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A predictive risk model for nonfatal opioid overdose in a statewide population of buprenorphine patients

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ABSTRACT

Background: Predicting which individuals who are prescribed buprenorphine for opioid use disorder are most likely to experience an overdose can help target interventions to prevent relapse and subsequent consequences.
Methods: We used Maryland prescription drug monitoring data from 2015 to identify risk factors for nonfatal opioid overdoses that were identified in hospital discharge records in 2016. We developed a predictive risk model for prospective nonfatal opioid overdoses among buprenorphine patients (N = 25,487). We estimated a series of models that included demographics plus opioid, buprenorphine and benzodiazepine prescription variables. We applied logistic regression to generate performance measures.
Results: About 3.24% of the study cohort had ≥1 nonfatal opioid overdoses. In the model with all predictors, odds of nonfatal overdoses among buprenorphine patients were higher among males (OR = 1.39, 95% CI:1.21–1.62) and those with more buprenorphine pharmacies (OR = 1.19, 95% CI:1.11–1.28), 1+ buprenorphine prescription paid by Medicaid (OR = 1.21, 95% CI:1.02–1.48), Medicare (OR = 1.93, 95% CI:1.63–2.43), or a commercial plan (OR = 1.98, 95% CI:1.30–2.89), 1+ opioid prescription paid by Medicare (OR = 1.30, 95% CI:1.03–1.68), and more benzodiazepine prescriptions (OR = 1.04, 95% CI:1.02–1.05). The odds were lower among those with longer days of buprenorphine (OR = 0.64, 95% CI:0.60-0.69) or opioid (OR = 0.79, 95% CI:0.65-0.95) supply. The model had moderate predictive ability (c-statistic = 0.69).
Conclusions: Several modifiable risk factors, such as length of buprenorphine treatment, may be targets for interventions to improve clinical care and reduce harms. This model could be practically implemented with common prescription-related information and allow payers and clinical systems to better target overdose risk reduction interventions, such as naloxone distribution.

1. Introduction

Opioid use disorder (OUD) places a significant burden on the healthcare system in the United States: about 70,000 fatal overdoses occurred in 2017 (Ahmad et al., 2018), and over 140,000 nonfatal opioid overdoses (NFOD) were treated in a hospital (Vivolo-Kantor et al., 2018). Increasing utilization of medications for OUD treatment is a key strategy for reducing the rising tide of opioid overdoses. Buprenorphine is one medication that helps manage the core symptoms of OUD, including craving and withdrawal (Schuckit, 2016). Under current regulations, buprenorphine can be prescribed for OUD by office-based clinicians with a federal prescribing waiver. Substantial research has demonstrated that buprenorphine maintenance reduces opioid misuse and overdose and improves retention in addiction treatment for people with OUD (Larochelle et al., 2018; Mattick et al., 2014; Sordo et al., 2017).

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Despite the effectiveness of the medication, patients using buprenorphine remain at risk for adverse outcomes compared to the general population due to the chronic and relapsing nature of OUD (Crane, 2013). In addition, not all buprenorphine care is equally effective; longer duration treatment with buprenorphine is significantly more effective than the use of buprenorphine as a short-term withdrawal management medication (Veilleux et al., 2010). Moreover, many patients who use buprenorphine are often simultaneously prescribed opioid analgesics and other controlled substances (Daubresse et al., 2017), a possible indicator of fragmented treatment and poor quality of care.

Population-level overdose surveillance among patients prescribed buprenorphine could help guide efforts to improve treatment quality and identify high-risk individuals for additional supports. While there is no universal database of patients treated with buprenorphine, buprenorphine prescribed in office-based settings typically appears in state-based prescription drug monitoring program (PDMP) data because buprenorphine is a controlled substance (a Schedule III partial opioid agonist). PDMPs are all-payer registries of patients who are prescribed and dispensed controlled substances through pharmacies. PDMPs have been used primarily to monitor and address aberrant or unsafe prescribing of opioid analgesics and benzodiazepines (Chang et al., 2016, 2018; Moyo et al., 2017; Rutkow et al., 2015). For example, recent initiatives have used prescription data linked to overdose records to help identify risk factors for overdose among patients prescribed opioid analgesics (Ferris et al., 2019; Geissert et al., 2018; Glanz et al., 2018; Oliva et al., 2017). Predictive models from these analyses can be translated into patient-specific summary overdose risk scores, which can serve as a decision support tool for clinicians and public health practitioners.

