Supplemental Online Content

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**eReferences**

This supplemental material has been provided by the authors to give readers additional information about their work.
### eTable 1. Descriptions of All Linked Administrative Databases Used in the Study

| Database                                      | Description                                                                                                                                                                                                 |
|-----------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Narcotics Monitoring System (NMS)             | The Narcotic Monitoring System is a mandatory prescription reporting system in Ontario, which is complete as of July 1, 2012. It captures all outpatient prescriptions for controlled substances in Ontario regardless of payment method. These include all prescription opioids, benzodiazepines (excluding zopiclone), and stimulants\(^1\). NMS was used to capture all MOUD prescriptions and opioid prescriptions. |
| Registered Persons Database (RPDB)            | The RPDB provides demographic information and vital statistics on all persons with an Ontario health card (i.e. OHIP number). We used the RPDB to assess sex, age, and postal code of each individual’s primary residence.                                                                   |
| Drug-Alcohol Related Death Database           | DDARD is a dataset of confirmed cause of death from the Office of the Chief Coroner of Ontario and allows the accurate identification of the cause of death. In accordance with Ontario’s Coroners Act, all deaths that are sudden and unexpected, or unnatural, must be reported to the Coroner’s Office. Opioid-related death was defined as an acute intoxication or toxicity death resulting from the direct contribution of an opioid\(^2\). |
| Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD) | Captures details on diagnoses and procedures for all inpatient hospital stays in Ontario. This dataset has been validated through a re-abstraction study which found that the re-abstractor agreed at least in part with the original coder regarding the most responsible diagnosis approximately 85% of the time\(^3\). |
| CIHI National Ambulatory Care Reporting System (NACRS) | Captures details on diagnoses and procedures for all emergency department visits in Ontario.                                                                                                                                                                      |
| CIHI Ontario Mental Health Reporting System (OMHRS) | The OMHRS database contains demographic, administrative and clinical information for all adult admissions to designated inpatient mental health beds in Ontario. This includes beds in general hospitals as well as in specialty psychiatric facilities. We used OMHRS records to identify psychiatric admissions for the purpose of understanding psychiatric co-morbidity. |
| Ontario Health Insurance Plan (OHIP) Database | This database reflects physician claims through the Ontario Health Insurance Plan. Elements in this dataset include the patient and physician identifiers, the code for service provided, date of service, and associated diagnosis. We used OHIP claims to understand physician specialty, assess healthcare utilization, and in the definition of alcohol use disorder. |
| Chronic Obstructive Pulmonary Disease (COPD) Validated Database | This database uses a validated definition to identify diagnosis dates for all people with COPD in Ontario (85.0% sensitivity, 78.4% specificity).\(^4\)                                                                 |
| HIV Validated Database                         | This database uses a validated definition to identify diagnosis dates for all people with HIV in Ontario (96.2% sensitivity, 99.6% specificity).\(^5\)                                                                 |
| Ontario Diabetes Database                     | This database uses a validated definition to identify diagnosis dates for all people with diabetes in Ontario (90.0% sensitivity, 97.7% specificity).\(^6\)                                                                 |
| ICES Physician Database (IPDB)                | IPDB is a dataset that contains yearly information about all physicians in Ontario including demographics, specialty, location and physician activity (billings, workload, types of services provided). For the purpose of our study, IPDB was used to ascertain provider specialty. |
### eTable 2. Covariate Definitions

