit Models</td></tr>
<tr><td colspan="4">SAS 9.4 14.1 (SAS Institute, Cary, NC)</td><td>STATA IC 15</td></tr>
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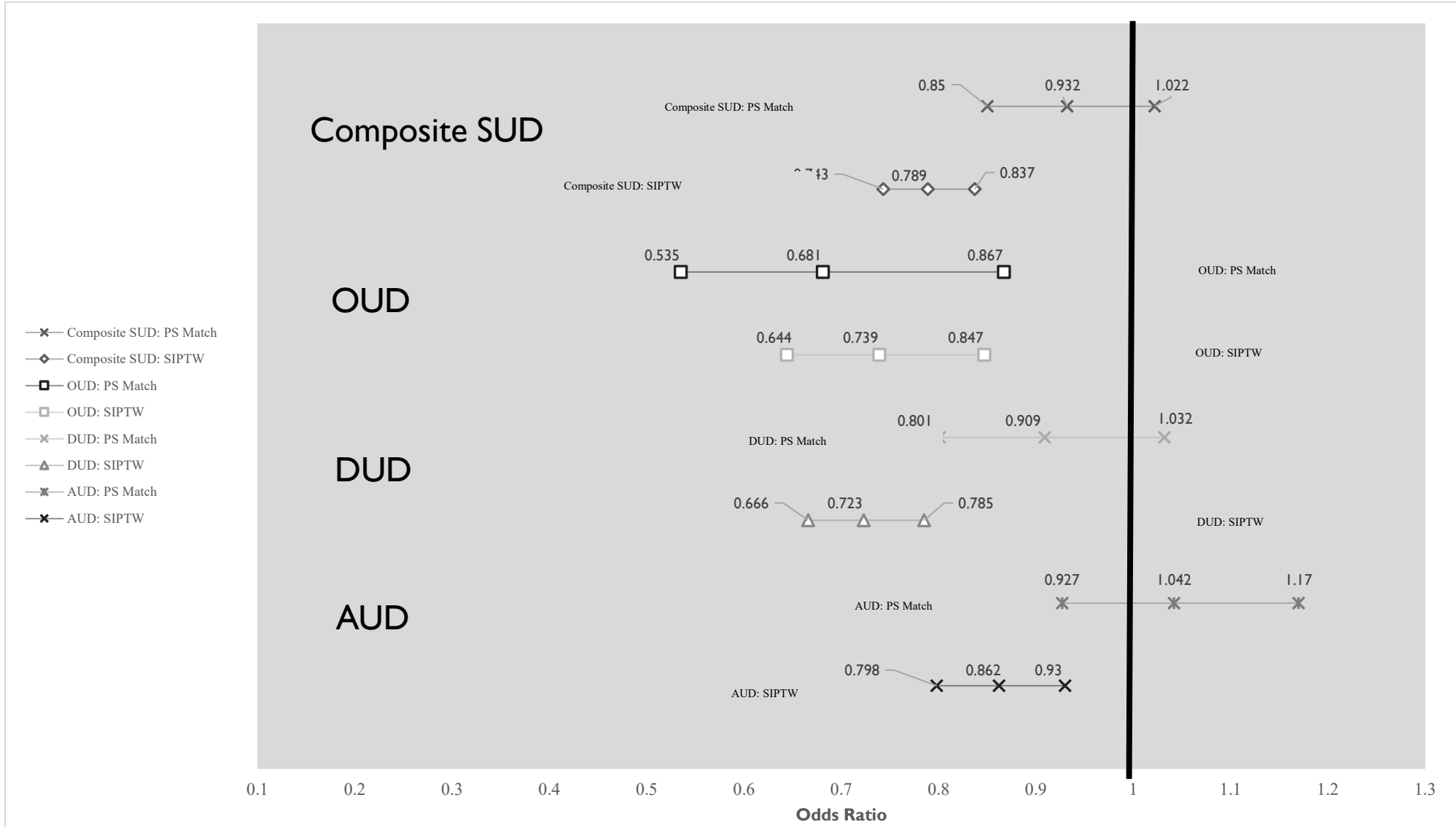
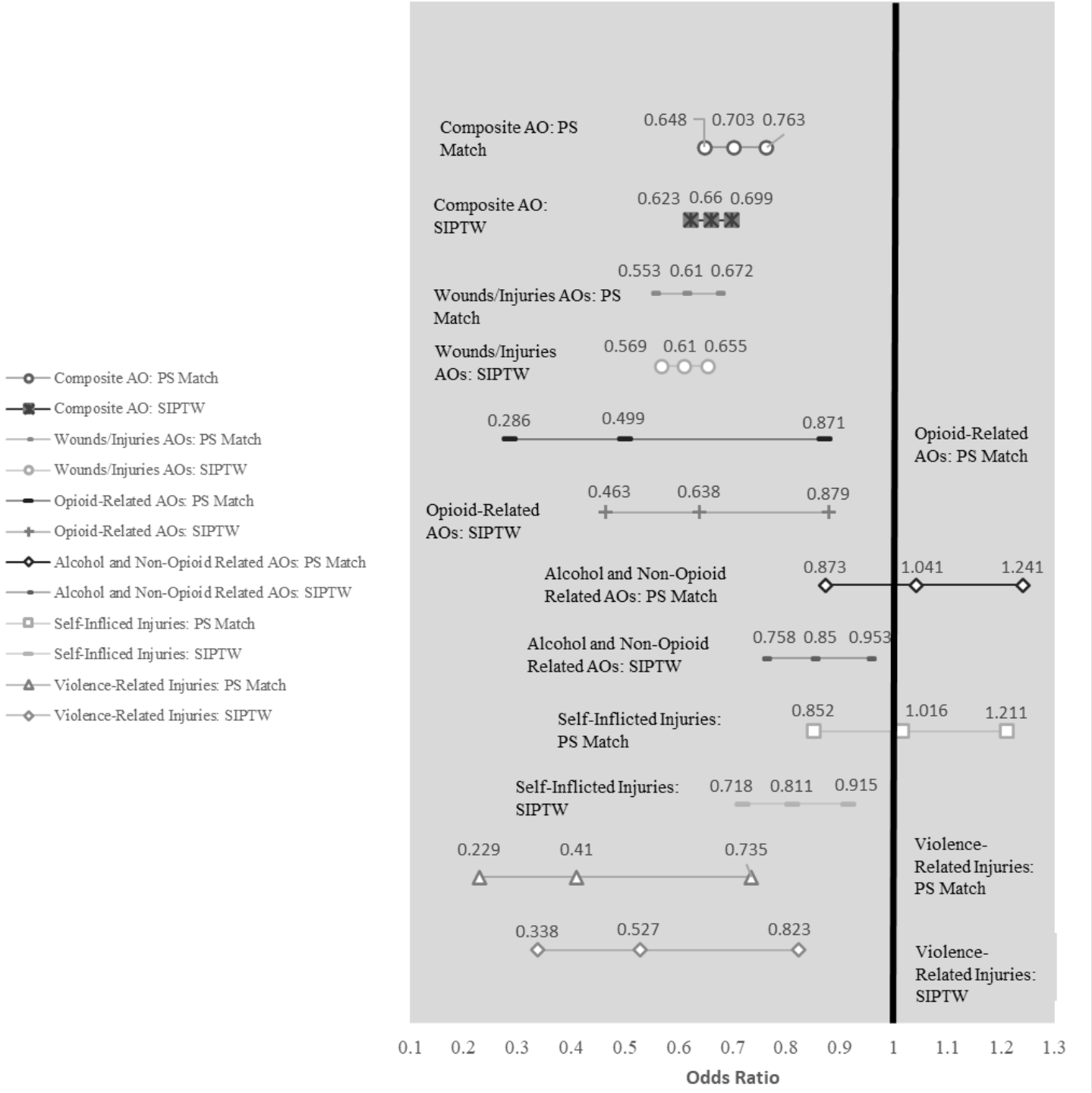
SUD DEVELOPMENT COMPARING VETERANS DISCONTINUING OPIOID THERAPY TO VETERANS CONTINUING CHRONIC OPIOID THERAPY:
PROPENSITY SCORE MATCHING AND SIPTW ANALYSES