We seek to extend the existing literature on the predictive utility of PDMP data for opioid overdoses to individuals who are prescribed buprenorphine. Our objective is to develop a predictive risk model for hospital encounters for NFOD among these patients. We assess how factors such as concurrent prescriptions for other controlled medications and information about treatment length and medication dose is predictive of overdose risk among these patients. We hypothesize that use of opioid analgesics and benzodiazepines will increase NFOD risk and that longer duration of buprenorphine will be protective against overdose risk. Finally, we assess the predictive validity of the model (i.e., the accuracy of the model in identifying buprenorphine patients who nonfatally overdose) with the goal of informing policymakers and clinicians about the possible value of a screening tool to target interventions.

2. Methods

2.1. Overview

This is a retrospective cohort study using data from the State of Maryland. The Institutional Review Boards at the Johns Hopkins Bloomberg School of Public Health and the Maryland Department of Health both approved the study. We look at prescription records in 2015 to predict risk of NFOD in 2016.

2.2. Data sources

In partnership with the Maryland Department of Health, we obtained patient data from (1) the Maryland PDMP, (2) all-payer hospital discharge records, and (3) investigated fatalities, including overdose deaths, from the Maryland Office of the Chief Medical Examiner (OCME) in 2015 and 2016.

2.2.1. PDMP records

The Maryland PDMP collects information on controlled substance prescriptions (Schedule II-V) dispensed within Maryland, including mail-order pharmacies dispensing into Maryland and prescribers dispensing stocked pharmaceuticals to patients to take home. However, the PDMP does not collect information on any controlled substance administered with assistance, such as inpatient, hospice inpatient, and opioid treatment programs (e.g., methadone maintenance). The PDMP files contained demographics (including sex and year of birth), medication documented by National Drug Code (NDC), quantity dispensed, days of supply, method of payment, unique prescriber ID, unique pharmacy ID, and ZIP code.

2.2.2. Hospital discharge records

The Maryland Hospital Services Cost Review Commission maintains an all-payer database of all discharges from hospital emergency departments and inpatient units. Hospital discharge records contained ICD-9/ICD-10 diagnosis information.

2.2.3. Office of the Chief Medical Examiner (OCME) records

The Maryland OCME includes a registry of all investigated fatalities, including overdose deaths. OCME deaths include results of toxicology screening. Opioid overdoses were identified as all deaths that were determined to involve an opioid of any kind (e.g., opioid analgesics, buprenorphine, and heroin). OCME data are used to exclude individuals from the sample who were known to have died during the study period as well as in a sensitivity analysis using any overdose (fatal or nonfatal) as the outcome.

2.2.4. Data linkage

We linked data from each of the sources at the individual level. Linkage was performed by the Chesapeake Regional Information System for our Patients (CRISP), the state-designated health information exchange in Maryland. CRISP links records together using a probabilistic algorithm applied to patient identifiers such as name, date of birth, sex, address, and social security number before de-identifying the data for the purposes of this study. All three files were linked through an encrypted patient ID supplied by CRISP.

2.3. Study subjects

All participants were required to have at least one buprenorphine prescription from the PDMP in 2015 (N = 28,348). Buprenorphine formulations of interest were those specifically indicated for OUD treatment (e.g., buprenorphine-naloxone) and excluded those indicated only for pain treatment (e.g., buprenorphine patch). In our main analysis, we excluded patients who 1) were younger than 18 or older than 80 (n = 228), 2) did not have a Maryland zip code at their latest PDMP encounter in 2015 (n = 2530) (i.e., who were not Maryland residents), 3) had unknown sex (n = 68), and 4) died during or before 2016 (n = 66). Our final analytic sample included 25,487 subjects.