| Variable                                      | Database       | Definition/Citation                                                                                                                                 |
|-----------------------------------------------|----------------|---------------------------------------------------------------------------------------------------------------------------------------------------|
| Age                                           | RPDB           | Age at index using birth date in RPDB                                                                                                               |
| Sex                                           | RPDB           | Sex as recorded in RPDB                                                                                                                              |
| Rurality of residence                         | RPDB           | Rurality of residence using person’s postal code                                                                                                    |
| Neighbourhood income quintile                 | RPDB           | Neighbourhood income quintile using person’s postal code                                                                                           |
| Harmful alcohol use or dependence             | OHIP, DAD, NACRS | Physician or hospital related visit for alcohol use disorder using codes below (primary diagnosis) in the 2 years prior to index date: <br>**ICD-10 Codes:** F10 K70 G31.2 G62.1 G72.1 I42.6 K29.2 K86.0 Z50.2 Z71.4 Z86.40 K85.2 <br>**OHIP Diagnosis Codes:** 291 303 |
| Harmful stimulant use or dependence           | DAD, NACRS     | Hospital visit for harmful stimulant use or dependence using codes below (primary diagnosis) in the 2 years prior to index date: <br>**ICD-10 CA codes:** F140 - F159, T436, T405 |
| Harmful sedative-hypnotic use or dependence   | DAD, NACRS     | Hospital visit for harmful sedative-hypnotic use or dependence using codes below (primary diagnosis) in the 2 years prior to index date: <br>**ICD-10 CA codes:** F131, F132, T423, T424, T426, T427 |
| Hospitalization or ED visit for depression in last 2 years | DAD, NACRS, OMHRS | Hospital visit for depression (primary diagnosis) in the 2 years prior to index date: <br>**OMHRS ICD9-CM codes:** DSM5CODE_DISCH1 = 296.2x, 296.3x, 296.9x, 300.4x, 311.x, 625.4x. <br>PROVDX_DSM5CODE_ADM1 =4 <br>**DAD/NACRS ICD-10-CA codes:** F32.x, F33.x, F34.1 |
| Hospitalization or ED visit for anxiety in last 2 years | DAD, NACRS, OMHRS | Hospital visit for anxiety (primary diagnosis) in the 2 years prior to index date: <br>**OMHRS ICD9-CM codes:** DSM5CODE_DISCH1 = 293.84, 300, 300.0x, 300.2x, 309.21, 313.23.PROVDX_DSM5CODE_ADM1 = 5 |
| Variable                                                                 | Database       | Definition/Citation                                                                                                                                 |
|-------------------------------------------------------------------------|----------------|---------------------------------------------------------------------------------------------------------------------------------------------------|
| John’s Hopkins Aggregated Diagnosis Groups (ADGs) 7                      | OHIP, DAD      | Patients were assigned a weighted score based on presence or absence of 32 ACG® System Aggregated Diagnosis Groups (ADGs) characterizing medical conditions based on their use of inpatient and outpatient health care services in the preceding 2 years 7. ADGs were summed and used as an ordinal variable. |
| Emergency Department Visits or hospitalization for opioid poisoning      | DAD, NACRS     | ED visit or inpatient hospitalization with diagnosis of opioid poisoning using codes below in 1 year prior to index date (admission diagnoses): **ICD-10 Codes:** T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 |
| Discipline of prescriber at initiation                                  | OHIP, IPDB     | Define pain prescriber as: 1) main specialty=anesthesiologist 2) physician billed at least 30 x A937 OHIP codes in the 365 days prior to index date.          |
| History of methadone in last 6 months                                   | NMS            | Any methadone in the 6 months prior to index (excluding index date).                                                                              |
| History of buprenorphine in last 6 months                               | NMS            | Any buprenorphine in the 6 months prior to index (excluding index date).                                                                          |
| Percentage missed doses                                                 | NMS            | Number of days during the treatment episode where daily buprenorphine dose=0 divided by total treatment episode in days.                            |
| Maximum dose                                                            | NMS            | Defined as the buprenorphine dose at taper start.                                                                                                 |
| Calendar year of buprenorphine discontinuation                          | NMS            | Buprenorphine treatment episode end date 2013-2015 vs. ≥2016.                                                                                   |

ICD-9: International Classification of Diseases, 9th Revision; ICD-10: International Classification of Diseases, 10th Revision; DAD: Discharge Abstract Database, NACRS: National Ambulatory Care Reporting System, OHIP: Ontario Health Insurance Plan, NMS: Narcotics Monitoring System, OMHRS: Ontario Mental Health Reporting System, RPDB: Registered Persons Database.
eFigure 1. Study Schematic