Opioid Related Adverse Event Development Comparing Veterans Discontinuing Opioid Therapy to Veterans Continuing Chronic Opioid Therapy:

Propensity Score Matching and SIPTW Analyses



OPIOID RELATED ADVERSE EVENT DEVELOPMENT COMPARING VETERANS CONTINUING COT TO VETERANS DISCONTINUING OPIOID THERAPY AMONG THE UNMATCHED, MATCHED, AND SIPTW SAMPLES

	Unmatched Sample of Veterans Continuing COT‡, Switching to Intermittent Opioid Therapy, and Discontinuing Opioid Therapy		Matched Sample of Veterans Continuing COT‡ and Veterans Discontinuing Opioid Therapy		Matched Sample (Continuing COT‡ vs Discontinuing Opioid Therapy) Odds Ratio (OR) and Confidence Interval (CI)⊠*			SIPTW® Sample of Veterans Continuing COT‡ and Veterans Discontinuing Opioid Therapy∞		SIPTW® Sample (Continuing COT‡ vs Discontinuing Opioid Therapy) Odds Ratio (OR) and Confidence Interval (CI)⊠*Ω		
	N=151,462		N=34,674					N=151,313				
	Continuing COT‡ N=128,816 N (%)	Discontinuing Opioid Therapy N=22,646 N (%)	Continuing COT‡ N=17,337 N (%)	Discontinuing Opioid Therapy N=17,337 N (%)	OR	Lower 95% CI	Upper 95% CI	Continuing COT‡ N=128,685 N (%)	Discontinuing Opioid Therapy N=22,628 N (%)	OR	Lower 95% CI	Upper 95% CI
Composite AOs	11528 (9.0)	1412 (6.2)	1517 (8.8)	1098 (6.3)	0.703	0.648	0.763	11,515 (9.0)	1,410 (6.2)	0.660	0.623	0.699
Wounds and Injuries	8050 (6.3)	928 (4.1)	1114 (6.4)	700 (4.0)	0.610	0.553	0.672	8,042 (6.3)	928 (4.1)	0.610	0.569	0.655
Opioid-Related	378 (0.3)	22 (0.1)	37 (0.2)	19 (0.1)	0.499	0.286	0.871	377 (0.3)	22 (0.1)	0.638	0.463	0.879
Alcohol and Non-Opioid Medication Related	2360 (1.8)	305 (1.4)	248 (1.4)	258 (1.5)	1.041	0.873	1.241	2,356 (1.8)	304 (1.3)	0.850	0.758	0.953
Self-Inflicted Injuries	2177 (1.7)	325 (1.4)	255 (1.5)	257 (1.5)	1.016	0.852	1.211	2,174 (1.7)	325 (1.4)	0.811	0.718	0.915
Violence-Related Injuries	206 (0.2)	24 (0.1)	39 (0.2)	16 (0.1)	0.410	0.229	0.735	206 (0.2)	23 (0.1)	0.527	0.338	0.823