2.4. Nonfatal Opioid Overdose (NFOD) outcomes

Our outcome of interest was a binary indicator of having experienced a NFOD event in 2016, derived from hospital discharge records. A NFOD was defined as any visit to a hospital emergency department or inpatient unit with an applicable diagnosis code for a heroin, methadone, or other opioid overdose (see Appendix 1 in Supplementary material). We dichotomized NFOD, as only 0.53% had multiple NFODs in the study period, resulting in insufficient statistical power to treat NFODs as a count variable. In a sensitivity analysis, we show that not excluding people who died during the study period and including fatal overdoses along with NFODs does not substantially alter our main findings (see Appendix 2 in Supplementary material).

2.5. Independent variables

We included demographic and prescription-related variables from

the PDMP in 2015. Demographic factors consisted of age in categories (18–34, 35–49, 50–64, and 65–80) and sex (male, female). We included opioid analgesic prescription variables that have been previously associated with overdose risk (Ferris et al., 2019). These included days of supply, number of unique prescribers and number of unique pharmacies; five binary indicators describing source of payment for prescription (cash/self-pay payment, Medicaid, Medicare, commercial insurance, and other sources) were also included. We then included the same set of variables constructed from buprenorphine-only prescriptions (e.g., days of buprenorphine supply, etc.). Finally, we included the number of prescriptions for benzodiazepines, which can also increase risk of respiratory depression for patients prescribed buprenorphine (McCance-Katz et al., 2010). All count variables (days of supply, numbers of unique prescribers, number of unique pharmacies, and number of prescriptions) were truncated at the top 1% (i.e., imputing the numerical value of the 99th percentile to all observations in the top 1%) to reduce the impact of outliers on the statistical models.

2.6. Statistical methods

We compared the demographic and prescription variables between those who did and did not experience a NFOD using Fisher's exact tests for binary/categorical variables and the Wilcoxon rank-sum test for count variables. We then estimated a series of logistic regression models in which the outcome was having NFOD and the predictors included demographic variables and different combination of prescription-related variables. Specifically, these models were: 1) demographics only; 2) demographics plus opioid analgesic variables; 3) demographics plus buprenorphine variables; 4) demographics, opioid analgesic variables and buprenorphine variables; and 5) demographics, opioid analgesic variables, buprenorphine variables and the number of benzodiazepine prescriptions. The purpose of estimating a series of models provides greater clarity about the possible additive value of different predictors in identifying NFOD risk. All model performance measures and their 95% Confidence Intervals (CIs) were derived from bootstrapping analyses of 300 iterations (Efron and Tibshirani, 1986; Mihaylova et al., 2011), a standard method in the field (Chang et al., 2017; Kharrazi et al., 2018). Performance measures we adopted included the C-statistic and Akaike's Information Criterion (AIC). C-statistic, or the area under a receiver operating characteristic curve, is the probability that a randomly selected patient who experienced 1 + NFOD had a higher risk score than a randomly selected patient who had not experienced a NFOD (Hanley and McNeil, 1982); the C-statistic ranges from 0 (the worst) to 1 (the best). Akaike's Information Criterion is a technique to estimate the likelihood of a model to predict the outcome based on the sample the model uses, and it is designed to pick the model that generates the probability distribution that is the closest to the true distribution (Bozdogan, 2000; Pan, 2001); the smaller the AIC, the better the model.

For the model with the best performance out of these five, we presented the odds ratios (ORs) associated with all variables included in the model and the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) at the predictive probability of top 5%, 10%, and 20%.

