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# Association between buprenorphine/naloxone and high-dose opioid analgesic prescribing in Kentucky, 2012–2017

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ABSTRACT

*Introduction:* Buprenorphine/naloxone treatment is a highly effective treatment for opioid use disorder decreasing illicit opioid use and both all-cause and opioid-involved overdose mortality. The purpose of this study was to investigate the relationships between buprenorphine/naloxone prescribing and high-dose opioid analgesic prescribing (HDOAP) over time.

*Methods:* This longitudinal study used 2012–2017 Kentucky All Schedule Prescription Electronic Reporting data and cross-lagged structural equation analysis. For each quarter-county observation, HDOAP rate (per 1,000 residents with opioid analgesic prescriptions) was used to predict buprenorphine/naloxone prescribing rate at the next quarter, and simultaneously buprenorphine/naloxone prescribing rate was used to predict HDOAP at the next quarter, accounting for baseline socioeconomic status, medical needs for opioid analgesics, and heroin availability.

*Results:* On average, HDOAP rates in Kentucky decreased by more than 10% ($p < .0001$) and buprenorphine/naloxone prescribing rates increased by more than 5% ($p < .0001$) per quarter over the study period. Every one-per-thousand higher HDOAP rate in an earlier quarter was associated with a 0.01/1,000 increase in the buprenorphine/naloxone prescribing rate in a later quarter ($p = .009$). Conversely, a one-unit higher buprenorphine/naloxone prescribing rate in an earlier quarter was associated with a 0.01/1,000 reduction in the HDOAP rate in a subsequent quarter ($p = .017$).

*Conclusions:* Our results indicate a significant reciprocal relationship between HDOAP and buprenorphine/naloxone prescribing and a clinically meaningful effect of buprenorphine/naloxone prescribing on reducing HDOAP. Future studies on buprenorphine/naloxone treatment expansion should take into account this bi-directional association in the context of longitudinal data and evaluate for public health benefits beyond the reduction of HDOAP.

## 1. Introduction

The opioid crisis in the United States has been attributed to over-prescribing opioid analgesics (OAs), including increased opioid prescribing and increased dosages (King et al., 2014). Patients receiving higher daily morphine-equivalent dosages are more likely to develop an opioid use disorder (OUD), transition to heroin, or to experience an overdose (Bohnert et al., 2011; Compton et al., 2016; Dunn et al., 2010; Han et al., 2017; Hirsch et al., 2014). To address the opioid overdose epidemic, reducing potentially risky prescribing practices to prevent new cases of OUD and related harms should be accompanied by increased OUD treatment for those already affected. Research shows that without adequate access to OUD treatment, patients with OUD may transition to the illicit drug market, which is associated with a higher risk of overdose (Conroy and Hill, 2014) and infectious disease (e.g., hepatitis C and HIV) (Havens et al., 2018). Thus, expanding the

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availability of effective OUD treatment is paramount given that approximately 80% of the 2.1 million Americans with OUD have not received evidence-based treatment (NIDA, 2018).

Methadone (a full opioid agonist) and buprenorphine (a partial opioid agonist) have been approved by the Food and Drug Administration (FDA) as effective treatments for OUD (Schuckit, 2016; Soyka, 2017) and are also included on the World Health Organization's list of essential medications (WHO, 2017). Methadone can only be dispensed through licensed opioid treatment programs in the United States. Buprenorphine can be prescribed by qualified physicians and other practitioners with a waiver to treat OUD in outpatient settings, under the Drug Addiction Treatment Act of 2000 (SAMHSA, 2016; Volkow, 2018). Due to federal restrictions on methadone treatment, expansion of buprenorphine has been a critical way to increase access to medications for OUD. As a partial mu-opioid agonist, buprenorphine, including buprenorphine/naloxone, has an improved safety profile over full mu-opioid agonists and has been demonstrated to decrease illicit opioid use as well as all-cause and opioid-related overdose mortality (Larochelle et al., 2018; Schwartz et al., 2013).

Far above the average national rates of opioid-related overdose deaths, Kentucky has maintained its rank in the top ten states with the highest opioid-related overdose mortality rates and the highest OA prescribing for many recent years (CDC, 2017; WONDER, 2012- 2017). In 2014, Kentucky was one of 27 states to expand their Medicaid program and add substance use treatment coverage to the traditional Medicaid program through the Affordable Care Act (ACA). Kentucky Medicaid covered buprenorphine/naloxone products but did not cover methadone (SAMHSA, 2018). From 2013–2016, Kentucky reported an unprecedented increase in the number of buprenorphine/naloxone doses dispensed (KASPER, 2017). Understanding how the expansion of buprenorphine/naloxone treatment affects OA prescribing and vice versa is important, but no study has examined this, to our knowledge.