Index event: Buprenorphine start date

Look back 30 days for buprenorphine use

60-day period of continuous buprenorphine use

Taper start date

Taper period

Outcome: look forward 548 days

Max follow up: April 30, 2020

Accrual period: Jan 1, 2013-Jan 1, 2019

Buprenorphine treatment episode
eAppendix. Calculation of Daily Dose

We calculated the buprenorphine dose for every day in the period of continuous buprenorphine use. During the study period, it would have been common for many patients to have daily witnessed ingestion of buprenorphine and for prescribers to give stable clients a maximum of 6 take-home doses per week or 13 take-home doses per 14 days (ie. one witnessed dose per 1-2 weeks). Prescriptions for buprenorphine in Ontario must include start and stop dates. Buprenorphine prescriptions are typically cancelled if the patient misses 5 or more doses and the pharmacist must contact the prescriber to determine if the dose should be adjusted in these situations, or the patient must see the prescriber to obtain a new prescription. Physicians would generally never prescribe excess supply of buprenorphine, and patients may only pick up their supply on a specified date. Daily dose calculations required data review and cleaning due to variations in clinical practice that exist and anomalies in how witnessed and take-home doses are entered into the NMS.

First, the author undertook a review of a random sample of 30 buprenorphine episodes to identify dispensing patterns and align these with common clinical practice. Following this, the days supplied variable was first corrected to account for instances when doses are witnessed in pharmacy and a take-home supply is dispensed on the same day, and these are entered as separate records within the database. The corrected days supplied was calculated by summing the days supply per person for prescriptions dispensed on the same service date for DINs that represented the same buprenorphine strength. The daily dose was then calculated as corrected quantity dispensed*strength/corrected days supplied. If there were two prescriptions with
different strengths dispensed on the same day with the same days supplied, the daily
doses were summed. If a new prescription was issued while there were still days
supplied remaining from an old prescription, a daily dose was calculated for the new
prescription and assigned as the patient’s daily dose moving forward. This would likely
reflect the practice of writing a new prescription in the case that buprenorphine take-
home doses were lost, but may misclassify rare cases where a dose increase was
made by adding additional doses to an existing prescription. If there was no dose for a
given day during the episode, the daily dose was zero.
eFigure 2. Cohort Assembly

1. **Initial cohort**
   - Adults >18 with a new buprenorphine prescription between Jan 1, 2013 - Jan 1, 2019 (new is defined by looking back 30 days to ensure no buprenorphine use in last 30 days). Index date is assigned as the date of the first buprenorphine prescription.

2. **Apply Exclusion Criteria**
   - Exclude individuals with missing/invalid IKN, those with missing age or sex, age<18 or age>105, death date prior to index date, individuals who are not an Ontario resident, episodes <60 days.

3. **Restrict to episodes involving a taper**
   - Restrict to episodes where daily dose was <2mg in the final dispense of the treatment episode OR where the dose at discontinuation was less than the dose 4 weeks earlier (i.e., dose is decreasing in the last 4 weeks of treatment).
   - Exclude episodes where dose never goes above 2 mg.

4. **Apply exclusions related to data quality**
   - Exclude episodes with tapering start dose of >32 mg, where there were >14 days of daily dose=0 in the last 28 days of the episode, episodes with no maximum dose lasting at least 7 consecutive days, and episodes with a taper rate <0.
eTable 3. Distribution of the Primary Exposure, Time to Taper Initiation

| Percentile | Days |
|------------|------|
| 95         | 626  |
| 90         | 446  |
| 75         | 249  |
| 50 (median)| 122  |
| 25         | 72   |
| 10         | 56   |
| 5          | 52   |
eFigure 3. Kaplan-Meier Curve of Time to Opioid Overdose Following Buprenorphine Taper, Stratified by Time to Taper Start ($P = .02$)

![Kaplan-Meier Curve of Time to Opioid Overdose Following Buprenorphine Taper, Stratified by Time to Taper Start](image1)

- Time to taper start ≤ 1 year
- Time to taper start > 1 year

eFigure 4. Kaplan-Meier Curve of Time to Opioid Overdose Following Buprenorphine Taper, Stratified by Milligrams Tapered per Month ($P < .001$)

![Kaplan-Meier Curve of Time to Opioid Overdose Following Buprenorphine Taper, Stratified by Milligrams Tapered per Month](image2)

- ≤ 2 mg tapered per month
- >2-4 mg tapered per month
- >4 mg tapered per month
eFigure 5. Kaplan-Meier Curve of Time to Opioid Overdose Following Buprenorphine Taper, Stratified by Percentage of Days Descending During the Taper Period (P < .001)

