Prescription Opioid Dispensing Patterns Prior to Heroin Overdose in a State Medicaid Program: a Case-Control Study

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BACKGROUND: A large proportion of individuals who use heroin report initiating opioid use with prescription opioids. However, patterns of prescription opioid use preceding heroin-related overdose have not been described.

OBJECTIVE: To describe prescription opioid use in the year preceding heroin overdose.

DESIGN: Case-control study comparing prescription opioid use with a heroin-involved overdose, non-heroin-involved opioid overdose, and non-overdose controls from 2015 to 2017.

PARTICIPANTS: Oregon Medicaid beneficiaries with linked administrative claims, vital statistics, and prescription drug monitoring program data.

MAIN MEASURES: Opioid, benzodiazepine, and other central nervous system depressant prescriptions preceding overdose; among individuals with one or more opioid prescription, we assessed morphine milligram equivalents per day, overlapping prescriptions, prescriptions from multiple prescribers, long-term use, and discontinuation of long-term use.

KEY RESULTS: We identified 1458 heroin-involved overdoses (191 fatal) and 2050 non-heroin-involved opioid overdoses (266 fatal). In the 365 days prior to their overdose, 45% of individuals with a heroin-involved overdose received at least one prescribed opioid compared with 78% of individuals who experienced a non-heroin-involved opioid overdose ($p < 0.001$). For both heroin- and non-heroin-involved overdose cases, the likelihood of receiving an opioid increased with age. Among heroin overdose cases with an opioid dispensed, the rate of multiple pharmacy use was the only high-risk opioid pattern that was greater than non-overdose controls (adjusted odds ratio 3.2; 95% confidence interval 1.48 to 6.95). Discontinuation of long-term opioid use was not common prior to heroin overdose and not higher than discontinuation rates among non-overdose controls.

CONCLUSIONS: Although individuals with a heroin-involved overdose were less likely to receive prescribed opioids in the year preceding their overdose relative to non-heroin opioid overdose cases, prescription opioid use was relatively common and increased with age. Discontinuation of long-term prescription opioid use was not associated with heroin-involved overdose.

KEY WORDS: prescription opioids; heroin; overdose.

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INTRODUCTION

The opioid epidemic has evolved over the last decade, shifting from being primarily related to prescription opioids (natural or semi-synthetic opioids) to heroin and illicitly manufactured synthetic opioids.^{1,2} Between 2008 and 2017, the rate of overdose deaths involving prescription opioids (natural or semi-synthetic opioids) increased 47% from 3.0 to 4.4 per 100,000.² In contrast, deaths involving heroin increased nearly fivefold from 1 to 4.9 deaths per 100,000 during the same period.² Heroin and synthetic opioids now account for the majority of all opioid-related fatalities in the USA.²

In contrast to the heroin epidemic of the 1960s, the recent rise in heroin use and overdose is closely related to the prescription opioid epidemic.^{3,4} Data from the National Survey on Drug Use and Health indicate that currently more than 80% of individuals who use heroin report initiating opioid use with prescription pain relievers.^{4,5} Expanding markets of lower cost, higher purity heroin can explain some of this transition.⁶ The epidemic continues to evolve and recent trends indicate the number of individuals who initiate opioid use with heroin has increased from 9% in 2005 to 32% in 2015.⁷ Despite this, there are growing concerns that efforts to reduce or place limits on opioid prescribing may be associated with substitution with other opioids including heroin. Epidemiologic trends in opioid overdose and studies of the abuse deterrent reformulation of oxycodone provide ecologic evidence suggesting that as

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prescription opioids become more difficult to misuse, individuals may substitute with other illicit opioids such as heroin.^{8–11}

Despite being a purported gateway to heroin, little is known about patterns of prescription opioid use that predict the transition. Opioid dispensing patterns that increase the risk for overdose (e.g., high dose, benzodiazepine co-prescribing) are well documented.¹² However, the extent to which these high-risk patterns are also present prior to heroin overdose is unclear. It is important to understand if these same predictors exist because 70% of individuals who report using heroin in the past year also report using prescription opioids.⁵ Furthermore, because disruption in access to prescribed opioids may hasten heroin use and overdose, other patterns that suggest discontinuation or dose reduction need to be explored. The objective of this study was to investigate the relationship between opioid dispensing patterns (including high-risk use and discontinuation) and heroin overdose.