INSTRUMENTAL VARIABLE ANALYSES RESULTS COMPARED TO PROPENSITY MATCHED AND SIPTW ANALYSES

Outcome	P.S. Matching	SIPTW	IV – 2SLS	IV - BiProbit
OUD	-	-	+	
DUD		-	+	+
AUD		-	+	+
Wounds Injuries	-	-	-	-
Opioid Accident Overdose	-	-		
Alcohol Other Drug Accidents		-		
Self Inflicted Injuries		-	-	
Violence Related Injuries	-	-		

NOTABLE LIMITATIONS

- Opioid medications obtained outside of the VHA may have lead to incorrectly classifying some discontinuers
  - A study has found that 32% of veterans on COT received concurrent non-VHA opioid prescriptions
- Unclear if the development of a SUD or AO was the result or the cause of opioid discontinuation
  - Unlikely to explain the largely null findings or reduced risks reported
- Only persons with their first 180-day period of COT were considered
  - Can not examine if the finding would differ by length of COT
- Geographic variation in AO and SUD rates could cause prescribers to discontinue opioids
  - If this is the case, the IV analysis results may not be valid as the IV would not only effect the treatment, but also the outcome
- Cause of death were not available which could underestimate the number of outcome events if the patient was not seen in a healthcare setting
  - A total of 147 patients died from any cause in the time period of 180 to 360 days after the index date.

CONCLUSIONS

- New diagnoses for **opioid-related adverse outcomes**, such as **overdose**, **self-inflicted injuries**, **accidents resulting in wounds/injuries**, may **be lower among veterans discontinuing opioids** when compared to those continuing COT.
- The association between discontinuing opioid therapy and newly diagnosed SUDs is less clear; however, some of our findings suggest that those that discontinuing COT may have lower rates of newly diagnosed OUD in VHA compared to those continuing COT

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MAIN INDEPENDENT VARIABLE

Membership in distinct opioid therapy trajectories

Veterans were followed for 720 days following their index date (i.e., first date of LTOT)

To develop group-based trajectory models (proc traj):

- Summed days of opioid coverage for each 180 day period over the 720 day period
- Estimated a group-based trajectory model with days covered in each 180 day period as the outcome variable

STATISTICAL ANALYSIS

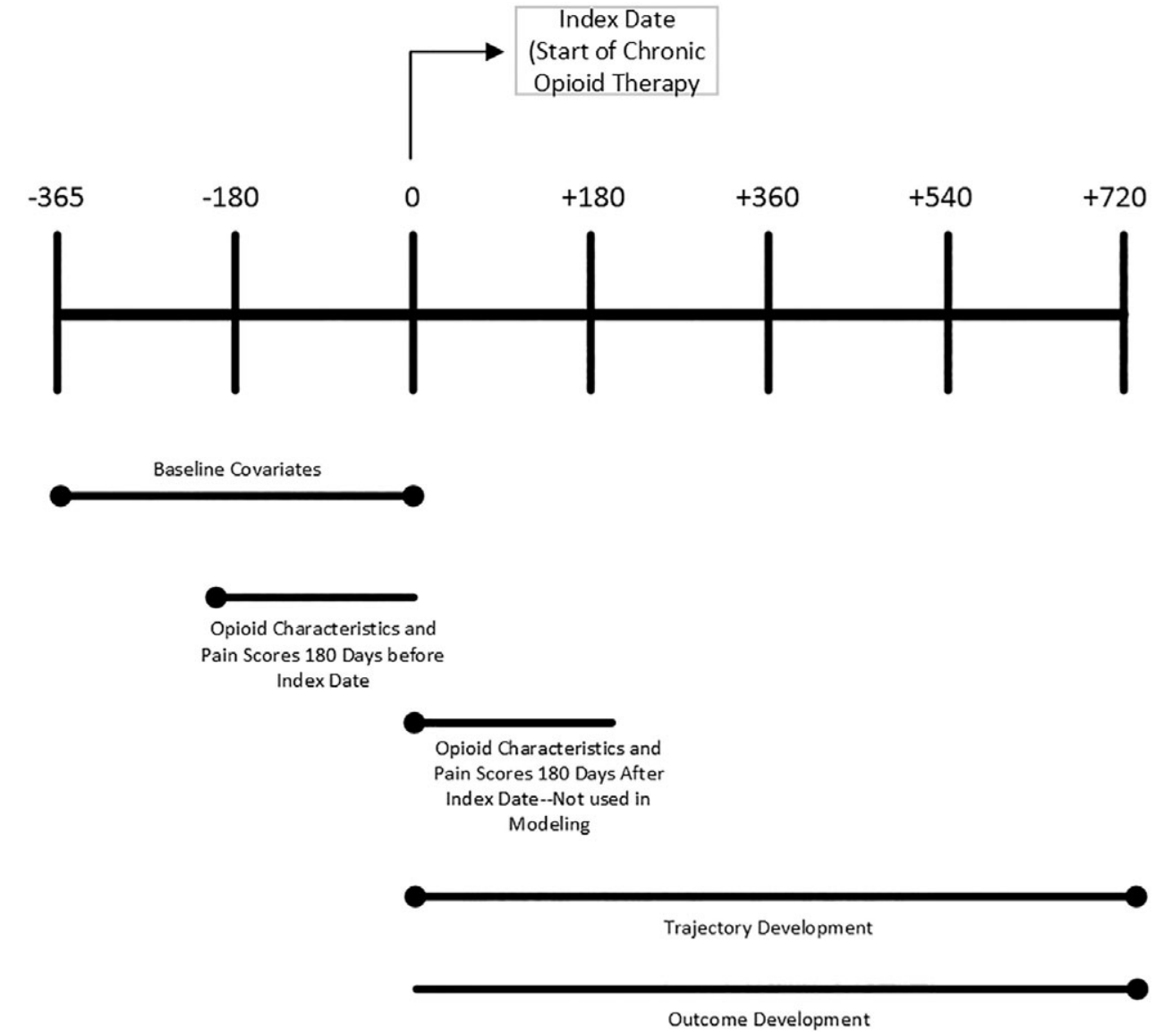
Veterans were followed until the first of one of the following:

- Censored (i.e., no inpatient or outpatient visit or pharmacy prescription fill in each 180-day period)
- End of the study period (720 days from the index date)
- End of the data (9/30/2015)
- Date of death
- Experienced the outcome of interest (i.e., specific potentially opioid-related adverse outcome or substance use disorder)

Two-step approach to modeling:

- Kaplan-Meier curves for each outcome
- Accelerated failure time models for each outcome

DIAGRAM OF STUDY TIME FRAME FOR STUDY MEASURES



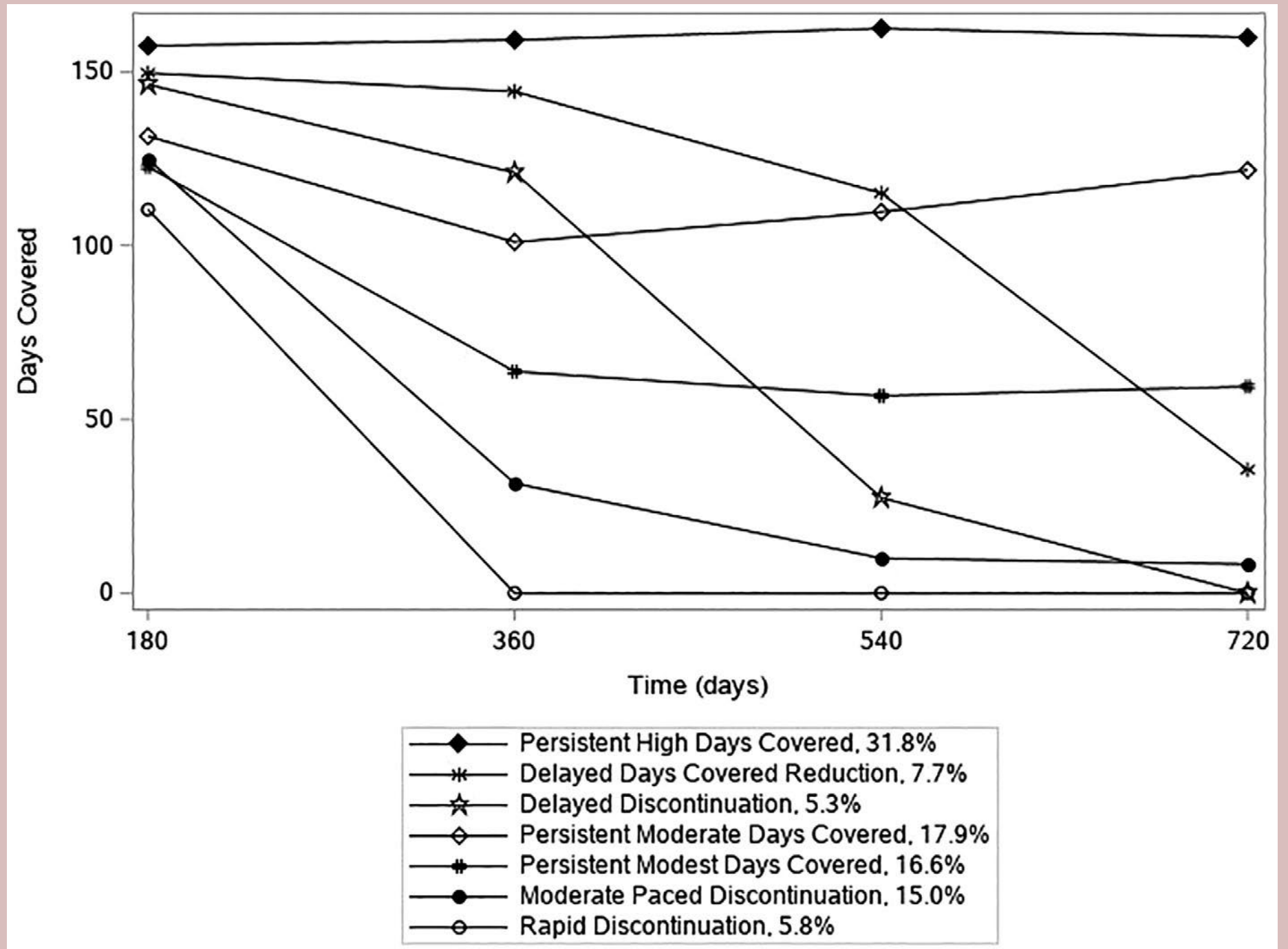

Days Covered
150
100
50
0
180
360
540
720
Time (days)
Persistent High Days Covered, 31.8%
Delayed Days Covered Reduction, 7.7%
Delayed Discontinuation, 5.3%
Persistent Moderate Days Covered, 17.9%
Persistent Modest Days Covered, 16.6%
Moderate Paced Discontinuation, 15.0%
Rapid Discontinuation, 5.8%

TABLE 5 Substance use disorders accelerated failure time model estimates: unadjusted versus adjusted

