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Patterns of Buprenorphine Initiation Treatment for Opioid Use Disorder and Association with Opioid-related Overdose Deaths

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Background

- Opioid Use Disorder (OUD) is a serious problem in the U.S.
- Estimated >2.7 million people with OUD in 2020[1]
- Estimated >80,000 opioid overdose deaths in 2021[2]
- Buprenorphine is one of three medications approved by the U.S. Food and Drug Administration for treatment of OUD

Background (cont.)

- The highest risk of treatment discontinuation occurs in the first 30 days[3-6]
- Treatment initiation on low dose (≤4mg) and shorter initial days' supply (≤7 days) was found to be significantly associated with treatment discontinuation[6,7]
- Little is known about the association between treatment initiation characteristics and short term (e.g., within a year) opioid overdose mortality

Study Objective:

To examine the association between the transmucosal (TM) buprenorphine treatment characteristics for OUD within the first 30 days of treatment and the incidence of opioid-related overdose deaths in the following 12-month period

Data Sources:

- Electronic prescription records for Schedule II-V controlled substances dispensed in Kentucky, provided by the Kentucky All Schedule Prescription Electronic Reporting (KASPER) program

- Electronic death certificate records provided by the Kentucky Office of Vital Statistics

Study Sample:

- Kentucky residents ≥ 18 years old
- Initiated TM buprenorphine treatment for OUD between Jan 1, 2017 and Nov 30, 2019
- No buprenorphine treatment in the 180-day look back eligibility window
- Did not die or switch to long-acting injectable (LAI) buprenorphine within the first 30 days of treatment

Study Measures:

Buprenorphine Treatment Characteristics

1) Daily dose of the initial prescription (≤ 8 mg; >8 to ≤ 16 mg; >16 mg)

2) Average daily dose for days covered within the first 30 days of treatment (≤ 8 mg; >8 to ≤ 16 mg; >16 mg)

3) Patient's adherence to treatment within the first 30 days of treatment, defined as the proportion of days covered (PDC) with buprenorphine (low [PDC< 0.4]; moderate [PDC: 0.4-0.8]; high [PDC≥0.8])

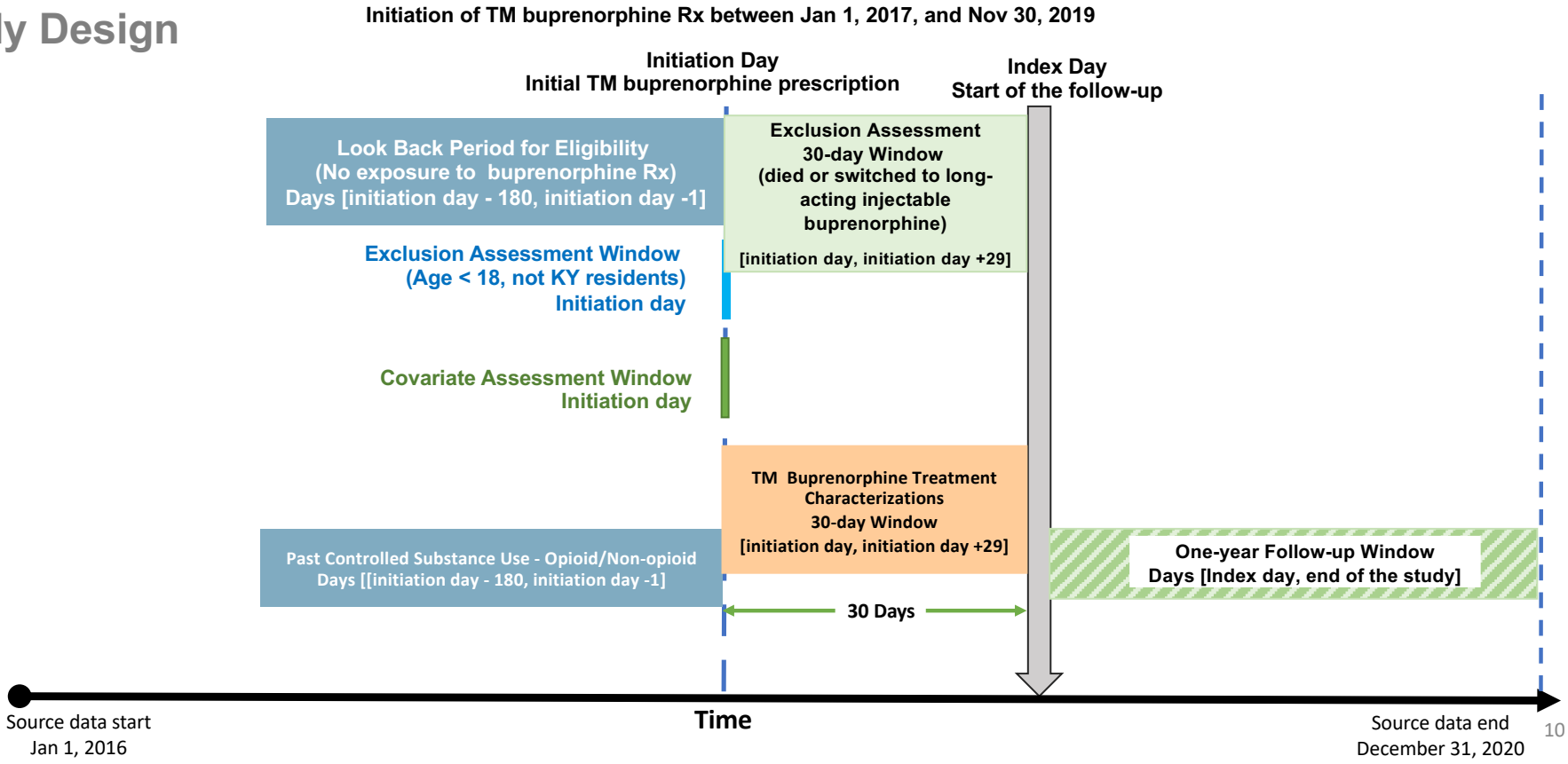
Outcome of Interest:

Opioid-related overdose deaths

Definition: death certificates with an underlying cause of death in the ICD-10 range X40-X44, X60-X64, X85, or Y10-Y14, and a contributing cause of death in the ICD-10 range T40.0-T40.4, or T40.6[8,9]

Deaths that did not meet this definition were classified as ***deaths from causes other than opioid overdose***, and these deaths were considered *competing risks* for opioid-related overdose deaths.

Study Design



Statistical Analysis:

- Cumulative incidence function (CIF)
- Multivariable Fine and Gray regression models[10] (subdistribution hazard models) for associations between each TM buprenorphine treatment initiation characteristic and opioid-related overdose death incidence, considering deaths from other causes as competing risks, and adjusting for patient demographics and controlled-substance use in the 180 days before treatment initiation
- Results from the models are reported as adjusted sub-hazard ratios [aSHR] with their 95% Confidence Intervals [95% CI]

Results:

- Study sample (n=49,857)
- 227 opioid-related overdose deaths
- 459 deaths from causes other than opioid-related overdose

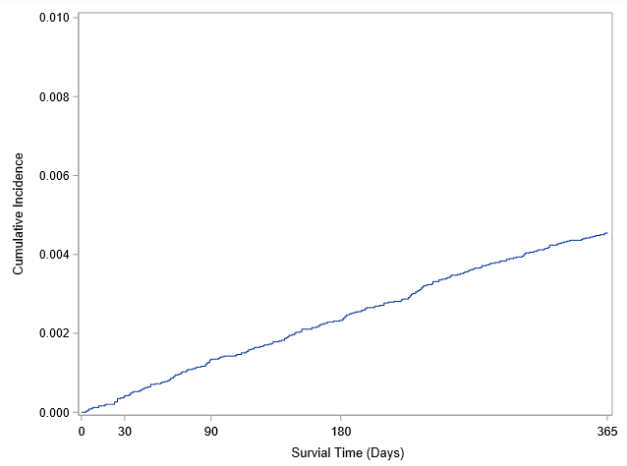
	N	Median Number of Days to Event	Lower Quartile	Upper Quartile
Censored (Alive)	49040	365	365	365
Censored (Switched to LAI[a] buprenorphine)	131	220	121	292
Opioid-related overdose death	227	171	80	256
Deaths from causes other than opioid overdose	459	187	89	277

[a]LAI: Long-acting injectable buprenorphine (i.e., Sublocade®).