3. Results

3.1. Sample characteristics by overdose status

Among the 25,487 individuals, 827 (3.24%) had one or more NFOD in 2016. Characteristics of the study sample are presented in Table 1. Patients with NFOD in 2016 were more likely to be male (63.85% vs 59.20%) and younger (mean ages: 36.54 vs 39.17). Individuals with NFOD, compared to those without, had shorter days of buprenorphine supply (123 vs. 173 days), had more unique pharmacies where they obtained buprenorphine (1.83 vs 1.71), had fewer buprenorphine prescriptions paid by cash (15.11% vs 18.54%) and commercial plans (50.67% vs 58.20%), and were more likely to have buprenorphine prescriptions paid by Medicaid (60.70% vs 46.95%). Furthermore, patients with NFOD, compared to those without, were more likely to have had opioid analgesic prescription (40.02% vs 29.90%), to have had more unique opioid analgesic prescribers (1.04 vs 0.69) and pharmacies (0.83 vs 0.57), and to have had opioid prescriptions paid by cash (10.52% vs 7.40%), Medicaid (18.26% vs 10.17%), and commercial plans (24.30% vs 19.90%). In addition, those with NFOD were also more likely to have any benzodiazepine prescription (31.08% vs 23.19%) and a higher number of benzodiazepine prescriptions (2.51 vs 1.77) than their counterparts.

3.2. Model performance measures

In Table 2, we present the C-statistics and AICs for five logistic regression models. The models differ by what predictors are included in the model. In these models, the C-statistic increased as the model added more variables: it increased from 0.57 (95% CIs 0.55-0.59) for model 1 (demographics only) to 0.69 (95% CIs 0.67-0.70) for model 5 (demographics, opioid analgesic, buprenorphine, and benzodiazepine predictors). Similarly, we saw a reduction of AIC from 7239 in model 1 (95% CIs 6,778-7,564) to 6844 in model 5 (95% CIs 6,402-7,169). Because the full model, which included all opioid, buprenorphine, and benzodiazepine variables (model 5), had the highest C-statistic and the lowest AIC, it was chosen as the preferred model for further analysis and discussion.

3.3. Predictors of prospective overdose outcomes of the final model

In Table 3, we present odds ratios associated with the variables in the full model (model 5). After controlling for other variables included in the models, being male was associated with an increase in odds of having NFOD (OR = 1.39 95% CIs 1.21–1.62). Older age groups were generally associated with lower odds of having NFOD: for example, relative to age 18–34, the ORs for age were significantly lower for all but the oldest age groups: age 35–49 OR = 0.65 (95% CIs 0.55-0.77), age 50–64 OR = 0.73 (95% CIs 0.60-0.88), and age 65–80 OR = 0.60 (95% CIs 0.26–1.09).

After controlling for other variables in the models, longer days of buprenorphine supply were significantly associated with lower odds of having NFOD (OR per 100 days = 0.65 95% CIs 0.60-0.69). A higher number of unique buprenorphine pharmacies was significantly associated with higher odds of having NFOD (OR per one additional unique buprenorphine pharmacy = 1.19 95% CIs 1.11–1.28), but a higher number of unique buprenorphine prescribers were not statistically significant. Having a buprenorphine prescription paid by Medicaid (OR = 1.21 95% CIs 1.02–1.48), Medicare (OR = 1.93 95% CIs 1.63–2.43), or commercial plans (OR = 1.98 95% CIs 1.30–2.89) was significantly associated with higher odds of having NFOD. Similarly, after holding constant other variables in the models, longer days of opioid supply were statistically significantly associated with lower odds of having NFOD (OR per 100 days = 0.79 95% CIs 0.65-0.95). Having an opioid prescription paid by Medicare (OR = 1.30 95% CIs 1.03–1.68) was also significantly associated with higher odds of having NFOD. Lastly, after holding other variables constant, having one or more benzodiazepine prescription was significantly associated with slightly higher odds of having NFOD (OR = 1.04 95% CIs 1.02–1.05).

3.4. Sensitivity, specificity, and predictive values of the final model

In Table 4 we present the sensitivity, specificity, PPV, and NPV at three thresholds of predicted probabilities derived from the model 5 to illustrate the implications of creating different cutoffs for being classified as "high risk" based on our predicted probabilities of NFOD. Raising the threshold (i.e., creating a more stringent cutoff for being

Table 1
Characteristics of the study sample and associations with experiencing a nonfatal opioid overdose in 2016.