	Trajectories (Total $n = 373\,941$, 100%)	AUD-alcohol use disorder estimate 95% confidence limits Pr > ChiSq		DUD-non-opioid drug use disorder estimate 95% confidence limits Pr > ChiSq		OUD-opioid use disorder estimate 95% confidence Limits Pr > ChiSq	
		Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]
Persistent opioid therapy	Referent = Persistent high days covered ($n = 130\,257$, 34.9%)						
	Persistent moderate days covered ($n = 67\,699$, 18.1%)	0.77 (0.73, 0.80) < 0.0001	0.93 (0.88, 0.97) 0.0018	0.66 (0.62, 0.69) < 0.0001	0.80 (0.77, 0.85) < 0.0001	0.46 (0.42, 0.50) < 0.0001	0.59(0.54, 0.64) < 0.0001
	Persistent modest days covered ($n = 67\,175$, 17.9%)	0.73 (0.70, 0.77) < 0.0001	0.89 (0.84, 0.93) < 0.0001	0.67 (0.63, 0.70) < 0.0001	0.80 (0.76, 0.84) < 0.0001	0.43 (0.39, 0.47) < 0.0001	0.54 (0.50, 0.59) < 0.0001
Reduced opioid therapy	Delayed days covered reduction ($n = 21\,450$, 5.7%)	1.31 (1.23, 1.39) < 0.0001	1.37 (1.29, 1.46) < 0.0001	1.55 (1.46, 1.64) < 0.0001	1.59 (1.50, 1.69) < 0.0001	1.42 (1.31, 1.54) < 0.0001	1.50 (1.39, 1.63) < 0.0001
Discontinued opioid therapy	Moderate paced discontinuation ($n = 47\,347$, 12.7%)	1.08 (1.03, 1.13) 0.0029	1.21 (1.15, 1.27) < 0.0001	1.15 (1.09, 1.20) < 0.0001	1.25 (1.19, 1.31) < 0.0001	0.83 (0.77, 0.89) < 0.0001	0.94 (0.87, 1.01) 0.0748
	Delayed discontinuation ($n = 15\,853$, 4.2%)	1.32 (1.23, 1.42) < 0.0001	1.43 (1.33, 1.54) < 0.0001	1.68 (1.58, 1.80) < 0.0001	1.81 (1.69, 1.93) < 0.0001	1.40 (1.28, 1.53) < 0.0001	1.50 (1.37, 1.65) < 0.0001
	Rapid discontinuation ($n = 24\,160$, 6.5%)	0.90 (0.84, 0.96) 0.0026	1.07 (1.00, 1.15) 0.0459	0.91 (0.85, 0.97) 0.0064	1.09 (1.02, 1.17) 0.0104	0.73 (0.66, 0.81) < 0.0001	0.86 (0.77, 0.95) 0.0035

TABLE 6 Potentially opioid -related adverse outcomes accelerated failure time model θ estimates: unadjusted versus adjusted

	Trajectories (total $n = 405\,631$, 100%)	Wounds/injuries estimate 95% confidence limits Pr > ChiSq		Alcohol and non-opioid overdoses estimate 95% confidence limits Pr > ChiSq		Opioid overdoses estimate 95% confidence limits Pr > ChiSq		Self-inflicted-injuries estimate 95% confidence limits Pr > ChiSq		Violence related injuries estimate 95% confidence limits Pr > ChiSq	
		Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]
Persistent opioid therapy	Referent = persistent High days covered ($n = 143\,950$, 35.5%)										
	Persistent moderate days covered ($n = 72\,092$, 17.8%)	1.03 (0.99, 1.07) 0.0965	1.00 (0.96, 1.03) 0.8958	0.82 (0.77, 0.87) < 0.0001	0.97 (0.91, 1.03) 0.3481	0.62 (0.53, 0.73) < 0.0001	0.67 (0.57, 0.79) < 0.0001	0.92 (0.86, 0.98) 0.0094	1.07 (1.01, 1.14) 0.0362	0.97 (0.80, 1.82) 0.7271	1.10 (0.90, 1.33) 0.3552
	Persistent modest days covered ($n = 71\,006$, 17.5%)	1.13 (1.09, 1.17) < 0.0001	1.10 (1.06, 1.14) < 0.0001	0.81 (0.76, 0.87) < 0.0001	0.98 (0.91, 1.04) 0.4795	0.66 (0.56, 0.77) < 0.0001	0.72 (0.61, 0.85) < 0.0001	1.00 (0.94, 1.06) 0.9355	1.15 (1.07, 1.22) < 0.0001	1.11 (0.92, 1.34) 0.2870	1.21 (0.99, 1.46) 0.0530
Reduced opioid therapy	Delayed days covered reduction ($n = 23\,927$, 5.9%)	1.19 (1.14, 1.26) < 0.0001	1.11 (1.05, 1.17) < 0.0001	1.71 (1.59, 1.83) < 0.0001	1.63 (1.51, 1.75) < 0.0001	1.20 (0.99, 1.45) 0.0565	1.16 (0.96, 1.40) 0.1341	1.67 (1.55, 1.80) < 0.0001	1.53 (1.42, 1.65) < 0.0001	1.78 (1.42, 2.23) < 0.0001	1.58 (1.25, 1.99) < 0.0001
Discontinued opioid therapy	Moderate paced discontinuation ($n = 51\,181$, 12.6%)	1.31 (1.26, 1.36) < 0.0001	1.24 (1.20, 1.29) < 0.0001	1.40 (1.32, 1.48) < 0.0001	1.45 (1.37, 1.55) < 0.0001	0.88 (0.75, 1.04) 0.1347	0.89 (0.75, 1.05) 0.1512	1.52 (1.43, 1.61) < 0.0001	1.50 (1.41, 1.77) < 0.0001	1.60 (1.33, 1.92) < 0.0001	1.48 (1.23, 1.79) < 0.0001
	Delayed discontinuation ($n = 17\,578$, 4.3%)	1.05 (0.99, 1.12) 0.1161	1.02 (0.96, 1.08) 0.5391	1.75 (1.62, 1.90) < 0.0001	1.75 (1.61, 1.90) < 0.0001	1.12(0.89, 1.40) 0.3341	1.11 (0.89, 1.39) 0.3602	1.73 (1.59, 1.88) < 0.0001	1.65 (1.52, 1.80) < 0.0001	1.65 (1.27, 2.15) 0.0002	1.57 (1.20, 2.04) 0.0009
	Rapid discontinuation ($n = 25\,897$, 6.4%)	0.77 (0.73, 0.82) < 0.0001	0.78 (0.73, 0.83) < 0.0001	1.13 (1.03, 1.23) 0.0068	1.26 (1.16, 1.37) < 0.0001	0.50 (0.38, 0.67) < 0.0001	0.54 (0.41, 0.71) <0.0001	1.17 (1.07, 1.28) 0.0005	1.28 (1.17, 1.40) < 0.0001	0.73 (0.52, 1.01) 0.0573	0.76 (0.55, 1.06) 0.1044