![Kaplan-Meier Curve of Time to Opioid Overdose Following Buprenorphine Taper, Stratified by Percentage of Days Descending During the Taper Period](image)

- % days decreasing ≤1.75%
- % days decreasing 1.76-3.5%
- % days decreasing >3.5%

eFigure 6. Kaplan-Meier Curve of Time to Opioid Overdose Following Buprenorphine Taper, Stratified by Taper Duration (P < .001)

![Kaplan-Meier Curve of Time to Opioid Overdose Following Buprenorphine Taper, Stratified by Taper Duration](image)

- Taper duration ≤6 months
- Taper duration >6-12 months
- Taper duration >12 months
eFigure 7. Kaplan-Meier Curve of Time to MOUD Reentry Following Buprenorphine Taper, Stratified by Time to Taper Start ($P = .12$)

![Kaplan-Meier Curve of Time to MOUD Reentry Following Buprenorphine Taper, Stratified by Time to Taper Start](image)

- Time to taper start ≤ 1 year
- Time to taper start >1 year

eFigure 8. Kaplan-Meier Curve of Time to MOUD Reentry Following Buprenorphine Taper, Stratified by Milligrams Tapered per Month ($P < .001$)

![Kaplan-Meier Curve of Time to MOUD Reentry Following Buprenorphine Taper, Stratified by Milligrams Tapered per Month](image)

- ≤2 mg tapered per month
- >2-4 mg tapered per month
- >4 mg tapered per month
eFigure 9. Kaplan-Meier Curve of Time to MOUD Reentry Following Buprenorphine Taper, Stratified by Percentage of Days the Dose Was Decreasing During the Taper Period (P < .001)

![Kaplan-Meier Curve](image1.png)

- ≤1.75% of days decreasing
- >1.75-3.5% of days decreasing
- >3.5% of days decreasing

eFigure 10. Kaplan-Meier Curve of Time to MOUD Reentry Following Buprenorphine Taper, Stratified by Taper Duration (P < .001)

![Kaplan-Meier Curve](image2.png)

- Taper duration ≤6 months
- Taper duration >6-12 months
- Taper duration >12 months

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eFigure 11. Kaplan-Meier Curve of Time to Prescription Opioid Use Following Buprenorphine Taper, Stratified by Time to Taper Start ($P = .34$)

![Graph showing Kaplan-Meier Curve with two lines representing different time to taper start groups.](image)

Time to taper start ≤1 year  
Time to taper start >1 year

eFigure 12. Kaplan-Meier Curve of Time to Prescription Opioid Use Following Buprenorphine Taper, Stratified by Milligrams Tapered per Month ($P < .001$)

![Graph showing Kaplan-Meier Curve with multiple lines representing different taper rates.](image)

≤2 mg tapered per month  
>2-4 mg tapered per month  
>4 mg tapered per month

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eFigure 13. Kaplan-Meier Curve of Time to Prescription Opioid Use Following Buprenorphine Taper, Stratified by Percentage of Days the Dose Was Decreasing During the Taper Period (P = .001)

![Kaplan-Meier Curve](image)

- ≤.75% days decreasing
- >1.75-3.5% days decreasing
- >3.5% days decreasing

eFigure 14. Kaplan-Meier Curve of Time to Prescription Opioid Use Following Buprenorphine Taper, Stratified by Taper Duration (P < .001)

![Kaplan-Meier Curve](image)

- Taper duration ≤6 months
- Taper duration >6-12 months
- Taper duration >12 months

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**eTable 4. Event Rates for Buprenorphine Taper Characteristics Associated With Treatment Reentry Within 18 Months Postdiscontinuation (N = 5449)**