	Total (%) N = 25,487	No Nonfatal Overdose (%) N = 24,660	1+ Nonfatal Overdose (%) N = 827	p-value
Demographics				
Male Sex**	59.35	59.20	63.85	0.008
Age, M(SD)**	39.09 (12.02)	39.17 (12.00)	36.54 (12.34)	< .0001
Categorical Age **				
Age 18 – 34	43.18	42.82	53.81	< .0001
Age 35 – 49	33.17	33.39	26.72	
Age 50 – 64	22.10	22.22	18.50	
Age 65 – 80	1.55	1.57	0.97	
Buprenorphine Variables				
Days of supply, M(SD)**	171.24 (126.34)	172.85 (126.48)	123.23 (111.88)	< .0001
Count of unique prescribers, M(SD)	1.76 (1.05)	1.76 (1.05)	1.76 (1.04)	0.919
Count of unique pharmacies, M(SD)**	1.72 (1.07)	1.71 (1.06)	1.83 (1.13)	0.001
1+ prescription paid by cash payment*	18.43	18.54	15.11	0.012
1+ prescription paid by Medicaid**	47.40	46.95	60.70	< .0001
1+ prescription paid by Medicare	4.77	4.75	5.44	0.361
1+ prescription paid by commercial plans**	57.96	58.20	50.67	< .0001
1+ prescription paid by other sources	2.58	2.57	2.90	0.505
Opioid Analgesic Variables				
1+ prescription**	30.23	29.90	40.02	< .0001
Days of supply, M(SD)**	16.74 (52.83)	16.62 (52.67)	20.33 (57.25)	< .0001
Count of unique prescribers, M(SD)**	0.70 (1.48)	0.69 (1.46)	1.04 (1.83)	< .0001
Count of unique pharmacies, M(SD)**	0.58 (1.15)	0.57 (1.14)	0.83 (1.37)	< .0001
1+ prescription paid by cash payment**	7.50	7.40	10.52	0.002
1+ prescription paid by Medicaid**	10.44	10.17	18.26	< .0001
1+ prescription paid by Medicare	2.35	2.33	2.90	0.292
1+ prescription paid by commercial plans**	20.04	19.90	24.30	0.002
1+ prescription paid by other sources	1.41	1.39	2.18	0.070
Benzodiazepine Variables				
1+ prescription**	23.44	23.19	31.08	< .0001
Count of prescriptions, M(SD)**	1.79 (4.38)	1.77 (4.35)	2.51 (5.13)	< .0001

*: $p < 0.05$ **: $p < 0.01$ (comparing two overdose sub-cohorts; estimated using Wilcoxon rank-sum test (for continuous variables) or Fisher's exact test for binary/categorical variables).

Table 2
C-statistics and Akaike's Information Criterions (AICs) for different models predicting nonfatal opioid overdoses (NFOD) in 2016.

Model (using 2015 Risk Factors)	C-statistics	AICs
1: Demographics	0.57 (0.55, 0.59)	7239 (6,778-7,564)
2: Demographics + Opioid Variables	0.62 (0.60, 0.64)	7127 (6,675-7,445)
3: Demographics + Buprenorphine Variables	0.67 (0.65, 0.69)	6949 (6,509-7,273)
4: Demographics + Opioid Variables + Buprenorphine Variables	0.68 (0.67, 0.70)	6873 (6,430-7,209)
5: Demographics + Opioid Variables + Buprenorphine Variables + Benzodiazepine fill	0.69 (0.67, 0.70)	6844 (6,402-7,169)

Demographic variables: male, four level of age category (18–34, 35–49, 50–64, 65–80)
Buprenorphine/Opioid variables: days of supply, count of unique prescribers, count of unique pharmacies, with 1+ prescription paid by cash payment, with 1+ prescription paid by Medicaid, with 1+ prescription paid by Medicare, with 1+ prescription paid by commercial plans, with 1+ prescription paid by other sources.
C-statistics is the probability that a randomly selected patient who experienced 1+NFOD had a higher risk score than a randomly selected patient who had not experienced a NFOD.
C-statistics and AICs were derived from bootstrapping analyses of 300 iterations.