METHODS

Data Sources

We conducted a case-control study to investigate the relationship between opioid dispensing patterns and heroin-involved overdose. Our analytic data source was linked data from Oregon's Medicaid, vital statistics (death certificate data), and prescription drug monitoring program (PDMP) from 2014 to 2017. Oregon Medicaid claims data were linked to PDMP data using a previously described probabilistic linkage based on patient name, date of birth, and zip code.^{13,14} We linked vital statistics and Medicaid data using social security number.

Case Definitions

Cases comprised individuals with a fatal or non-fatal heroin-involved overdose between January 1, 2015, and December 31, 2017. We used vital statistics to identify individuals with a fatal overdose with an International Statistical Classification of Diseases and Related Health Problems (ICD) 10th revision code indicating heroin involvement (S1 Table). To identify non-fatal overdoses, we used Medicaid medical claims data to identify emergency department (ED) encounters or hospitalizations with an ICD-9 or ICD-10 code for heroin-involved poisoning (any diagnosis code position). We selected the first overdose (fatal or non-fatal) as the case index event. If fatal and non-fatal events occurred on the same day, the case was designated as fatal.

We first compared heroin-involved overdose cases to opioid overdose cases that did not involve heroin. Similar to heroin-involved overdose cases, we used vital statistics and Medicaid claims data to identify non-heroin fatal and non-fatal opioid overdoses respectively (S2 Table). We excluded fatalities that reported an ICD-10 code indicating synthetic opioids (T40.4) because rates of overdose involving illicitly manufactured synthetic opioids in Oregon have been relatively

low.¹⁵ We also excluded T40.6 (other and unspecified narcotics) because of a lack of specificity.

Exposures

We used Oregon's PDMP data to identify controlled substance dispensing in the year preceding each patient's index date. We characterized patterns of dispensing for opioids (excluding buprenorphine), benzodiazepines, and other central nervous system (CNS) depressants (i.e., carisoprodol, eszopiclone, suvorexant, zaleplon, zolpidem), using National Drug Codes.¹⁶ The complete list of drugs is summarized in S3 Table. For individuals with an overdose (heroin and non-heroin), our primary analysis characterized the proportion of individuals with an opioid, benzodiazepine, or other CNS depressant medication dispensed within 7, 30, 90, and 365 days of their overdose date.

Patterns of Opioid Dispensing

A secondary objective was to investigate specific opioid dispensing patterns among all opioid overdose cases (heroin involved and not involved) relative to individuals with one or more dispensed opioid who did not have an overdose (non-overdose controls). To increase comparability, we restricted overdose cases to those with one or more dispensed opioid in the year preceding their overdose. For each heroin-involved overdose case with an opioid dispensed in the year prior to overdose, we randomly selected four non-overdose control patients who had an opioid dispensed in the year preceding each case's overdose date. Controls were matched on sex and age (in 10-year bins: <20; 20–29; 30–39; 40–49; 50–59; ≥60 years). We assigned the case's index date (overdose date) to each of their respective four controls to ensure that the exposure periods included the same calendar time period.

Within the subset of individuals with an opioid dispensed in the year before their index date, we compared high-risk dispensing patterns in those with a heroin-involved overdose to the non-overdose control group. High-risk opioid dispensing patterns included opioid-opioid overlap, opioid-benzodiazepine overlap, and opioid-non-benzodiazepine sedative overlap. Using dates and days' supply variables in PDMP data, we identified overlap in cases in which two or more prescriptions overlapped by one or more days. We identified multiple provider episodes defined by having four or more prescribers or four or more pharmacies in a 180-day period.¹⁷ We also identified patients whose average opioid daily dose was more than 90 morphine milligram equivalents (MME) by dividing each patient's total MME over the year by the number of opioid days' supply dispensed in the year.¹⁶ We considered each prescription independently to estimate an average dose per day across all dispensed prescriptions.¹⁶

Finally, we explored the relationship between heroin-involved overdose and prescription opioid discontinuation among individuals who were on long-term opioid therapy prior to their index date. In the year preceding each

individual's index date, we first identified those who had 90 or more consecutive days (without gaps) with an opioid available using dispensing dates and days' supply. Among individuals who had multiple 90-day episodes, we selected the first episode chronologically. We defined discontinuation of therapy if the individual had 45 or more consecutive days without an opioid dispensing after their 90-day continuous therapy episode.