To fill this gap, our study measured population-level indicators for high-dose OA prescribing and buprenorphine/naloxone prescribing using prescription drug monitoring program (PDMP) data and investigated the reciprocal relationships between buprenorphine/naloxone prescribing and high-dose OA prescribing over time. We hypothesized that high-dose OA prescribing will positively predict buprenorphine/naloxone prescribing, and simultaneously buprenorphine/naloxone prescribing will negatively predict high-dose OA prescribing, after adjusting for baseline differences in socio-economic status, medical indications for OAs, and heroin availability.

## 2. Conceptual framework

A conceptual framework that hypothesizes a mechanism for a reciprocal relationship between high-dose OA prescribing and buprenorphine/naloxone prescribing at the county level was developed (Fig. 1). High-dose OA prescribing in an earlier quarter may be associated with increased buprenorphine/naloxone prescribing in a subsequent quarter because increased high-dose OA prescribing is associated with increased risk of OUD (Chou et al., 2014; Edlund et al., 2014; Sullivan et al., 2010), which may result in increased demand for buprenorphine/naloxone treatment. Simultaneously, buprenorphine/naloxone prescribing in an earlier quarter may be associated with decreased high-dose OA prescribing in a subsequent quarter as patients receiving buprenorphine/naloxone treatment for OUD may not continue seeking prescription OAs (Saloner et al., 2017).

Multiple factors related to the hypothesized relationship were identified from the literature, including socio-economic status, medical indications for OAs (i.e., the prevalence and incidence of painful conditions traditionally treated with OAs), and availability of heroin. Non-metropolitan counties, typically characterized by lower socio-economic status relative to metropolitan counterparts, are more likely to have higher traumatic injury, comorbidity, and cancer rates (Moy et al., 2017), and more limited access to OUD treatment (Dunn et al., 2016; Rosenblatt et al., 2015), but may be less exposed to heroin (SAMHSA, 2012). Consequently, non-metropolitan county status is significantly associated with higher OA prescribing (Guy et al., 2017; Luu et al., 2018). Rates of painful conditions, such as acute traumatic injuries, chronic non-cancer pain, or late-stage cancer, are substantially and positively associated with OA prescribing (Gomes et al., 2011; Guy et al., 2017; Luu et al., 2018). Concerns highlighted in previous research suggest that limiting OA prescriptions (supply) without providing adequate capacity for OUD treatment (to reduce the demand) may result in a transition to heroin (Dowell et al., 2017). How increased heroin availability in communities affects the volume of dispensed OAs or buprenorphine/naloxone has not been well-established.

## 3. Methods

### 3.1. Measurements and data sources

Measures for high-dose OA prescribing and buprenorphine/naloxone prescribing were determined from 32,338,535 opioid prescriptions dispensed to Kentucky residents and reported to Kentucky's PDMP (the Kentucky All Schedule Prescription Electronic Reporting) from 2012 to 2017. High-dose OA prescribing at the person-level was defined as at least seven consecutive days with a daily cumulative dose of 100 morphine milligram equivalents (MME) or more. Buprenorphine/naloxone prescribing at the person level was determined by at least one buprenorphine/naloxone transmucosal (i.e., sublingual or buccal products) prescription dispensed to a person. The Kentucky Board of Medical Licensure prohibits off-label prescribing of transmucosal buprenorphine products that are FDA-approved for OUD and limits the prescribing of buprenorphine mono products for OUD to pregnant women and those with documented hypersensitivities to naloxone (KBML, 2015).

Two measures of interest for the statistical analysis were defined at county-level (a sample size of 120 Kentucky counties): (1) quarterly county rate of residents with high-dose OA prescribing per 1,000 residents with OA prescriptions; and (2) quarterly county rate of residents with buprenorphine/naloxone per 1,000 residents with OA prescriptions.

As described in the conceptual framework, county-level factors that could affect the relationship between rates of high-dose OA prescribing and buprenorphine/naloxone prescribing are socio-economic status, medical indications for OAs, and heroin availability. A dichotomized variable for county metropolitan status was created using the U.S. Department of Agriculture Economic Research Service Rural-Urban Continuum Code (RUCC) 2013. Metropolitan and non-metropolitan counties were indicated by RUCC codes 1–3 and RUCC codes 4–9, respectively (ERS, 2013). Baseline proxy measures for prevalence and incidence of pain conditions that have been treated traditionally with OAs were (1) rates of emergency department (ED) visits due to acute traumatic injury for the first quarter of 2012, (2) rates of inpatient hospitalizations and ED visits involving chronic non-cancer pain for the first quarter of 2012, and (3) rates of cancer deaths in 2012. Heroin availability in a county was measured as the rate of county resident ED visits for treatment of heroin-related overdoses per 1,000 residents in 2012. These covariates were computed from ED visits and inpatient hospitalizations claim data (the Kentucky Office of Health Data and Analytics) and death certificate data (the Kentucky Office of Vital Statistics).