"high risk") increased sensitivity and NPV and decreased specificity and PPV. Approximately 25.89% of subjects with > 1 NFOD were among the top 10% of the prospective predicted probabilities, while 90.53% of subjects without NFOD were among the bottom 90% of the prospective predicted probabilities. About 8.41% of subjects among the top 10% of prospective predicted probabilities had > 1 NFOD event in 2016, while 97.33% of the remaining sample (those among the bottom 90% of predicted probabilities) had no such event. After relaxing the threshold of predicted probabilities from top 5% to top 20% (i.e., making the cutoff less stringent), the number of patients we could correctly capture as having > 1 NFOD event was about 2.7 times higher (from 127 to 351 prospectively).

4. Discussion

This study developed and evaluated the performance of a model to predict nonfatal overdoses among patients filling prescriptions for buprenorphine as documented by Maryland's PDMP during 2015-2016. We identified NFOD treated in all Maryland hospitals by linking the PDMP data to emergency department and inpatient records from Maryland's all-payer hospital database. Although buprenorphine treatment is known to curb overdose risk for patients with opioid use disorder (Sordo et al., 2017), patients in this group remain highly vulnerable to treatment discontinuation, relapse and subsequent overdose. By identifying profiles of people at higher overdose risk, it may be possible to support interventions to improve the quality of care for patients with buprenorphine.

We found that males and individuals younger than 35 filling buprenorphine were at especially high risk of NFOD relative to other buprenorphine patients, which is consistent with other data showing that males and younger patients are generally at elevated risk of overdose (Centers for Disease Control and Prevention, 2018). Similar to prior studies, we found that odds of NFOD were lower among individuals who had longer duration of buprenorphine fills (Bell et al., 2009; Larochelle et al., 2018). This is consistent with recommendations that patients have the ability to maintain treatment of indefinite

Table 3
Odds ratios (ORs) derived from the model with all prescription and demographic risk factors predicting nonfatal opioid overdoses (NFOD) in 2016.

	1 + NFOD in 2016 aOR (95% CI)
Intercept	0.02 (0.02, 0.03)
Demographics	
Male	1.39 (1.21, 1.62)
Age	
18 – 34	REF
35 – 49	0.65 (0.55, 0.77)
50 – 64	0.73 (0.60, 0.88)
65 – 80	0.60 (0.26, 1.09)
Buprenorphine Variables	
Days of supply (per 100 days)	0.64 (0.60, 0.69)
Count of unique prescribers	1.05 (0.98, 1.13)
Count of unique pharmacies	1.19 (1.11, 1.28)
1 + prescription paid by cash payment	0.93 (0.73, 1.11)
1 + prescription paid by Medicaid	1.21 (1.02, 1.48)
1 + prescription paid by Medicare	1.93 (1.63, 2.43)
1 + prescription paid by commercial plans	1.98 (1.30, 2.89)
1 + prescription paid by other sources	1.56 (0.95, 2.34)
Opioid Variables	
Days of supply (per 100 days)	0.79 (0.65, 0.95)
Count of unique prescribers	1.09 (1.00, 1.18)
Count of unique pharmacies	1.00 (0.86, 1.15)
1 + prescription paid by cash payment	1.01 (0.76, 1.30)
1 + prescription paid by Medicaid	1.07 (0.81, 1.38)
1 + prescription paid by Medicare	1.30 (1.03, 1.68)
1 + prescription paid by commercial plans	1.08 (0.58, 1.72)
1 + prescription paid by other sources	1.22 (0.61, 1.88)
Benzodiazepine Variables	
Count of prescriptions	1.04 (1.02, 1.05)

Note. Estimates are from model 5, which included demographic, opioid, buprenorphine, and benzodiazepine variables.
ORs and 95% CIs were derived from bootstrapping analyses of 300 iterations.

Table 4
Sensitivity, specificity, positive predictive value, and negative predictive value by different thresholds of predicted probability for nonfatal opioid overdoses (NFOD) in 2016.