Analysis

For our primary analysis, we compared antecedent opioid dispensing patterns for patients with a heroin-involved overdose to patients with a non-heroin opioid overdose by overdose disposition (fatal vs non-fatal), demographics (age, race, sex), and comorbidity. To characterize comorbidity, we used conditions and coding defined in the Elixhauser Comorbidity Index.¹⁸

Univariate comparisons were analyzed using chi-square, parametric, and non-parametric statistical tests as appropriate for categorical or continuous variables. To evaluate the relationship between opioid dispensing patterns and heroin involvement, we also used multivariate logistic regression analysis to control for demographics and comorbidity reporting both crude and adjusted odds ratios. We examined opioid dispensing pattern heterogeneity within demographic or overdose disposition subgroups (sex, age, urban/rural, year of overdose, fatal/non-fatal) using tests of interaction to determine if opioid dispensing patterns differed between these groups.

In a secondary analysis, we compared high-risk dispensing patterns in heroin-involved overdose cases with an opioid dispensed in the year preceding overdose to matched non-overdose controls using both univariate statistics and conditional multivariate logistic regression. We included variables in the multivariate models that were significant at the 0.25 level for univariate comparisons. We also report the subset of non-heroin opioid overdose cases which had an opioid dispensed in the prior year as a qualitative contrast. To ensure complete capture of comorbidity diagnoses, we re-analyzed multivariate logistic regression models restricting to individuals who had continuous Medicaid enrollment for the year preceding their index event. We conducted our statistical analysis using SAS software version 9.4 (SAS Institute Inc., Cary, NC).

Compliance with Ethical Standards

We obtained Institutional Review Board (IRB) approval before obtaining the data. The data were pre-existing de-identified health claims data, so we did not need to obtain informed consent.

RESULTS

Between 2015 and 2017, we identified 3508 individuals who experienced a fatal ($n = 457$, 13%) or non-fatal ($n = 3051$, 87%) opioid overdose. As summarized in Table 1, 1458

individuals had an overdose with a diagnosis or contributing cause involving heroin and 2050 did not. Compared with individuals with a non-heroin opioid overdose, individuals with heroin-involved overdose were more likely to be male (68% vs 38%; $p < 0.001$), live in an urban area (78% vs 62%; $p < 0.001$), and be younger than 30 years of age (45% vs 22%; $p < 0.001$). Individuals with heroin-involved overdose were less likely to be White (55% vs 63%; $p < 0.001$), though missing data were substantial. With the exception of misuse of alcohol (28% vs 20%; $p < 0.001$) and drugs (80% vs 49%; $p < 0.001$), individuals with heroin involvement had fewer comorbid conditions compared to those without heroin involvement (3.1 vs 4.3; $p < 0.001$).

Figure 1 summarizes opioid dispensing patterns within 7, 30, 90, and 365 days of an individual's overdose date. In the year prior to overdose, 45% of heroin-involved overdose cases had an opioid dispensed to them compared with 78% of non-heroin opioid overdose cases ($p < 0.001$). While opioid dispensing was lower among heroin-involved overdose cases compared with non-heroin opioid overdoses at all time intervals, the difference was particularly large in the 7 days (4% vs 29%; $p < 0.001$) and 30 days (11% vs 53%; $p < 0.001$) prior to overdose. The use of benzodiazepines (18% vs 42%; $p < 0.001$) and other CNS depressants (4% vs 12%; $p < 0.001$) was also less common among heroin-involved cases in the 365 days preceding overdose (S4 Table).

As shown in Table 2, the association between opioid dispensing patterns and heroin-involved overdose did not differ significantly across subgroups. In general, individuals with an opioid overdose that did not involve heroin were consistently more likely to have an opioid dispensed across all subgroups analyzed. Although the proportion of heroin-involved overdose cases with a dispensed opioid for individuals age 50 and over was nearly twice that of individuals less than 30, this trend was similar for overdose cases that did not involve heroin (the test of interaction $p = 0.67$).

Opioid Dispensing Patterns

In Table 3, we summarize demographics and comorbid conditions among overdose cases (with and without heroin involvement) and age- and sex-matched non-overdose controls with one or more opioids dispensed in the year preceding their index date. We specifically compared heroin-involved overdose cases ($n = 655$) to age- and sex-matched non-overdose controls with one or more dispensed opioids ($n = 2620$). Relative to non-overdose controls, heroin-involved overdose cases were more likely to be White (59% vs 55%; $p = 0.027$) and live in an urban area (78% vs 60%; $p < 0.001$). Although individuals with a heroin-involved overdose had fewer comorbid diagnoses than overdose cases without heroin involvement, they had more comorbid diagnoses than non-overdose controls (3.7 vs 0.9; $p < 0.001$).