### 3.2. Statistical analyses

#### 3.2.1. Descriptive analysis

The state-wide trends in quarterly high-dose OA prescribing and buprenorphine/naloxone prescribing rates are depicted in a line graph. The geographical distributions of county-level high-dose OA prescribing and buprenorphine/naloxone prescribing rates are visualized

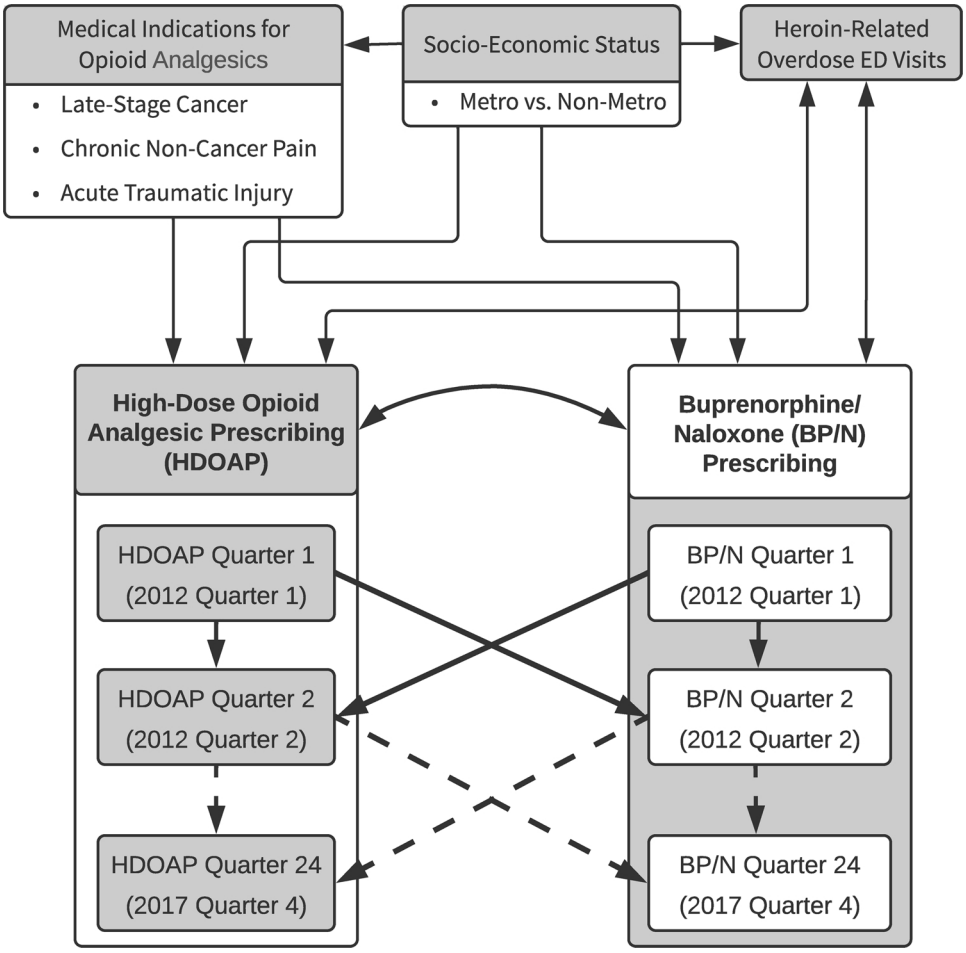



**Fig. 1.** Conceptual Framework Depicting a Hypothesized Mechanism for a Reciprocal Relationship between High-Dose Opioid Analgesic Prescribing and Buprenorphine/Naloxone Prescribing.

with choropleth maps created in ArcGIS 10.4 package at baseline (the first quarter of 2012) and the end of the study period (the fourth quarter of 2017). The same quarterly breaks were used for classifying the prescribing measures at baseline and the end of the study period. The county-level numbers of residents with high-dose OA prescribing and residents with buprenorphine/naloxone prescriptions are provided for 120 Kentucky counties at 24 quarters from 2012 to 2017 in the Appendix.