	% (95% CI)
Top 5% of Predicted Probability	
Sensitivity	15.40 (12.90, 18.43)
Specificity	95.35 (95.26, 95.47)
Positive Predictive Value	9.97 (8.17, 12.19)
Negative Predictive Value	97.10 (96.90, 97.37)
Top 10% of Predicted Probability	
Sensitivity	25.89 (22.77, 29.43)
Specificity	90.53 (90.40, 90.68)
Positive Predictive Value	8.41 (7.13, 9.60)
Negative Predictive Value	97.33 (97.13, 97.55)
Top 20% of Predicted Probability	
Sensitivity	42.45 (38.21, 45.71)
Specificity	80.75 (80.60, 80.88)
Positive Predictive Value	6.89 (6.08, 7.57)
Negative Predictive Value	97.67 (97.43, 97.89)

Note. Estimates are from model 5, which included demographic, opioid, buprenorphine, and benzodiazepine variables.
All measures were derived from bootstrapping analyses of 300 iterations.

duration, as remaining in treatment with buprenorphine can help manage physiological triggers for relapse (Substance Abuse and Mental Health Services Administration, 2016).

We further hypothesized that use of opioid analgesics and benzodiazepines alongside buprenorphine would increase overdose risk. We found that number of benzodiazepine prescriptions was indeed associated with higher overdose risk, although only by a small magnitude. In unadjusted analyses, we also found that longer duration of opioid analgesic prescriptions during the study period was associated with higher overdose risk, but this association was reversed to show significantly lower overdose risk in adjusted analysis. Specifically, an additional 100 days of opioid analgesic prescriptions was associated with 21% lower odds of overdose (OR = 0.79). Further clarification of the contribution of opioid analgesics to overdose risk in this population requires a greater understanding of the factors that may independently be driving patients to concurrently use opioid analgesics and buprenorphine.

This finding also highlights the need for better individualized care plans for buprenorphine patients, as concurrent use of other substances may not be as straightforwardly associated with risk as previously thought (Martin et al., 2018). Opioid analgesics likely play a different role in overdose risk among patients using buprenorphine than in the general population. Buprenorphine pharmacologically imposes a ceiling effect on all opioids (Walsh and Eissenberg, 2003) which may blunt their potency in patients maintained on opioids. Additionally, since chronic pain and opioid dependence are often overlapping syndromes, many patients stable on opioid analgesics may use these medications as alternatives to illicit opioids (Manhapra et al., 2017). It is conceivable that prescribed opioids may incur lower risk compared to other alternative substances of higher potency such as heroin and fentanyl. Another reason to consider the separate pharmacological profiles of buprenorphine versus other opioids is that buprenorphine has one of the highest morphine milligram equivalent (MME) factors, even though it carries a lower overdose risk. While our model did not examine cumulative opioid dosage, it is important that any model that does assess daily dosage separate buprenorphine from other opioid analgesics to calculate MME for the purposes of assessing overdose risk (Centers for Disease Control and Prevention, 2017).

Our model is likely to be useful for targeting services or resources to high-risk patients using buprenorphine. It is developed using pharmacy fill records, which are readily accessible to many clinical systems and payers, and is relatively straightforward to implement, since it is a retrospective regression-based analysis of a calendar year of data. The model demonstrated acceptable predictive ability for NFOD occurring in the next year (C-statistic = 0.69). From a diagnostic perspective, the current model is best conceived as a tool for "ruling in" high-risk individuals. For example, setting a threshold at the top 5% of the current model would correctly identify 97.92% of all individuals who did not overdose, but this score would only have a positive predictive value of 8.98%, meaning that most individuals in this group will not in fact experience an overdose. Thus, this model may have greatest utility for "light touch" interventions, such as prioritizing individuals for naloxone distribution, or as a first-stage screening tool for higher intensity services like more frequent contact with patients, case management or behavioral therapies. Even though the model has low sensitivity for NFOD, many individuals who may be "flagged" by the model may also be at risk for other adverse outcomes associated with opioid use.