Table 4 summarizes the prevalence of opioid dispensing patterns known to increase the risk of overdose. In the

Table 1 Demographic and Comorbid Diagnoses for Individuals with Opioid-Related Overdose

	Heroin involved	Non-heroin involved	<i>p</i> value
<i>N</i>	1458	2050	
Overdose			0.91
Fatal	191 (13.1)	266 (13.0)	
Non-fatal	1267 (86.9)	1784 (87.0)	
Sex			< 0.001
Female	472 (32.4)	1270 (62.0)	
Male	986 (67.6)	780 (38.1)	
Race			< 0.001
White	805 (55.2)	1284 (62.6)	
Black	35 (2.4)	79 (3.9)	
Asian	6 (0.4)	13 (0.6)	
Native American	31 (2.1)	56 (2.7)	
Other	119 (8.2)	105 (5.1)	
Unknown	462 (31.7)	513 (25.0)	
ZIP code designation			< 0.001
Urban	1140 (78.2)	1260 (61.5)	
Rural	318 (21.8)	790 (38.5)	
Age in years			< 0.001
< 30	654 (44.9)	456 (22.2)	
30–49	597 (41.0)	814 (39.7)	
≥ 50	207 (14.2)	780 (38.1)	
Elixhauser diagnoses			
AIDS	12 (0.8)	21 (1.0)	0.54
Alcohol misuse	406 (27.8)	408 (19.9)	< 0.001
Deficiency anemia	115 (7.9)	327 (16.0)	< 0.001
Rheumatoid arthritis	22 (1.5)	129 (6.3)	< 0.001
Blood loss anemia	8 (0.5)	47 (2.3)	< 0.001
Congestive heart failure	33 (2.3)	166 (8.1)	< 0.001
Chronic lung disease	241 (16.5)	702 (34.2)	< 0.001
Coagulopathy	49 (3.4)	98 (4.8)	0.04
Depression	408 (28.0)	954 (46.5)	< 0.001
Diabetes, uncomplicated	42 (2.9)	129 (6.3)	< 0.001
Diabetes, complicated	37 (2.5)	225 (11.0)	< 0.001
Drug misuse	1163 (79.8)	1007 (49.1)	< 0.001
Hypertension, uncomplicated	223 (15.3)	769 (37.5)	< 0.001
Hypertension, complicated	3 (0.2)	17 (0.8)	0.02
Hypothyroidism	37 (2.5)	208 (10.1)	< 0.001
Liver disease	263 (18.0)	307 (15.0)	0.02
Lymphoma	3 (0.2)	14 (0.7)	0.05
Fluid and electrolyte disorders	278 (19.1)	595 (29.0)	< 0.001
Metastatic cancer	3 (0.2)	44 (2.1)	< 0.001
Other neurological disorders	537 (36.8)	783 (38.2)	0.44
Obesity	64 (4.4)	419 (20.4)	< 0.001
Paralysis	9 (0.6)	64 (3.1)	< 0.001
Peripheral vascular disorders	22 (1.5)	124 (6)	< 0.001
Psychoses	325 (22.3)	613 (29.9)	< 0.001
Pulmonary circulation disorders	23 (1.6)	70 (3.4)	< 0.001
Renal failure	27 (1.9)	153 (7.5)	< 0.001
Solid tumor without metastasis	1 (0.1)	77 (3.8)	< 0.001
Peptic ulcer disease	2 (0.1)	30 (1.5)	< 0.001
Valvular disease	43 (2.9)	81 (4)	0.11
Weight loss	53 (3.6)	136 (6.6)	< 0.001
Average no. conditions (SD)	3.1 (2.5)	4.3 (3.2)	< 0.001

Percentages are in parentheses

univariate analysis, several opioid dispensing patterns were significantly more prevalent among heroin-involved overdose cases compared with matched controls. After statistical adjustment, only multiple pharmacy episodes remained statistically significant (aOR 3.21; 95% CI 1.48 to 6.95). High-risk opioid dispensing patterns were uniformly more prevalent among non-heroin overdose cases compared with both heroin-involved cases and non-overdose controls.

Long-term opioid therapy was uncommon among heroin-involved overdose cases (7%) and non-overdose controls (5%). Among individuals with long-term opioid therapy, 4% of those with a heroin-involved overdose discontinued opioids prior to overdosing compared with 8% of controls ($p = 0.35$).