[a]Adjusted for race, age group, gender, index year, marital status, rural–urban commuting area, eCCI categories, pain condition, antidepressant use, benzodiazepine use, skeletal muscle relaxant use, non-opioid analgesic use, hypnotics and non-benzodiazepine sedative use, mental health conditions, potentially opioid-related adverse outcomes, and mean number of clinic visits by type.

NOTABLE FINDINGS

Veterans following persistent days covered trajectories with low levels of opioid days covered were associated with lower risk of overdose and SUD as compared to those prescribed opioids daily.

Veterans following the rapid discontinuation trajectory had lower risk of overdose and OUD and higher risk of AUD, DUD and alcohol and non-opioid overdoses, and self-inflicted injuries as compared to those following the trajectory with daily coverage.

Veterans following trajectories characterized by gradual discontinuation or gradual reductions in opioid days covered were associated with elevated risks for all types of SUDs as well as for self-inflicted injuries, violence-related injuries, and wounds/injuries as compared to those prescribed opioids on a daily basis.

RELATED TO PERSISTENT HIGH DAYS COVERED, ARE OPIOID-RELATED RISKS LOWER WHEN PERSONS DISCONTINUE LONG-TERM OPIOID THERAPY?

- Mixed
  - Rapid discontinuation was associated with a lower risk of the outcomes most related to opioid therapy (i.e., OUD and opioid overdose) and higher for other outcomes (e.g., self-inflicted injuries)
  - Delayed discontinuation was associated with an elevated risk of OUD

AMONG THE DISCONTINUATION STRATEGIES, ARE THERE DIFFERENCES IN OPIOID-RELATED RISKS BETWEEN IMMEDIATE DISCONTINUATION COMPARED TO MORE GRADUAL DISCONTINUATION OF LONG-TERM OPIOID THERAPY?

- Our data suggest that more delayed discontinuation strategies were associated with higher risks for nearly all outcomes compared to rapid discontinuation

LIMITATIONS

- Cross-sectional design—reverse causality may explain some of the findings
- No data to explore physical functioning or self-reported pain levels
- Opioid prescriptions not paid for by VHA not captured
- Unmeasured confounders (e.g., incarceration, homelessness, social support)
- Only 4 time periods of 180 days does not provide granularity on more frequent intervals (e.g., weekly, monthly)
- Accidents resulting in wounds/injuries may not be opioid-related
- Older data (i.e., 2008-2015)

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CONCLUSIONS:

1. *Veterans following opioid trajectories of persistent modest days covered and persistent moderated days covered were associated with the lowest rates of SUDs and most of the other opioid-related adverse outcomes.*
2. *Veterans following trajectories characterized by gradual discontinuation/reductions were associated with the highest rates of SUDs and the other opioid-related adverse outcomes.*
3. *Should tapering/discontinuation be started, clinicians need to be very cautious and follow-up frequently as this may put patients at risk, particularly if they have been on opioids for extended lengths prior to tapering/discontinuing.*