|                      | Total Number of Individuals | Number of individuals with treatment re-entry | Treatment re-entry rate per 100 Person-Years |
|----------------------|-----------------------------|-----------------------------------------------|---------------------------------------------|
| **Time to Taper Initiation** |                             |                                               |                                             |
| <1 year              | 4680                        | 2921                                          | 97.45                                       |
| >1 year              | 769                         | 439                                           | 90.04                                       |
| **Taper Rate per Month** |                             |                                               |                                             |
| ≤2 milligrams/month  | 3147                        | 1811                                          | 84.03                                       |
| >2 to ≤4 milligrams/month | 963                      | 626                                           | 105.24                                      |
| >4 milligrams/month  | 1339                        | 923                                           | 125.56                                      |
| **Percentage of days during which dose was decreasing** |                             |                                               |                                             |
| ≤1.75%               | 1847                        | 1128                                          | 96.53                                       |
| >1.75 to ≤3.5%       | 1179                        | 638                                           | 73.79                                       |
| >3.5%                | 2423                        | 1594                                          | 109.79                                      |
| **Taper duration**   |                             |                                               |                                             |
| <6 months            | 3756                        | 2491                                          | 109.35                                      |
| >6 to ≤12 months     | 865                         | 446                                           | 71.08                                       |
| >1 year              | 828                         | 423                                           | 72.99                                       |
### eTable 5. Recurrent Event Analysis of Buprenorphine Taper Characteristics Associated With Opioid Overdose Within 18 Months Posttreatment Discontinuation (N = 6451)

| Time to Taper Initiation | Total Number of Individuals | Number of individuals with opioid overdose | Overdose Rate per 100 Person-Years | Adjusted Hazard Ratio (95% CI) |
|--------------------------|-----------------------------|------------------------------------------|-----------------------------------|-----------------------------|
| <1 year                  | 5544                        | 353                                      | 10.56                             | 1.00 [Reference]            |
| >1 year                  | 907                         | 38                                       | 6.85                              | 0.69 (0.49-0.98)            |
| Taper Rate per Month     |                             |                                          |                                    |                             |
| <2 milligrams/month      | 3689                        | 175                                      | 7.09                              | 0.63 (0.46-0.87)            |
| >2 to ≤4 milligrams/month| 1141                        | 76                                       | 11.72                             | 0.70 (0.52-0.93)            |
| >4 milligrams/month      | 1621                        | 140                                      | 17.92                             | 1.00 [Reference]            |
| Percentage of days during which dose was decreasing |                             |                                          |                                    |                             |
| <1.75%                   | 2165                        | 80                                       | 5.93                              | 0.61 (0.42-0.89)            |
| >1.75 to ≤3.5%           | 1387                        | 86                                       | 8.90                              | 0.83 (0.61-1.13)            |
| >3.5%                    | 2899                        | 225                                      | 14.22                             | 1.00 [Reference]            |
| Taper duration           |                             |                                          |                                    |                             |
| <6 months                | 4554                        | 301                                      | 11.74                             | 1.00 [Reference]            |
| >6 to ≤12 months         | 992                         | 58                                       | 8.25                              | 1.18 (0.85-1.65)            |
| >1 year                  | 905                         | 32                                       | 5.08                              | 0.90 (0.57-1.40)            |

The proportional hazards assumption was not violated when time-varying covariates were added (p=0.91), nor when examining the martingale residuals.
### eTable 6. Recurrent Event Analysis of Buprenorphine Taper Characteristics Associated With Treatment Reentry Within 18 Months Postdiscontinuation (N = 6086)\(^a\)

| Time to Taper Initiation | Adjusted Hazard Ratio (95% CI) |
|--------------------------|-------------------------------|
| <1 year                  | 1.00 [Reference]              |
| >1 year                  | 0.95 (0.85-1.05)              |

| Taper Rate per Month\(^*\) | 182 days | 365 days | 548 days |
|----------------------------|----------|----------|----------|
| <2 milligrams/month        | 0.82 (0.72-0.94) | 0.95 (0.75-1.19) | 1.09 (0.77-1.55) |
| >2 to ≤4 milligrams/month  | 1.00 (0.88-1.14) | 1.17 (0.91-1.15) | 1.38 (0.93-2.05) |
| >4 milligrams/month        | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] |

| Percentage of days during which dose was decreasing | 182 days | 365 days | 548 days |
|-----------------------------------------------------|----------|----------|----------|
| <1.75%                                              | 1.27 (1.14-1.42) |          |          |
| >1.75 to ≤3.5%                                      | 0.92 (0.83-1.02) |          |          |
| >3.5%                                               | 1.00 [Reference] |          |          |

| Taper duration\(^b\) | 182 days | 365 days | 548 days |
|-----------------------|----------|----------|----------|
| <6 months             | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] |
| >6 to ≤12 months      | 0.69 (0.61-0.80) | 0.60 (0.46-0.78) | 0.51 (0.34-0.77) |
| >1 year               | 0.62 (0.53-0.72) | 0.46 (0.34-0.63) | 0.34 (0.21-0.55) |

\(^a\) Note N=6,086 as outcome window was shifted 14 days in this analysis to account for the fact that discontinuation was defined as no return to buprenorphine within 14 days.