Screening tools such as this one may be of value to addiction treatment practitioners, especially office-based prescribers who often have access to PDMP records and can use these records to track patient history or progress in treatment. Providing up-to-date information on prescription fills through PDMPs or integrated electronic medical records for buprenorphine patients can help prescribers to optimize treatment for their patients, for example by reconciling prescriptions given by other clinicians and coordinating pain management and opioid use disorder treatment. Objective risk information can also enhance communication between primary care providers (where buprenorphine is often prescribed) and specialty addiction treatment providers to enhance their ability to work in a coordinated fashion (e.g., in a "hub-and-spoke" system of care) (Saloner et al., 2018).

Developing models that are sensitive to the unique risk factors of patients filling buprenorphine is of particular importance in addiction medicine efforts, especially as PDMPs are increasingly being envisioned as tools for surveillance of overdose risk at the same time as efforts being made to expand access to buprenorphine for OUD treatment. Our

study can also inform efforts to empirically develop predictors of quality of care for buprenorphine treatment, as it is one of the few studies to assess prescription-related risk factors for overdose in a representative patient population. There is currently an active debate, for example, about the risk associated with chronic benzodiazepine use among buprenorphine patients (Martin et al., 2018).

Our study is subject to several limitations. First, although the PDMP captures the large majority of all buprenorphine prescriptions, it misses buprenorphine dispensed to patients directly through opioid treatment programs and in hospitals. In Maryland, opioid treatment programs served approximately 1700 buprenorphine patients in 2016, compared to 25,487 patients identified via prescription drug monitoring program (PDMP) (Systems Evaluation Center, 2016). Our study also does not include prescriptions that are dispensed to Maryland patients by out-of-state pharmacies. Second, while most of the buprenorphine formulations we considered are prescribed for the treatment of opioid use disorder, some providers prescribe these medications off-label for pain management, and PDMP data does not include diagnosis codes for such identification. These patients may differ in important unobserved ways in regard to their clinical needs and overdose risks. Third, our prescription records cannot account for other aspects of clinical care for substance use disorders such as receipt of counseling. Fourth, our data only include pharmaceuticals legally prescribed to patients and miss prescription drugs obtained illicitly (including diverted buprenorphine) and illicit drugs such as heroin and fentanyl which are increasingly implicated in overdoses. Fifth, as with all studies examining prescription drug use, we cannot ascertain whether patients take the medications that they are prescribed. Assessing adherence is an important target for further research. Sixth, we did not set the requirement of the minimum opioid treatment history in 2015 to be included in the study given that we did not have a large number of eligible study subjects to begin with, and we think our approach is a more realistic “use case” when health plans or policymakers want to do a point-in-time assessment of risk for people who they have observed over the prior year. A useful extension to this study would be to use an “episode of care” approach to follow a cohort of patients initiating buprenorphine treatment and examining risk of NFOD after a period of initial treatment. Seventh, prescriptions dispensed in 2014 which were consumed in part in 2015 would not be captured. However, this may be inevitable for studies deriving prescription information from claims data. Lastly, as our data measure NFOD treated in Maryland hospitals, we miss NFOD that do not result in transfer to a hospital (e.g., if an individual refuses transport), and we miss treatment received out-of-state.

5. Conclusions

People who fill buprenorphine prescriptions are at an elevated risk of opioid overdose compared to the general population due to their history of opioid use disorder and the chronic and relapsing nature of addiction. Our study finds that it is possible to predict nonfatal overdose risk among this patient population with moderate accuracy, and there are several modifiable risk and protective factors that could be addressed through clinical efforts. Ensuring that patients are maintained on buprenorphine for a longer duration of time is protective against overdose. Clinical systems can focus on boosting treatment duration as well as care improvement efforts to reduce fragmentation in care.

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Contributors

HC designed the study, managed data, performed analyses, and drafted the manuscript. NK, KS, LF, and ME provided critical comments and revised the manuscript. TR managed data, provided critical comments and revised the manuscript. BL, KJ and JW secured data, provided critical comments and revised the manuscript. BS designed the study, secured data, and drafted the manuscript. All authors contributed to and approved of the final version of the manuscript.

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Appendix A. Supplementary data

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