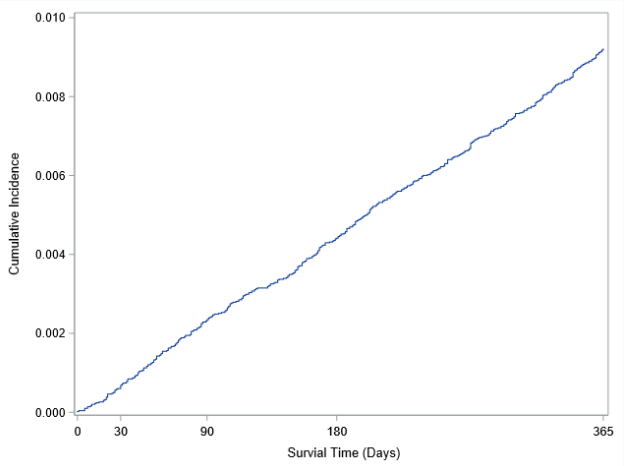
Results:

Cumulative Incidence Function

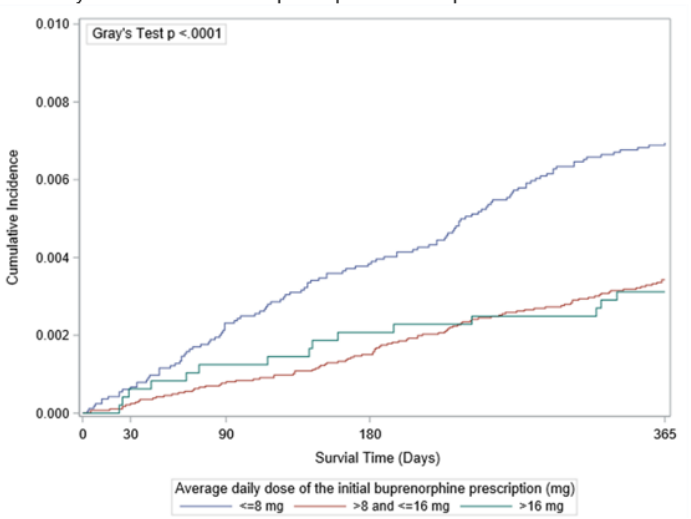
A) Opioid-Related Overdose Deaths



B) Deaths from Causes Other than Opioid-related Overdose



Cumulative Incidence Function for Opioid-related Overdose Deaths, by Average Daily Dose of the Initial Buprenorphine Prescription

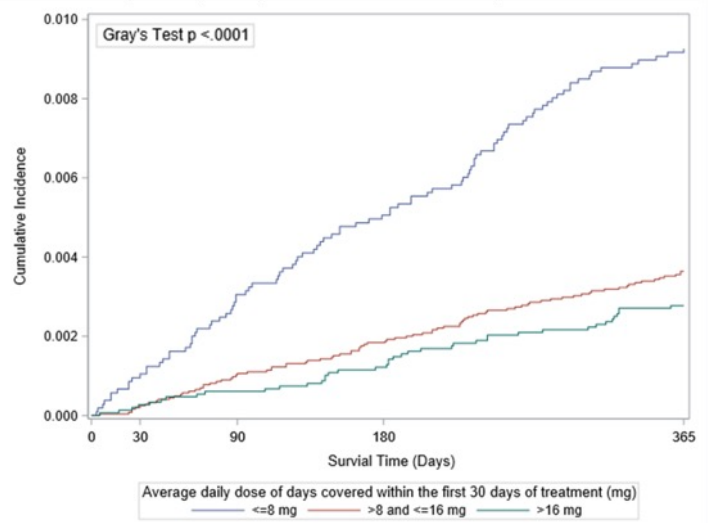


Subdistribution Hazard Model for Average Daily Dose of the Initial Buprenorphine Prescription and the Incidence of Opioid-Related Overdose Death

Characteristic	aSHR[1]	95%CI	p-value
Average daily dose of the initial prescription			
<=8 mg	—	—	
> 8 and ≤ 16 mg	0.58	0.44, 0.76	<0.001
> 16 mg	0.47	0.27, 0.80	0.006

[1]aSHR - Subdistribution Hazard Ratio adjusted for age group (18-24, 25-34, 35-44, 45-54, 55-65, 65+), sex (F, M), Rural/Urban residency, and dispensed controlled substances (opioid, benzodiazepine, or other non-opioid controlled substance) in the 180-day window before treatment initiation

Cumulative Incidence Function for Opioid-related Overdose Deaths, by Average Daily Dose for the First 30 Days of Treatment