### *3.2.2. Cross-lagged structural equation analysis*

We used structural equation modeling (SEM) path analysis to build and evaluate the network of relationships between high-dose OA prescribing and buprenorphine/naloxone prescribing, accounting at baseline for metropolitan status, rates of acute traumatic injuries, chronic non-cancer pain, cancer deaths, and heroin-related overdose ED visits. Compared to traditional regression, the path analysis allows modeling of several outcomes and relations simultaneously (as well as estimating overall fit simultaneously) while accounting for omitted risk factors and measurement errors, examination of the direction of the relationships, and evaluation of a dominant effect in the bi-directional relationship. Specifically, SEM makes the cross-lagged panel approach and reciprocal relationship evaluation possible; one direction was estimated taking into account the reverse direction at the same time. We started with a model including all variables and links identified from the conceptual framework (Fig. 1). To examine the hypothesized reciprocal relationship between high-dose OA prescribing and buprenorphine/naloxone prescribing at the county level across 24 quarter time points from 2012 to 2017, we employed the cross-lagged panel approach (Kearney, 2017; Kenny, 2014). For each lag, the high-dose OA prescribing rate at an earlier quarter was used to predict buprenorphine/naloxone prescribing rate at the subsequent quarter, and simultaneously buprenorphine/naloxone prescribing rate in an earlier quarter was used to predict high-dose OA prescribing at the subsequent quarter. One assumption of the cross-lagged panel analysis is that the relationships between these variables stay the same from quarter to quarter (Kearney, 2017). Therefore, the coefficient estimates for each direction of the bi-directional relationship were constrained to be the same across the time points. Autoregressive coefficients for correlations of each variable between time points (i.e., correlations between a high-dose OA prescribing rate at an earlier quarter and a high-dose OA prescribing rate at the subsequent quarter, or correlations between a buprenorphine/naloxone prescribing rate at an earlier quarter and a buprenorphine/naloxone prescribing rate at the subsequent quarter) were controlled for stability over time. Other variables and paths that were potentially related to the relationship between high-dose OA prescribing and buprenorphine/naloxone prescribing were specified with a temporal flow to ensure that exposures at an earlier time point were used to predict outcomes at a later time point. For example, high-dose OA prescribing rate at the first quarter of 2012 was used to predict an annual rate of heroin-related ED visits at the end of 2012, or the annual rate of heroin-related ED visits in 2012 was used to predict buprenorphine/naloxone prescribing at the first quarter of 2013.

A backward variable and pathway selection were performed for model building. Starting with the predefined conceptual framework-based model, the variable or link with the highest p-value above a .05 significance level was dropped, and the model was re-evaluated for the

next candidate variable/link to be dropped until a parsimonious model was reached. Cancer mortality and acute traumatic injury along with their associated paths at baseline were excluded from the final model. The goodness-of-fit of the final model was evaluated by the ratio of the model chi-square to the degrees of freedom, the Root Mean Square Error of Approximation (RMSEA) with 90% confidence interval (CI), the Comparative Fit Index (CFI), and the Tucker-Lewis Index (TLI) (Cangur and Ercan, 2015; Hooper et al., 2008).

Additionally, to determine the dominant direction of the reciprocal relationship between high-dose OA prescribing and buprenorphine/naloxone prescribing, we obtained standardized regression coefficients for both directions from fitting the final model with the high-dose OA prescribing and buprenorphine/naloxone prescribing rates that were standardized by the grand mean and standard deviation for all time points. We computed the 95% CI for the estimated standardized coefficients for each direction of the relationship between high-dose OA prescribing and buprenorphine/naloxone prescribing. Then we compared the absolute values of the two corresponding CI boundaries. If the 95% CIs for the absolute values do not overlap, there is a significant difference between the absolute value of the two standardized coefficients, suggesting that one direction of the relationship is significantly stronger or more prominent than the other direction.

The study was approved by the University of Kentucky Institutional Review Board as part of the Kentucky Data-Driven Responses to Prescription Drug Misuse, funded by the Bureau of Justice Assistance. Data management and descriptive analyses were conducted using SAS® 9.4. Mplus7 was used for the cross-lagged structural equation analysis.

## 4. Results

### 4.1. Descriptive results

The line graph shows a declining trend in the high-dose OA prescribing rates and an increasing trend in the buprenorphine/naloxone prescribing rates at the state level from the first quarter of 2012 to the fourth quarter of 2017 (Fig. 2). At the state level, on average, for every 1,000 residents with OA prescriptions, there were 75 residents with high-dose OA prescribing and about 20 residents with buprenorphine/naloxone prescribing in the first quarter of 2012. By the end of the study period, the last quarter of 2017, there were less than 50 residents with high-dose OA prescribing and almost 70 residents with buprenorphine/naloxone prescribing per 1,000 residents with OA prescriptions.

The choropleth map for high-dose OA prescribing shows that in a fourth of the Kentucky counties, more than 1 out of 10 residents with OA prescriptions were prescribed at least 100 MME for seven consecutive days or more (rates of > 100/1,000) (Fig. 3). By the last quarter of 2017, only 11 out of the 120 counties had a high-dose OA prescribing rate greater than 60/1,000. The buprenorphine/naloxone prescribing rates increased in the majority of Kentucky counties from the first quarter of 2012 to the fourth quarter of 2017. Fig. 3 also indicates a considerable decline in the high-dose OA prescribing rates in Kentucky Appalachian counties during the study period with a substantial concurrent increase in the buprenorphine/naloxone prescribing rates.