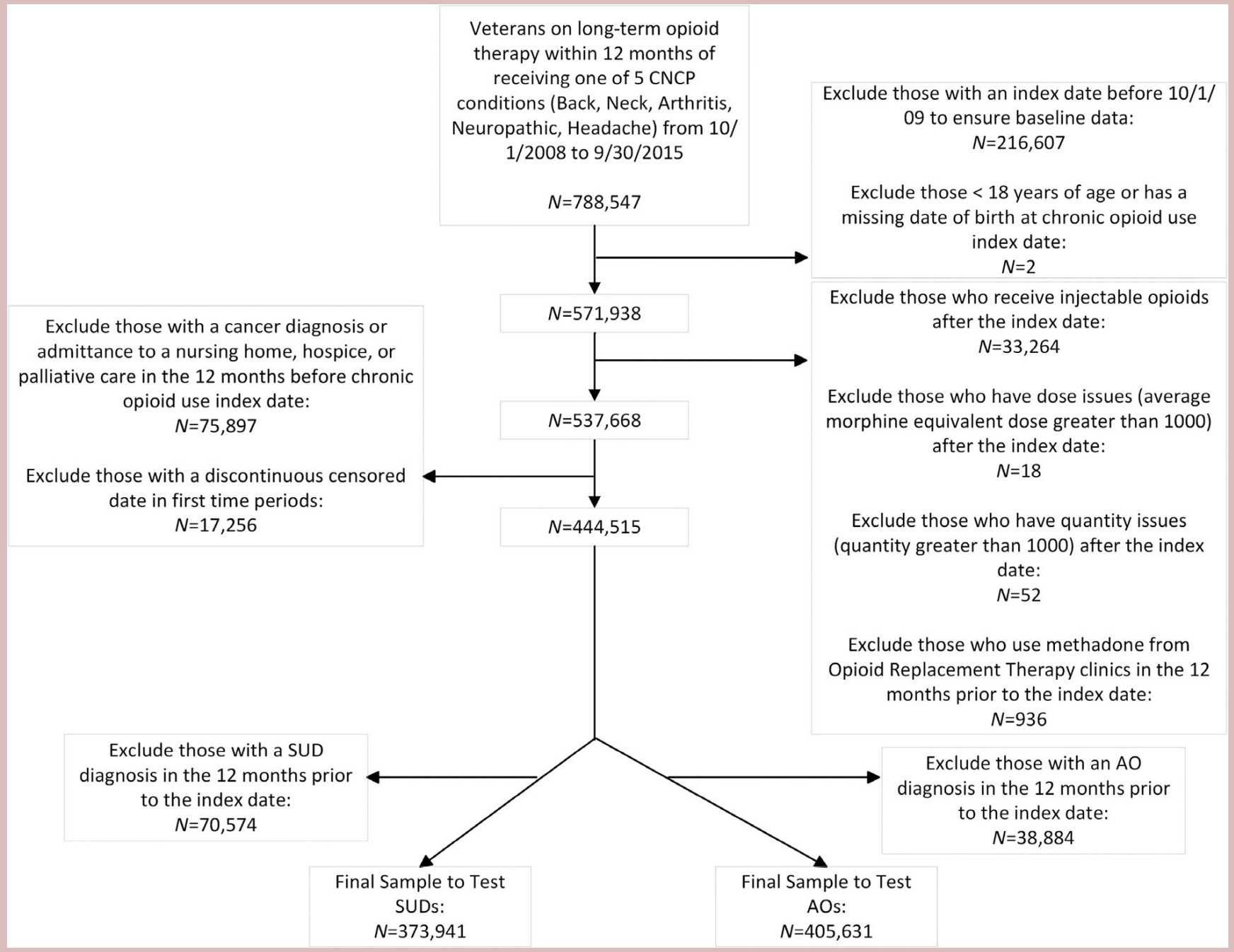
Veterans on long-term opioid therapy within 12 months of receiving one of 5 CNCP conditions (Back, Neck, Arthritis, Neuropathic, Headache) from 10/1/2008 to 9/30/2015
N=788,547
Exclude those with an index date before 10/1/09 to ensure baseline data:
N=216,607
Exclude those < 18 years of age or has a missing date of birth at chronic opioid use index date:
N=2
N=571,938
Exclude those who receive injectable opioids after the index date:
N=33,264
Exclude those who have dose issues (average morphine equivalent dose greater than 1000) after the index date:
N=18
Exclude those who have quantity issues (quantity greater than 1000) after the index date:
N=52
Exclude those who use methadone from Opioid Replacement Therapy clinics in the 12 months prior to the index date:
N=936
Exclude those with a cancer diagnosis or admittance to a nursing home, hospice, or palliative care in the 12 months before chronic opioid use index date:
N=75,897
Exclude those with a discontinuous censored date in first time periods:
N=17,256
N=537,668
N=444,515
Exclude those with a SUD diagnosis in the 12 months prior to the index date:
N=70,574
Exclude those with an AO diagnosis in the 12 months prior to the index date:
N=38,884
Final Sample to Test SUDs:
N=373,941
Final Sample to Test AOs:
N=405,631

Table 1. Key Demographics, Clinical Characteristics and Opioid use Measures for Patients in the Cohort Testing Development of Substance Use Disorders									
		Persistent Opioid Therapy			Reduced Opioid Therapy	Discontinued Opioid Therapy			
	Total Sample (N=373,941)	Persistent, High Days Covered (N=130,257, 34.9%)	Persistent, Moderate Days Covered (N=67,699, 18.1%)	Persistent Modest Days Covered (N=67,175, 17.9%)	Delayed Days Covered Reduction (N=21,450, 5.7%)	Moderate Paced Discontinuation (N=47,347, 12.7%)	Delayed Discontinuation (N=15,853, 4.2%)	Rapid Discontinuation (N=24,160, 6.5%)	P Value[a]
Race, (n, %)									<.0001
White	262,992 (70.33)	97,048 (74.51)	47,609 (70.32)	43,688 (65.04)	15,289 (71.28)	31,352 (66.22)	11,224 (70.80)	16,782 (69.46)	
Black	58,727 (15.70)	17,271 (13.26)	10,706 (15.81)	12,621 (18.79)	3,321 (15.48)	8,694 (18.36)	2,427 (15.31)	3,687 (15.26)	
Multiracial	10,771 (2.88)	3,294 (2.53)	2,029 (3.00)	2,170 (3.23)	621 (2.90)	1,497 (3.16)	472 (2.98)	688 (2.85)	
Other	26,266 (7.02)	7,229 (5.55)	4,622 (6.83)	5,912 (8.80)	1,420 (6.62)	4,019 (8.49)	1,096 (6.91)	1,968 (8.15)	
Unknown	15,185 (4.06)	5,415 (4.16)	2,733 (4.04)	2,784 (4.14)	799 (3.72)	1,785 (3.77)	634 (4.00)	1,035 (4.28)	
Age, (mean, SD)									
	57.86 (14.75)	56.48 (14.06)	59.51 (14.28)	59.24 (14.83)	56.80 (15.06)	57.74 (15.48)	57.06 (15.58)	58.57 (16.16)	<.0001
Gender, (n, %)									<.0001
Male	341,183 (91.24)	119,836 (92.00)	61,930 (91.48)	60,870(90.61)	19,523(91.02)	42,666(90.11)	14,424(90.99)	21,934(90.79)	