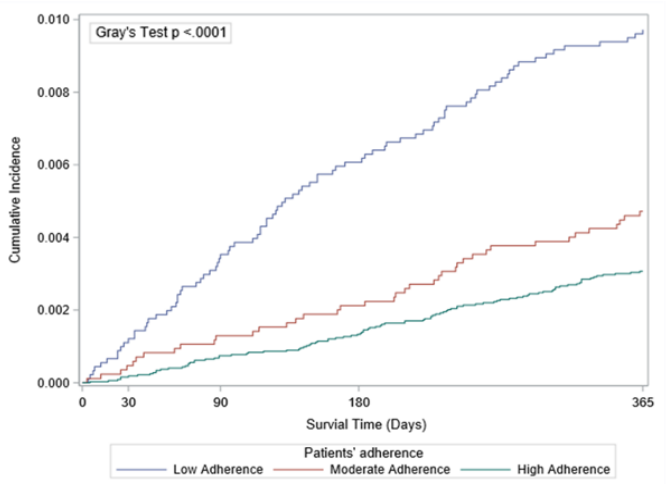


Subdistribution Hazard Model for Average Daily Dose within the First 30 Days of Treatment and the Incidence of Opioid-Related Overdose Death

Characteristic	aSHR[1]	95% CI	p-value
Average daily dose within the first 30 days of treatment			
≤ 8 mg	—	—	
> 8 and ≤ 16 mg	0.45	0.33, 0.59	<0.001
> 16 mg	0.36	0.25, 0.52	<0.001

[1]aSHR - Subdistribution Hazard Ratio adjusted for age group (18-24, 25-34, 35-44, 45-54, 55-65, 65+), sex (F, M), Rural/Urban residency, and dispensed controlled substances (opioid, benzodiazepine, or other non-opioid controlled substance) in the 180-day window before treatment initiation

Cumulative Incidence Function for Opioid-related Overdose Death, by Level of Patients' Adherence to Treatments within the First 30 days of Treatment Initiation



Subdistribution Hazard Model for Patients' Adherence and the Incidence of Opioid-Related Overdose Deaths, Stratified by Follow-Up Time (1 to 180 Days, and 181 to 365 Days).

	Day 1 to Day 180			Day 181 to Day 365		
Characteristic	**aSHR[1]**	**95% CI**	**p-value**	**aSHR[1]**	**95% CI**	**p-value**
Patients' adherence						
Low adherence (PDC[2]<0.4)	—	—		—	—	
Moderate adherence (0.4≤PDC<0.8)	0.39	0.23, 0.66	<0.001	0.80	0.46, 1.39	0.438
High adherence (PDC≥0.8)	0.24	0.16, 0.36	<0.001	0.56	0.36, 0.86	0.008

[1]aSHR - Subdistribution Hazard Ratio adjusted for age group (18-24, 25-34, 35-44, 45-54, 55-65, 65+), sex (F, M), Rural/Urban residency, and dispensed controlled substances (opioid, benzodiazepine, or other non-opioid controlled substance) in the 180-day window before treatment initiation
[1]PDC (Percentage of Days Covered) within the 30 days of treatment initiation

Subdistribution Hazard Regression Model for the Association between Opioid-related Overdose Death and the Daily Dose of the Initial Prescription, Adjusted for the Patients' Adherence within the First 30 Days of Treatment.

Characteristic	aSHR[1]	95% CI[2]	p-value
Daily dose of the initial buprenorphine prescription			
≤ 8 mg	—	—	
> 8 and ≤ 16 mg	0.72	0.55, 0.95	0.021
> 16 mg	0.59	0.35, 1.02	0.058
Patients' adherence			
Low adherence (PDC[3]<0.4)	—	—	
Moderate adherence (0.4≤PDC<0.8)	0.61	0.42, 0.89	<0.001
High adherence (PDC≥0.8)	0.41	0.30, 0.54	<0.001

[1]aSHR = Subdistribution Hazard Ratio adjusted for age at initiation, gender, rural/urban residency, receipt of benzodiazepine, receipt of other non-opioid, receipt of opioid analgesics in 180 days before initiation
[2]CI = Confidence Interval
[3]PDC= Proportion of days covered
Note: The interaction between the average daily dose of the initial prescription and patients' adherence was insignificant (p=0.394) and therefore was not included.

Limitations:

- KASPER data includes only prescriptions dispensed in Kentucky pharmacies
- Limited available demographic and socioeconomic variables
- Possible data entry errors for the days' supply
- Treatment characteristics based on prescription records; Impossible to confirm whether a patient took the medication as reflected in the prescription record

Conclusions:

Higher daily dose and greater patients' adherence within 30 days of buprenorphine treatment initiation were associated with lower opioid-related overdose death incidence, highlighting the importance of the prescribing decisions and retaining patients in the early stage of buprenorphine treatment for opioid use disorder.

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