### 4.2. A relationship between high-dose OA prescribing and buprenorphine/naloxone prescribing

Fig. 4 presents regression coefficient estimates corresponding to the examined directions (with standard errors in parentheses). For example, the coefficient for the relationship between high-dose OA prescribing at the first quarter of 2012 and buprenorphine/naloxone prescribing rate at the second quarter of 2012 (and any consecutive quarters) is 0.012 (p = .009), indicating that on average, every one-per-thousand higher high-dose OA prescribing rate in an earlier quarter was associated with a significant, 0.012/1,000 increase in the buprenorphine/naloxone prescribing rate in a later quarter. In other words, for every additional 1,000 residents with high-dose OA prescribing in an earlier quarter, the mean change in buprenorphine/naloxone prescribing was estimated to increase by 12 residents in the subsequent quarter. Alternatively, the coefficient for the relationship between buprenorphine/naloxone prescribing at the first quarter of 2012 and high-dose OA prescribing at the second quarter of 2012 is −0.006 (p = .017)

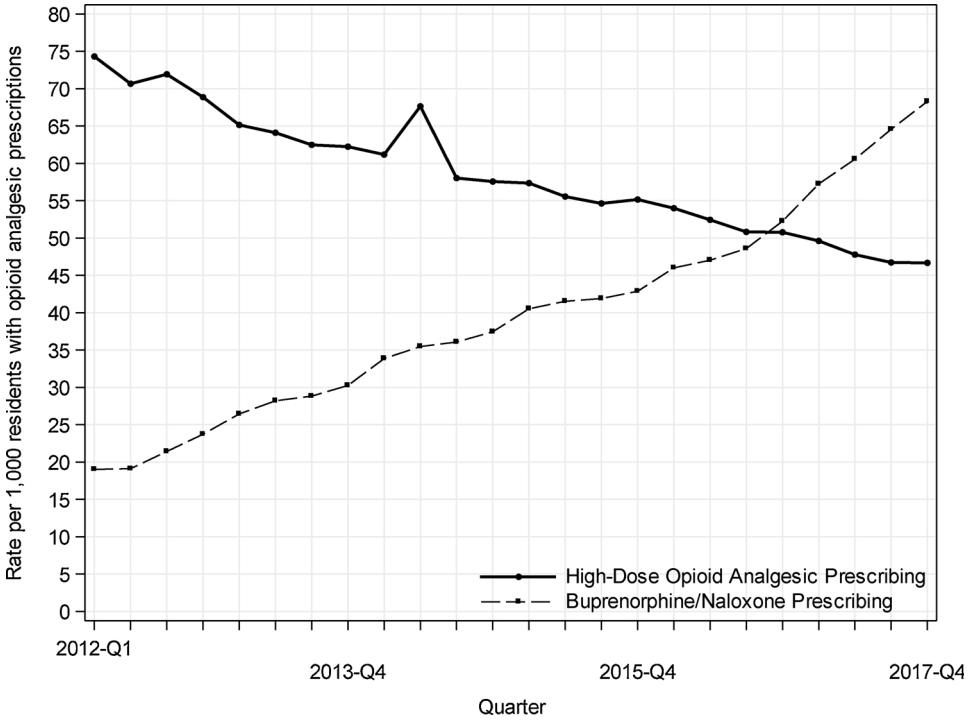



**Fig. 2.** State Rates of High-Dose Opioid Analgesic Prescribing and Buprenorphine/Naloxone Prescribing by Quarter, Kentucky 2012–2017.