Our findings were generally similar when we restricted our sample to individuals with continuous Medicaid enrollment in the year prior to their index date (S5–S9 Tables).

DISCUSSION

To our knowledge, this is the first study to specifically contrast opioid dispensing patterns between individuals with a heroin-involved or non-heroin-involved opioid overdose. Nearly half of individuals (45%) who experienced a heroin overdose had an opioid dispensed in the year prior to the overdose. However, opioid dispensing was less common in the period

Figure 1 Opioid dispensing in the 7, 30, 90, and 365 days preceding opioid overdose; all differences statistically significant ($p < 0.001$).

immediately preceding the overdose. Only 11% of individuals who experienced heroin overdose had an opioid dispensed in the 30 days prior to overdose. In contrast, 53% of individuals with a non-heroin opioid overdose had an opioid dispensed in the 30 days prior to overdose. Those experiencing a heroin-involved overdose were also substantially less likely to have a benzodiazepine dispense prior to overdose. With the exception of age, exposure to prescribed opioids was generally uniform across all demographic characteristics. For both heroin-involved and non-heroin overdose groups, opioid dispensing increased with age. Among individuals who were dispensed opioids prior to overdose, the only high-risk dispensing pattern

that was elevated relative to non-overdose controls was controlled substances dispensed from four or more pharmacies in a 180-day period. Although long-term opioid therapy was uncommon, we found no evidence that discontinuation of long-term opioid therapy was associated with heroin-involved opioid overdose.

Our findings have several implications. First, we found a large proportion of individuals who are actively using heroin are also receiving opioids dispensed through the healthcare system. Ethnographic data suggest that individuals who inject heroin often supplement with prescription opioids.¹⁹ The source of these opioids is likely a mix of diverted and

Table 2 Percentage of Overdose Cases with a Dispensed Opioid in the Year Preceding Overdose by Demographic Subgroup

	Heroin involved	Non-heroin involved	Crude OR (95% CI)	Interaction p value	Adjusted OR* (95% CI)	Interaction p value
Overall percentage	44.9	77.6	0.24 (0.20, 0.27)		0.43 (0.36, 0.51)	
By sex				0.81		0.80
Female	49.8	79.8	0.25 (0.20, 0.32)		0.43 (0.33, 0.56)	
Male	42.6	74.0	0.26 (0.21, 0.32)		0.41 (0.33, 0.52)	
By age category				0.39		0.67
< 30	36.2	63.4	0.33 (0.26, 0.42)		0.47 (0.36, 0.63)	
30–49	49.6	78.5	0.27 (0.21, 0.34)		0.4 (0.31, 0.53)	
≥ 50	58.9	84.9	0.26 (0.18, 0.36)		0.41 (0.27, 0.61)	
By urbanicity				0.04		0.18
Urban	45.0	75.4	0.27 (0.22, 0.32)		0.46 (0.38, 0.57)	
Rural	44.7	81.0	0.19 (0.14, 0.25)		0.35 (0.25, 0.49)	
Race				0.81		0.37
White	48.2	79.3	0.24 (0.20, 0.29)		0.46 (0.36, 0.58)	
Other	40.9	74.7	0.23 (0.19, 0.29)		0.39 (0.3, 0.51)	
Year				0.49		0.83
2015	46.8	77.1	0.26 (0.20, 0.33)		0.46 (0.34, 0.61)	
2016	45.8	80.1	0.21 (0.16, 0.27)		0.40 (0.3, 0.55)	
2017	41.9	75.4	0.24 (0.18, 0.3)		0.43 (0.31, 0.58)	
Fatality				0.47		0.32
Yes	41.4	77.4	0.21 (0.14, 0.31)		0.35 (0.22, 0.55)	
No	45.5	77.6	0.24 (0.21, 0.28)		0.45 (0.37, 0.54)	

p values reflect subgroup differences between overdose type

*Logistic regression models adjusted for sex, race, urbanicity, age category, and the following Elixhauser comorbidities: alcohol misuse; deficiency anemia; rheumatoid arthritis; blood loss anemia; congestive heart failure; chronic lung disease; coagulopathy; depression; diabetes, uncomplicated; diabetes, complicated; drug misuse; hypertension, uncomplicated; hypertension, complicated; hypothyroidism; liver disease; lymphoma; fluid and electrolyte disorders; metastatic cancer; obesity; paralysis; peripheral vascular disorders; psychoses; pulmonary circulation disorders; renal failure; solid tumor without metastasis; peptic ulcer disease; valvular disease; weight loss