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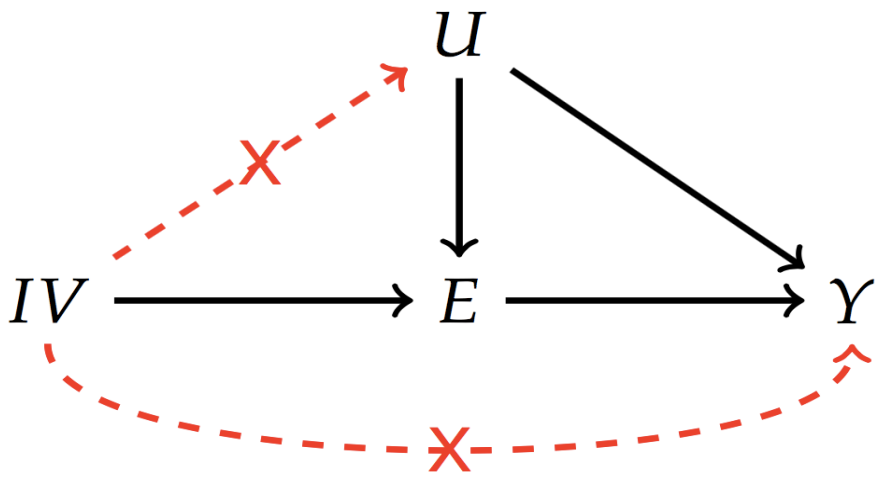
Pain Condition, (n, %)									<.0001
Back and/or Neck Pain Only	82,785 (22.14)	33,489 (25.71)	13,840 (20.44)	13,113 (19.52)	4,824 (22.49)	9,142 (19.31)	3,447 (21.74)	4,930 (20.41)	
Arthritis Only	101,630 (27.18)	32,691 (25.10)	18,828 (27.81)	18,657 (27.77)	5,803 (27.05)	13,773 (29.09)	4,486 (28.30)	7,392 (30.60)	
Headaches Only	4,811 (1.29)	1,682 (1.29)	764 (1.13)	786 (1.17)	310 (1.45)	713 (1.51)	213 (1.34)	343 (1.42)	
Neuropathic Pain Only	8,988 (2.40)	3,271 (2.51)	1,651 (2.44)	1,546 (2.30)	495 (2.31)	1,033 (2.18)	389 (2.45)	603 (2.50)	
Arthritis and Back and/or Neck Pain Only	89,818 (24.02)	30,747 (23.60)	16,634 (24.57)	16,779 (24.98)	5,074 (23.66)	11,354 (23.98)	3,610 (22.77)	5,620 (23.26)	
Arthritis, Back and/or Neck Pain, and Headaches Only	13,607 (3.64)	4,389 (3.37)	2,431 (3.59)	2,651 (3.95)	790 (3.68)	1,904 (4.02)	609 (3.84)	833 (3.45)	
Neuropathic Pain and One or More Others	54,525 (14.58)	17,904 (13.75)	10,451 (15.44)	10,412 (15.50)	3,078 (14.35)	7,029 (14.85)	2,341 (14.77)	3,310 (13.70)	
All Tracer Pain Conditions	1,854 (0.50)	595 (0.46)	360 (0.53)	402 (0.60)	103 (0.48)	243 (0.51)	56 (0.35)	95 (0.39)	
Other Multiple Pain Conditions	15,923 (4.26)	5,489 (4.21)	2,740 (4.05)	2,829 (4.21)	973 (4.54)	2,156 (4.55)	702 (4.43)	1,034 (4.28)	
Opioid Duration of Action (180 Days Prior to and including the Index Date), (n, %)									<.0001
No Opioid Use	207,077 (55.38)	83,403 (64.03)	29,583 (43.70)	29,003 (43.18)	12,293 (57.31)	26,800 (56.60)	9,497 (59.91)	16,498 (68.29)	
Long-Acting Only	1,442 (0.39)	614 (0.47)	299 (0.44)	199 (0.30)	77 (0.36)	141 (0.30)	56 (0.35)	56 (0.23)	
Short-Acting Only	163,401 (43.70)	45,486 (34.92)	37,403 (55.25)	37,615 (56.00)	8,962 (41.78)	20,201 (42.67)	6,208 (39.16)	7,526 (31.15)	
Combination of Long and Short-Acting	2,021 (0.54)	754 (0.58)	414 (0.61)	358 (0.53)	118 (0.55)	205 (0.43)	92 (0.58)	80 (0.33)	

IV MODELS

Endogeneity Problem:



U might be complaints about dose
Geographic variation is a common IV

Wald Estimator:

$$Wald = \frac{\text{Difference in outcome due to treatment}}{\text{Difference in take-up due to treatment}}.$$

Two stage least squares

Econ 140

- First stage: use OLS to estimate reduced form for the right-hand side endogenous variable W_i:

$$W_i = \pi_{10} + \pi_{11} X_i + \pi_{12} NK_i + \varepsilon_{1i}$$

- Second stage: use predictions from the first stage for $\hat{W}_i$:

$$H_i = a_1 + b_1 \hat{W}_i + u_i$$