\(^b\) The proportional hazards assumption was violated when time-varying covariates were added (p<0.001) and in examining the martingale residuals, therefore Hazard Rates are reported at three times over the follow-up period for taper rate and taper duration.
eTable 7. Event Rates for Recurrent Event Analysis of Buprenorphine Taper Characteristics Associated With OAT Reentry Within 18 Months Postdiscontinuation (N = 6086)

|                                | Total Number of Individuals | Number of individuals with treatment re-entry | Treatment re-entry rate per 100 Person-Years |
|--------------------------------|------------------------------|-----------------------------------------------|---------------------------------------------|
| **Time to Taper Initiation**   |                              |                                               |                                             |
| <1 year                        | 5235                         | 3316                                          | 100.64                                      |
| >1 year                        | 852                          | 487                                           | 90.84                                       |
| **Taper Rate per Month**       |                              |                                               |                                             |
| <2 milligrams/month            | 3558                         | 2074                                          | 86.38                                       |
| >2 to ≤4 milligrams/month      | 1069                         | 709                                           | 110.47                                      |
| >4 milligrams/month            | 1459                         | 1020                                          | 129.42                                      |
| **Percentage of days during which dose was decreasing** | |                                               |                                             |
| <1.75%                         | 2084                         | 1278                                          | 97.96                                       |
| >1.75 to ≤3.5%                 | 1320                         | 730                                           | 77.00                                       |
| >3.5%                          | 2682                         | 1795                                          | 113.74                                      |
| **Taper duration**             |                              |                                               |                                             |
| <6 months                      | 4258                         | 2867                                          | 113.37                                      |
| >6 to ≤12 months               | 950                          | 487                                           | 70.77                                       |
| >1 year                        | 878                          | 449                                           | 73.15                                       |
## eTable 8. Recurrent Events Analysis of Buprenorphine Prescribing Characteristics Associated With Return to Prescription Opioids Within 18 Months Posttreatment Discontinuation (N = 6451)

| Time to Taper Initiation | Total Number of Individuals | Number of individuals with relapse to prescription opioids | Treatment re-entry rate per 100 Person-Years | Adjusted Hazard Ratio (95% CI) |
|--------------------------|-----------------------------|----------------------------------------------------------|---------------------------------------------|------------------------------|
| ≤1 year                  | 5544                        | 449                                                      | 14.20                                       | 1.00 [Reference]             |
| >1 year                  | 907                         | 68                                                       | 13.21                                       | 0.86 (0.66-1.12)             |

### Taper Rate per Month

| Taper Rate per Month | Total Number of Individual | Number of individuals with relapse to prescription opioids | Treatment re-entry rate per 100 Person-Years | Adjusted Hazard Ratio (95% CI) |
|----------------------|----------------------------|----------------------------------------------------------|---------------------------------------------|------------------------------|
| ≤2 milligrams/month  | 3689                       | 261                                                      | 11.13                                       | 0.68 (0.51-0.91)             |
| >2 to ≤4 milligrams/month | 1141                       | 98                                                       | 16.03                                       | 0.94 (0.73-1.22)             |
| >4 milligrams/month  | 1621                       | 158                                                      | 21.92                                       | 1.00 [Reference]             |

### Percentage of days during which dose was decreasing

| Percentage of days during which dose was decreasing | Total Number of Individuals | Number of individuals with relapse to prescription opioids | Treatment re-entry rate per 100 Person-Years | Adjusted Hazard Ratio (95% CI) |
|-----------------------------------------------------|----------------------------|----------------------------------------------------------|---------------------------------------------|------------------------------|
| ≤1.75%                                              | 2165                       | 142                                                      | 11.09                                       | 1.02 (0.75-1.38)             |
| >1.75 to ≤3.5%                                      | 1387                       | 120                                                      | 13.21                                       | 1.18 (0.90-1.55)             |
| >3.5%                                               | 2899                       | 255                                                      | 17.13                                       | 1.00 [Reference]             |