Table 3 Demographic and Comorbid Diagnoses Among Individuals with an Opioid Overdose (with and without Heroin Involvement) and Age- and Sex-Matched Non-overdose Controls with One or More Opioid Dispensed in the Year Preceding Index Date

	Non-heroin involved	Heroin involved	Non-overdose	<i>p</i> value
<i>N</i>	1590	655	2620	
Overdose				
Fatal	206 (13.0)	79 (12.1)	NA	
Non-fatal	1384 (87.0)	576 (87.9)	NA	
Sex				1.000
Female	1013 (63.7)	235 (35.9)	940 (35.9)	
Male	577 (36.3)	420 (64.1)	1680 (64.1)	
Race				.027
White	1018 (64.0)	388 (59.2)	1447 (55.2)	
Black	52 (3.3)	21 (3.2)	54 (2.1)	
Asian	9 (0.6)	3 (0.5)	38 (1.5)	
Native American	50 (3.1)	16 (2.4)	52 (2.0)	
Other	70 (4.4)	41 (6.3)	210 (8.0)	
Unknown	391 (24.6)	186 (28.4)	819 (31.3)	
ZIP designation				< .001
Urban	950 (59.8)	513 (78.3)	1568 (59.9)	
Rural	640 (40.3)	142 (21.7)	1052 (40.2)	
Age				1.000
<30	289 (18.2)	237 (36.2)	948 (36.2)	
30–49	639 (40.2)	296 (45.2)	1184 (45.2)	
≥50	662 (41.6)	122 (18.6)	488 (18.6)	
Elixhauser diagnoses				
AIDS	16 (1.0)	7 (1.1)	5 (0.2)	.004
Alcohol misuse	320 (20.1)	212 (32.4)	149 (5.7)	< .001
Deficiency anemia	288 (18.1)	72 (11.0)	78 (3.0)	< .001
Rheumatoid arthritis	117 (7.4)	20 (3.1)	42 (1.6)	.015
Blood loss anemia	40 (2.5)	4 (0.6)	28 (1.1)	.287
Congestive heart failure	146 (9.2)	18 (2.7)	22 (0.8)	< .001
Chronic lung disease	571 (35.9)	152 (23.2)	253 (9.7)	< .001
Coagulopathy	88 (5.5)	29 (4.4)	27 (1.0)	< .001
Depression	770 (48.4)	238 (36.3)	286 (10.9)	< .001
Diabetes, uncomplicated	112 (7.0)	28 (4.3)	54 (2.1)	.001
Diabetes, complicated	198 (12.5)	28 (4.3)	64 (2.4)	.011
Drug abuse	761 (47.9)	515 (78.6)	202 (7.7)	< .001
Hypertension, uncomplicated	663 (41.7)	147 (22.4)	287 (11.0)	< .001
Hypertension, complicated	14 (0.9)	2 (0.3)	1 (0.04)	.104
Hypothyroidism	181 (11.4)	27 (4.1)	77 (2.9)	.122
Liver disease	257 (16.2)	165 (25.2)	58 (2.2)	< .001
Lymphoma	13 (0.8)	3 (0.5)	1 (0.04)	.027
Fluid and electrolyte disorders	492 (30.9)	163 (24.9)	87 (3.3)	< .001
Metastatic cancer	41 (2.6)	3 (0.5)	9 (0.3)	.716
Other neurological disorders	605 (38.1)	276 (42.1)	92 (3.5)	< .001
Obesity	372 (23.4)	42 (6.4)	209 (8.0)	.178
Paralysis	58 (3.7)	8 (1.2)	11 (0.4)	.037
Peripheral vascular disorders	106 (6.7)	16 (2.4)	27 (1.0)	.004
Psychoses	499 (31.4)	178 (27.2)	164 (6.3)	< .001
Pulmonary circulation disorders	60 (3.8)	13 (2.0)	7 (0.3)	< .001
Renal failure	135 (8.5)	21 (3.2)	20 (0.8)	< .001
Solid tumor without metastasis	66 (4.2)	1 (0.2)	20 (0.8)	.100
Peptic ulcer disease	25 (1.6)	2 (0.3)	11 (0.4)	1.000
Valvular disease	72 (4.5)	25 (3.8)	17 (0.7)	< .001
Weight loss	115 (7.2)	33 (5.0)	43 (1.6)	< .001
Average no. conditions (SD)	4.5 (3.3)	3.7 (2.8)	0.9 (1.6)	< .001