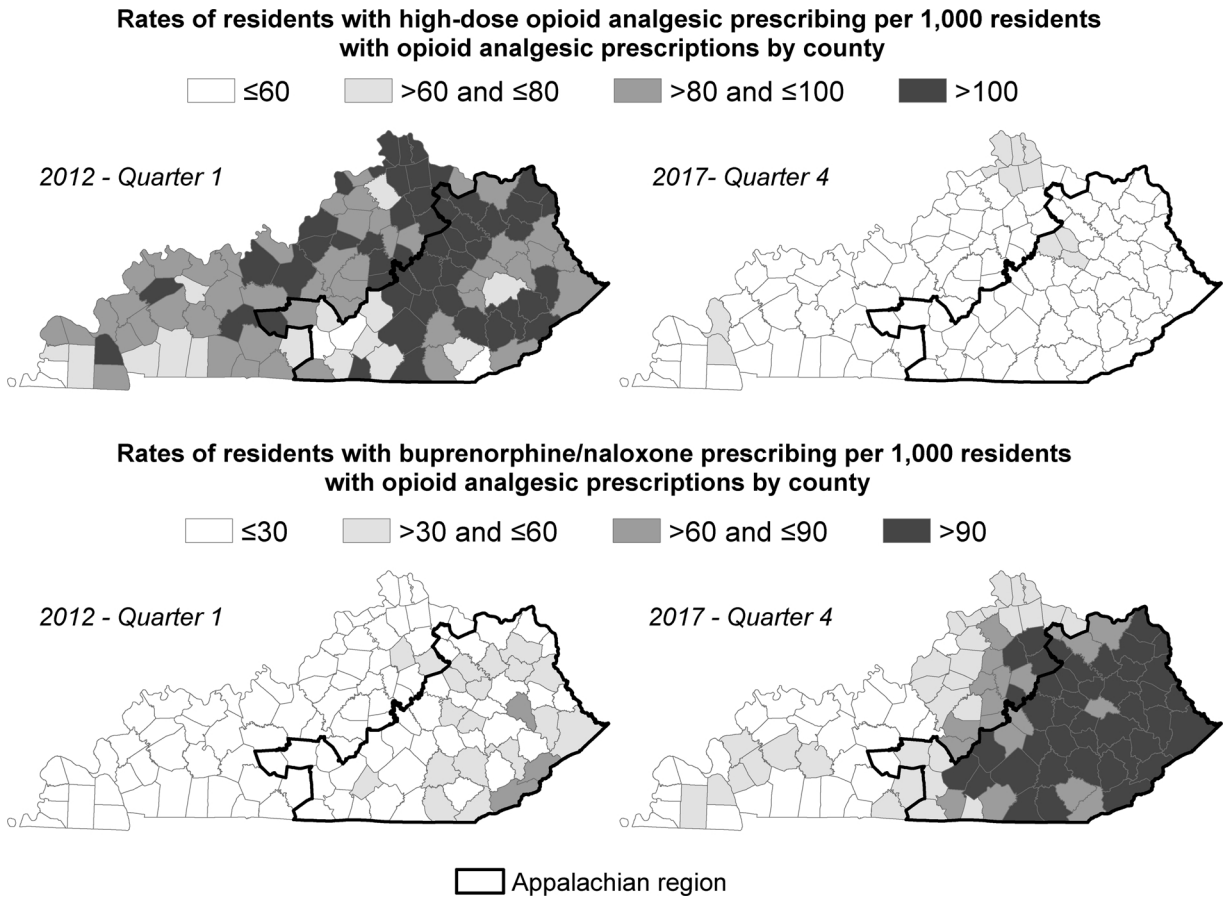
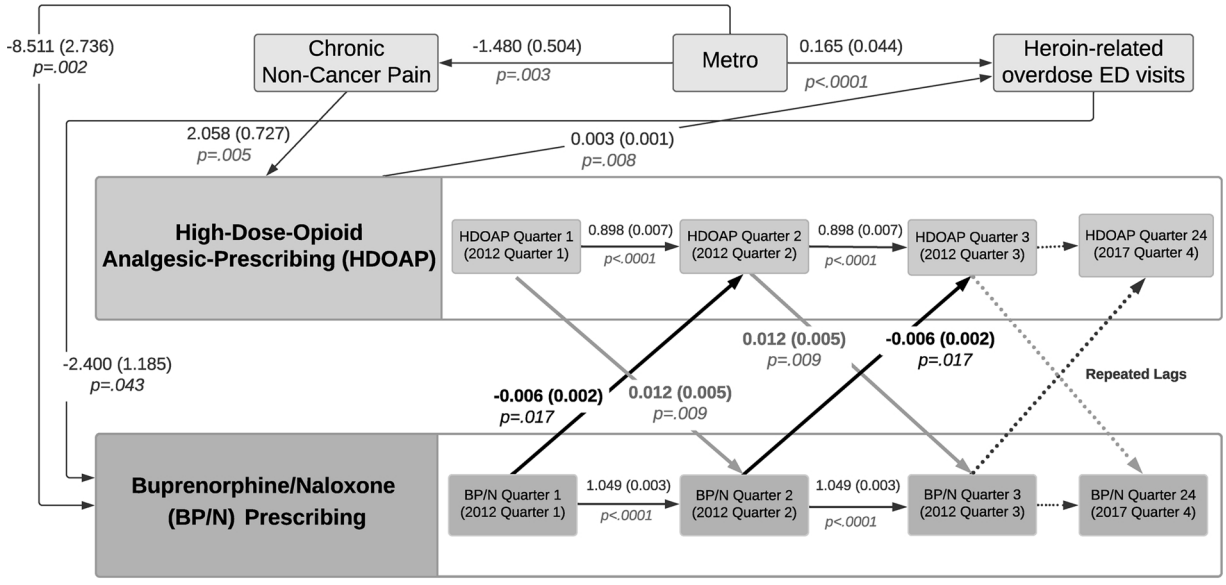



**Fig. 3.** Quarterly Rates of High-Dose Opioid Analgesic Prescribing and Buprenorphine/Naloxone Prescribing by County, Kentucky 2012 and 2017.

and remains the same for any subsequent lag of measures. This means that a one-unit increase in the buprenorphine/naloxone prescribing rate in an earlier quarter was associated with a significant, 0.006/1,000 reduction in the high-dose OA prescribing rate in a subsequent quarter. For example, for each additional 1,000 residents with buprenorphine/naloxone prescribing in an earlier quarter, the mean change in high-dose OA prescribing was estimated to decrease by six residents in the subsequent quarter.