### Taper duration

| Taper duration | Total Number of Individuals | Number of individuals with relapse to prescription opioids | Treatment re-entry rate per 100 Person-Years | Adjusted Hazard Ratio (95% CI) |
|----------------|----------------------------|----------------------------------------------------------|---------------------------------------------|------------------------------|
| <6 months     | 4554                       | 385                                                      | 15.97                                       | 1.00 [Reference]             |
| >6 to ≤12 months | 992                        | 76                                                       | 11.46                                       | 0.97 (0.74-1.29)             |
| >1 year       | 905                        | 56                                                       | 9.27                                        | 0.86 (0.61-1.20)             |

The proportional hazards assumption was not violated when time-varying covariates were added (p=0.14), nor when examining the martingale residuals.
**eTable 9. Sensitivity Analysis of Buprenorphine Taper Characteristics Associated With Opioid Overdose Within 18 Months Postdiscontinuation Among Those With Successful Taper (End Dose ≤2 mg) (N = 3154)**

|                                           | Total Number of Individuals | Number of individuals with opioid overdose | Overdose Rate per 100 Person-Years | Adjusted Hazard Ratio (95% CI) |
|------------------------------------------|----------------------------|------------------------------------------|------------------------------------|-------------------------------|
| **Time to Taper Initiation**             |                            |                                          |                                    |                               |
| <1 year                                  | 2740                       | 142                                      | 6.89                               | 1.00 [Reference]              |
| >1 year                                  | 414                        | 14                                       | 4.29                               | 0.63 (0.36-1.11)              |
| **Taper Rate per Month**                 |                            |                                          |                                    |                               |
| <2 milligrams/month                      | 2398                       | 99                                       | 5.39                               | 0.56 (0.32-0.96)              |
| >2 to ≤4 milligrams/month                | 422                        | 25                                       | 7.74                               | 0.51 (0.29-0.87)              |
| >4 milligrams/month                      | 334                        | 32                                       | 14.03                              | 1.00 [Reference]              |
| **Percentage of days during which dose was decreasing** |                            |                                          |                                    |                               |
| ≤1.75%                                   | 1379                       | 38                                       | 3.88                               | 0.55 (0.32-0.97)              |
| >1.75 to ≤3.5%                           | 810                        | 45                                       | 6.69                               | 0.86 (0.53-1.40)              |
| >3.5%                                    | 9651                       | 73                                       | 9.95                               | 1.00 [Reference]              |
| **Taper duration**                       |                            |                                          |                                    |                               |
| ≤6 months                                | 1729                       | 99                                       | 7.67                               | 1.00 [Reference]              |
| >6 to ≤12 months                         | 698                        | 39                                       | 7.20                               | 1.28 (0.82-2.00)              |
| >1 year                                  | 727                        | 18                                       | 3.24                               | 0.70 (0.37-1.30)              |

The proportional hazards assumption was not violated when time-varying covariates were added (p=0.48), nor when examining the martingale residuals.
eTable 10. Multivariable Cause-Specific and Subdistribution Hazards Models of Buprenorphine Taper Characteristics Associated With Opioid Overdose Within 18 Months Posttreatment Discontinuation (N = 5774)