p values reflect differences between heroin-involved overdose and non-overdose controls

prescribed.²⁰ Because these individuals are receiving opioids through traditional healthcare channels, there may be opportunities for clinicians to screen and engage these patients in treatment. Second, in contrast to non-heroin overdose cases, traditional high-risk opioid dispensing patterns (e.g., dose, opioid/benzodiazepine overlap) were not associated with heroin-involved overdose, suggesting alternative pathways to overdose. The possible misuse- or diversion-related indicator of multiple pharmacy use was the only dispensing pattern that remained significant in our models after statistical adjustment. Finally, we found no association between discontinuation of long-term opioid therapy and heroin-involved overdose. There

are growing concerns that misapplication of patient-centered prescribing guidelines by healthcare systems, insurers, and pharmacy benefit managers may be forcing involuntary discontinuations or dose reductions that lead to harms, including overdose, suicide, or substitution with illicit opioids.^{21,22} In a study of over 100,000 individuals on chronic opioid therapy with commercial or Medicare Advantage coverage, Fenton et al. reported the percentage of patients tapering their dose more than doubled between 2008 and 2017.²³ Emerging data suggest that rapid tapering or abrupt discontinuation of chronic opioid therapy can harm patients.^{24–27} Using data from the Vermont Medicaid program, Mark et al. reported that rapid

Table 4 Opioid Dispensing Patterns Among Individuals with an Opioid Overdose (with and without Heroin Involvement) and Age- and Sex-Matched Non-overdose Controls with One or More Opioid Dispensed in the Year Preceding Index Date. Crude and Adjusted Odds Ratios Reflect Conditional Logistic Regressions Comparing Heroin-Involved Overdose Cases and Matched Control Group

	Non-heroin involved	Heroin involved	Non-overdose	Crude OR (95% CI)	Adjusted OR (95% CI) [‡]	p value
N	1590	655	2620			
Average number of opioid prescriptions dispensed, M (SD)	11.9 (11.7)	4.5 (6.0)	3.3 (5.3)	1.03 (1.02, 1.05)	1.00 (0.97, 1.02)	.83
Average MME per day, M (SD)	55.9 (49.1)	43.6 (31.7)	39.4 (26.6)	1.05 (1.02, 1.08)	1.02 (0.96, 1.09)	.48
Any opioid over 90 MME per day	224 (14.1)	37 (5.7)	101 (3.9)	1.49 (1.01, 2.19)	1.62 (0.69, 3.81)	.27
Overlapping prescriptions*						
Opioid/opioid overlap	993 (62.5)	178 (27.2)	482 (18.4)	1.71 (1.39, 2.10)	0.95 (0.63, 1.42)	.79
Opioid/benzodiazepine overlap	674 (42.4)	113 (17.3)	254 (9.7)	1.97 (1.54, 2.51)	0.80 (0.50, 1.29)	.36
Opioid/sedative overlap	185 (11.6)	22 (3.4)	57 (2.2)	1.58 (0.95, 2.61)	0.78 (0.29, 2.08)	.62
Multiple prescriber episode	503 (31.6)	124 (18.9)	189 (7.2)	3.10 (2.41, 4.00)	1.44 (0.87, 2.37)	.15
Multiple pharmacy episode	216 (13.6)	71 (10.8)	49 (1.9)	6.23 (4.27, 9.08)	3.21 (1.48, 6.95)	< .01
≥ 90 consecutive days of a dispensed opioid	469 (29.5)	47 (7.2)	123 (4.7)	1.59 (1.12, 2.27)	1.49 (0.76, 2.89)	.24
Discontinuation [†]	27 (5.8)	2 (4.3)	10 (8.1)	1.99 (0.42, 9.45)	0.33 (0.03, 3.44)	0.35

Statistical analyses reflect comparison between heroin-involved overdose cases and the non-overdose control group

MME morphine milligram equivalents

*One or more days of overlap

[†]45 consecutive days of no dispensed opioids available; odds ratios are from unconditional logistic regressions