Table 1 shows that the size of the effect of buprenorphine/naloxone prescribing on high-dose OA prescribing was higher than the effect in the opposite direction (i.e., the effect of high-dose OA prescribing on BP/N prescribing) in terms of absolute value, -0.013 versus 0.005,




Notes: The regression coefficients for the association between HDOAP and BP/N are constrained across the 24 lags. Standard errors are given in parentheses.

**Fig. 4.** Directions With Regression Coefficient Estimates From the Final Structural Equation Model.

**Table 1**
Standardized coefficients of the reciprocal relationship between high-dose opioid analgesic prescribing and buprenorphine/naloxone prescribing.

| Direction | Standardized β Coefficient Estimate | Standard Error | 95% Confidence Interval |
|---|---|---|---|
| Buprenorphine/naloxone prescribing →High-dose opioid analgesic prescribing | −0.013 | 0.006 | −0.025; −0.001 |
| High-dose opioid analgesic prescribing → Buprenorphine/naloxone prescribing | 0.005 | 0.002 | 0.001; 0.009 |

respectively. However, because the 95% CIs for the absolute values of the estimated effect sizes overlapped (95% CI for the absolute value of the effect size for "buprenorphine/naloxone prescribing →high-dose OA prescribing": [0.001; 0.025]; 95% CI for the absolute value of the effect size for "high-dose OA prescribing → buprenorphine/naloxone prescribing": [0.001; 0.009]), we did not have enough evidence to conclude that there was a significant difference in the effect sizes of these two directions or a significantly dominant direction in the bi-directional relationship.

The autoregressive coefficient estimates of high-dose OA prescribing representing correlations of high-dose OA prescribing within time-points suggest that high-dose OA prescribing rates decreased by more than 10% per quarter ($\beta = 0.898$, $p < .0001$; Fig. 4). The autoregressive coefficient estimates of buprenorphine/naloxone prescribing rate are 1.049 ($p < .0001$; Fig. 4) for every lag, indicating that the buprenorphine/naloxone prescribing rate increased by more than 5% per quarter over the study period.

### 4.3. Other Relationships Other relationships

Metropolitan counties were associated with lower on average buprenorphine/naloxone prescribing rate (−8.511 /1,000; $p = .002$) compared with non-metropolitan counties, lower chronic non-cancer pain rates (−1.480/1,000; $p = .003$), and higher rates of heroin-related ED visits (0.165/1,000; $p < .0001$). Counties with one unit (i.e., 1/1,000) higher chronic non-cancer pain rates experienced 2.058/1,000 higher quarterly high-dose OA prescribing rates ($p = .005$). We did not find significant associations between acute traumatic injury rates or cancer death rates with high-dose OA prescribing. Every one unit (1/1,000) increase in the county quarterly high-dose OA prescribing rate was associated with a 0.003/1,000 increase in the annual heroin overdose ED visit rate ($p = .008$). A one unit increase in the annual heroin overdose ED visit rate was associated with a 2.4-unit decrease (−2.400/1,000) in the buprenorphine/naloxone prescribing rate ($p = .043$). A significant pathway from the rates of buprenorphine/naloxone prescribing to the rates of heroin-related ED visits was not observed.

In assessing the goodness-of-fit statistics of the final model, the ratio of the model chi-square to the degrees of freedom was 1.186 (1,263 degrees of freedom), RMSEA was 0.039 (90% CI: [0.031; 0.047]), and CFI and TLI were 0.992, suggesting that our model fits well.

## 5. Discussion

We found a significant reciprocal relationship between high-dose OA prescribing and buprenorphine/naloxone prescribing, after adjusting for baseline differences in socio-economic characteristics, medical indications for OAs, and heroin availability. Our study provides population-level evidence that an increase in buprenorphine/naloxone prescribing is associated with a meaningful decrease in high-dose OA prescribing. This finding agreed with our hypotheses that high-dose OA prescribing is a positive predictor of buprenorphine/naloxone prescribing, and conversely buprenorphine/naloxone prescribing is a negative predictor of high-dose OA prescribing. These results can be explained by, although not causally proven by, the fact that high-dose OA prescribing was associated with increased risk of OUD (Han et al., 2017), which can be treated effectively with buprenorphine/naloxone. There is also evidence of discontinuing prescription OAs if a person received buprenorphine/naloxone treatment for OUD (Hser et al., 2016).