| Time to Taper Initiation | Total Number of Individuals | Individuals with opioid overdose (N) | Overdose Rate per 100 Person-Years | Adjusted Cause-Specific Hazard Ratio (95% CI) | Adjusted Subdistribution Hazard Ratio (95% CI) |
|-------------------------|-----------------------------|-------------------------------------|------------------------------------|--------------------------------------------|---------------------------------------------|
| <1 year                 | 4954                        | 315                                 | 10.35                             | 1.00 [Reference]                           | 1.00 [Reference]                           |
| >1 year                 | 820                         | 34                                  | 6.73                              | 0.69 (0.48-0.997)                          | 0.69 (0.48-1.00)                           |
| Taper Rate per Month    |                             |                                     |                                    |                                            |                                            |
| ≤2 milligrams/month     | 3258                        | 154                                 | 6.95                              | 0.65 (0.46-0.91)                           | 0.87 (0.63-1.20)                           |
| >2 to ≤4 milligrams/month | 1026                      | 69                                  | 11.48                             | 0.69 (0.51-0.93)                           | 0.82 (0.61-1.10)                           |
| >4 milligrams/month     | 1490                        | 126                                 | 17.27                             | 1.00 [Reference]                           | 1.00 [Reference]                           |
| Percentage of days during which dose was decreasing |                             |                                     |                                    |                                            |                                            |
| <1.75%                  | 1914                        | 71                                  | 5.87                              | 0.64 (0.43-0.95)                           | 0.55 (0.37-0.82)                           |
| >1.75 to ≤3.5%          | 1241                        | 76                                  | 8.63                              | 0.84 (0.61-1.16)                           | 0.83 (0.61-1.12)                           |
| >3.5%                   | 2619                        | 202                                 | 13.87                             | 1.00 [Reference]                           | 1.00 [Reference]                           |
| Taper duration          |                             |                                     |                                    |                                            |                                            |
| ≤6 months               | 4024                        | 270                                 | 11.70                             | 1.00 [Reference]                           | 1.00 [Reference]                           |
| >6 to ≤12 months        | 898                         | 52                                  | 8.10                              | 1.12 (0.79-1.60)                           | 1.23 (0.86-1.75)                           |
| >1 year                 | 852                         | 27                                  | 4.52                              | 0.75 (0.47-1.21)                           | 0.84 (0.51-1.37)                           |
Table 11. Cause-Specific and Subdistribution Hazards Recurrent Event Analysis of Buprenorphine Taper Characteristics Associated With Opioid Overdose Within 18 Months Posttreatment Discontinuation (N = 6451)

|                       | Total Number of Individuals | Number of individuals with opioid overdose | Overdose Rate per 100 Person-Years | Cause-Specific Adjusted Hazard Ratio (95% CI) | Subdistribution Adjusted Hazard Ratio (95% CI) |
|-----------------------|-----------------------------|-------------------------------------------|-----------------------------------|-----------------------------------------------|-----------------------------------------------|
| **Time to Taper Initiation** |                             |                                           |                                   |                                               |                                               |
| <1 year               | 5544                        | 353                                       | 10.56                             | 1.00 [Reference]                              | 1.00 [Reference]                              |
| >1 year               | 907                         | 38                                        | 6.85                              | 0.69 (0.49-0.98)                              | 0.70 (0.49-0.99)                              |
| **Taper Rate per Month** |                             |                                           |                                   |                                               |                                               |
| <2 milligrams/month   | 3689                        | 175                                       | 7.09                              | 0.63 (0.46-0.87)                              | 0.84 (0.62-1.14)                              |
| >2 to ≤4 milligrams/month | 1141                  | 76                                        | 11.72                             | 0.70 (0.52-0.93)                              | 0.81 (0.61-1.08)                              |
| >4 milligrams/month   | 1621                        | 140                                       | 17.92                             | 1.00 [Reference]                              | 1.00 [Reference]                              |
| **Percentage of days during which dose was decreasing** |                             |                                           |                                   |                                               |                                               |
| ≤1.75%                | 2165                        | 80                                        | 5.93                              | 0.61 (0.42-0.89)                              | 0.53 (0.37-0.77)                              |
| >1.75% to ≤3.5%       | 1387                        | 86                                        | 8.90                              | 0.83 (0.61-1.13)                              | 0.83 (0.62-1.11)                              |
| >3.5%                 | 2899                        | 225                                       | 14.22                             | 1.00 [Reference]                              | 1.00 [Reference]                              |
| **Taper duration**    |                             |                                           |                                   |                                               |                                               |
| ≤6 months             | 4554                        | 301                                       | 11.74                             | 1.00 [Reference]                              | 1.00 [Reference]                              |
| >6 to ≤12 months      | 992                         | 58                                        | 8.25                              | 1.18 (0.85-1.65)                              | 1.30 (0.93-1.82)                              |
| >1 year               | 905                         | 32                                        | 5.08                              | 0.90 (0.57-1.40)                              | 1.00 (0.63-1.58)                              |
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