[‡]Logistic regression model adjusted for race, urbanicity, and the following Elixhauser comorbidities: alcohol misuse; deficiency anemia; rheumatoid arthritis; blood loss anemia; congestive heart failure; chronic lung disease; coagulopathy; depression; diabetes, uncomplicated; diabetes, complicated; drug misuse; hypertension, uncomplicated; hypertension, complicated; hypothyroidism; liver disease; lymphoma; fluid and electrolyte disorders; metastatic cancer; obesity; paralysis; peripheral vascular disorders; psychoses; pulmonary circulation disorders; renal failure; solid tumor without metastasis; peptic ulcer disease; valvular disease; weight loss

opioid tapering was associated with a significant increase in opioid-related adverse events.²⁴ Glanz et al. used a nested case-control study of people with long-term opioid therapy from a large integrated healthcare system and found that while sustained opioid discontinuation was associated with a reduced odds of opioid overdose, dosing variability, possibly reflecting attempted tapering, was associated with a significant increase in overdose.²⁵ A recently published large cohort analysis in the Veterans Health Administration observed that discontinuing opioid therapy was associated with a significant increase in the risk of overdose or suicide and that the risk increased as the duration of opioid therapy increased.²⁶ However, none of these studies specifically evaluated the relationship between dose reduction or discontinuation and heroin-related outcomes.

Our results have several limitations. First, this study was a case-control design which precludes firm conclusions about causality. Our study uses data from the Oregon Medicaid program and may not reflect the overdose or prescription opioid use epidemiology for other parts of the country. There is considerable variation in both opioid prescribing and rates of heroin-involved overdose across the USA.^{28,29} Rates of heroin-related overdose are three to five times higher in the Northeast and Midwest than Western states,³⁰ and in 2017, Oregon had among the lowest heroin-involved overdose death rates in the country, although county-level trends vary markedly.¹⁵ We used matching and multivariate logistic regression models to control for measured confounders for our comparison of heroin-involved overdose and non-overdose controls. However, we recognize that unmeasured factors that are difficult to measure using administrative data (e.g., tobacco use,

weight, socioeconomic disparities) may remain as residual confounders. We relied on Oregon Medicaid administrative claims data and vital statistics to identify overdose cases. A recent validation work suggests that administrative codes have very high predictive ability (positive predictive value = 95%; negative predictive value = 98%) for identifying heroin-involved overdose.³¹ Oregon has a centralized medical examiner system model to certify deaths, which has been shown to provide more consistent and specific reporting of implicated drugs.^{32,33} Finally, although we observed low rates of long-term opioid therapy and lower discontinuation rates, our study only captured opioid use in the year immediately preceding an overdose. Although quantitative data are sparse, findings from a community-based sample of 383 people using non-prescribed opioid analgesics suggest that the rate of heroin initiation is less than 3% per year.³⁴ Because of the limited window of ascertainment in our study, the extent to which we can determine whether reductions in opioid prescribing contribute to new heroin use remains uncertain. Longitudinal studies with an extended follow-up period may be needed.

Although it is clear that prescription opioid misuse greatly increases the risk of, and often precedes, heroin initiation and use,^{5,6,35} the premise that supply-side restrictions for prescription opioids are driving the rise in heroin use and overdose is not strongly supported by the existing literature. Although we found that disruption of long-term opioid therapy was uncommon and not associated with a heroin-involved overdose, our analyses are not definitive. A growing literature suggests that disruption or discontinuation of long-term opioid therapy is associated with overdose, suicide, and other harms. As the trajectory of prescription opioid use in the country continues to

decline, there is urgent need to identify harms associated with opioid dose reduction and discontinuation.

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Compliance with Ethical Standards:

This study was approved by the Oregon Health & Science University Institutional Review Board (IRB) approval before obtaining the data. The data were pre-existing de-identified health claims data, so we did not need to obtain informed consent.

Conflict of Interest: Dr. Hartung reports grants from the Centers for Disease Control and Prevention, during the conduct of the study and grants from National Multiple Sclerosis Society, outside the submitted work. Ms. Johnston reports grants from the Centers for Disease Control and Prevention, during the conduct of the study. Ms. Hallvik reports grants from the Centers for Disease Control and Prevention, during the conduct of the study. Ms. Leitchling reports grants from the Centers for Disease Control and Prevention, during the conduct of the study. Mr. Geddes has nothing to disclose. Dr. Hildebran reports grants from the Centers for Disease Control and Prevention, during the conduct of the study. Dr. Keast reports grants from the Centers for Disease Control and Prevention, during the conduct of the study. grants from Otsuka Pharmaceuticals, and grants from Amgen, outside the submitted work. Dr. Chan has nothing to disclose. Dr. Korthuis reports grants from the Centers for Disease Control and Prevention, during the conduct of the study.

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