Similar to nation-wide trends, our study observed an upward trend in buprenorphine/naloxone treatment in parallel with a downward trend in high-dose OA prescribing in Kentucky. Although we were not able to compare directly with previous state reports due to measurement differences (prescription level vs. patient level), these trends appear to be consistent with an increase in buprenorphine/naloxone prescriptions and a decrease in OA prescriptions during the period from 2013 to 2016 (KASPER, 2017). Specifically, we note that the increase in buprenorphine/naloxone prescribing mainly occurred in Appalachia Kentucky, which had a higher rate of high-dose OA prescribing at the start of the observation period and has been an area of the country with particularly high rates of opioid-overdose deaths (Buchanich et al., 2016). Implementation of the Drug Addiction Treatment Act of 2000 with expanded patient limits for waivered providers in Kentucky, perceived need among the medical community to provide life-saving treatment for OUD, and being an ACA expansion state which covered buprenorphine treatment (Knudsen et al., 2015), may be critical contributors to this increase, particularly when methadone treatment of OUD remained an uncovered treatment service by Kentucky state Medicaid managed care organizations. Given historically high OA prescribing rates in Appalachia, the increase in buprenorphine/naloxone treatment may be a first step for persons living in this area affected by OUD in order to reduce harms and begin the recovery process.

We report that counties with higher heroin-related ED visit rates tended to have lower buprenorphine/naloxone prescribing rates. It is possible that patients with OUD, who were residing in a county where heroin was available, may seek illicit drugs such as heroin instead of seeking OUD treatment because it is relatively inexpensive and more easily accessible than treatment (Compton and Wargo, 2018). A previous study indicated that difficulties in accessing OUD treatment may induce a shift in heroin use (Saloner et al., 2017). This result provides important evidence to support the improved availability of buprenorphine/naloxone, particularly at EDs where patients present with opioid-related harms such as overdose or injection-related infections (e.g., cellulitis). Initiating buprenorphine/naloxone treatment for the underlying OUD at the ED is not only logical but also improves linkage to ongoing outpatient care of OUD (D'Onofrio et al., 2017, 2015).

Our study also suggests that higher high-dose OA prescribing rates were associated with increased heroin-related ED visit rates at baseline (2012). In April 2012, Kentucky enacted comprehensive legislation that effectively closed rogue pain clinics or "pill mills" in Kentucky and mandated the use of the PDMP (HB1, 2012). One possible explanation is that as "doctor shopping" became more difficult, heroin became cheaper and more easily accessible, especially in communities with a large number of residents with OUD. Perhaps, the association between county rates of high-dose OA prescribing and heroin ED visits at baseline in our model reflects these changes. PDMP patient reports can help clinicians identify patients with substance use disorder and improve patient care and transitions of care (Lowry, 2018). Early identification of OUD and linkage to medication for OUD treatment is increasingly important as the illicit heroin supply now frequently contains highly potent synthetic opioids (e.g., fentanyl or fentanyl analogs), resulting in increased numbers of overdose deaths.

While data related to methadone treatment are not available due to strict confidentiality requirements governing federal opioid treatment programs that dispense methadone, PDMP data are a potential resource

to monitor and evaluate the effect of OUD treatment using buprenorphine pharmacotherapies. However, the use of PDMP data for this purpose has been limited. Our study is the first to utilize PDMP data to provide a better understanding of longitudinal effects of buprenorphine/naloxone treatment on reducing high-dose OA prescribing at a population level. In the context of needing to expand evidence-based OUD medication treatment, monitoring buprenorphine prescribing plays an important role in informing public policy demonstrating its positive impacts despite ongoing diversion concerns, guiding interventions and education, and identifying potential gaps (Lofwall and Havens, 2012; Lofwall and Walsh, 2014). This study may motivate relevant future studies or be replicated for other states. Using the cross-lagged structural equation model for multiple repeated measurements of a set of variables enabled us to examine the reciprocal relationship between buprenorphine/naloxone prescribing and high-dose OA prescribing, as well as other related temporal directionalities, which have not been reported previously in the literature. Future studies on buprenorphine/naloxone treatment expansion should take into account this bi-directional association in the context of longitudinal panel data and evaluate for public health benefits beyond reduction of high-dose OA prescribing, such as decreases in prescription-opioid overdose mortality and morbidity.

Our analyses were based on PDMP data, which represent dispensed prescriptions rather than actual utilization by patients (i.e., there is no information on whether individuals receiving dispensed prescriptions take the dispensed medication, or take the medications as prescribed), and cannot account for OA diversion. Second, to explore time-varying factors (such as chronic non-cancer pain prevalence or heroin availability) and additional pathways associated with the network of the relationship between buprenorphine/naloxone prescribing and high-dose OA prescribing, a larger sample size is required. Third, individual-level inferences cannot be made from our county-level analysis. Fourth, while Kentucky medical regulations prohibit off-label prescribing of buprenorphine/naloxone for pain, we cannot be certain that all prescriptions were in compliance with these regulations. Lastly, with the observational study, we can make assumptions about directionality, but not causality.

## Contributors

HL completed the literature search with input from SS, ML, and TRF. HL designed the study with refinement from SS. HL analyzed the data. All authors provided data interpretation. HL and SS wrote the manuscript with contribution from all co-authors. HB provided overall advice and input on methodology and statistical analysis. All authors provided substantial revision and edits of the manuscript and approved the final manuscript.

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## Declaration of Competing Interest

No conflict declared.

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugalcdep.2019.107606.

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