Drug and Alcohol Dependence 200 (2019) 34–39

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Full length article

Overdose following initiation of naltrexone and buprenorphine medication treatment for opioid use disorder in a United States commercially insured cohort

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ARTICLE INFO

Keywords:
Injectable naltrexone
Oral naltrexone
Buprenorphine
Opioid use disorder
Overdose

ABSTRACT

Background and aims: Despite the growing opioid overdose crisis, medication treatment for opioid use disorder remains uncommon. The comparative effectiveness of buprenorphine and naltrexone treatment in reducing overdose and the comparative risks of discontinuing treatment in the real world, remain uncertain. Our aim was to examine the effectiveness of medications for opioid use disorder in preventing opioid-related overdose.
Design: Retrospective cohort study
Setting: United States.
Patients: 46,846 commercially insured individuals diagnosed with opioid use disorder and initiating medication treatment between 2010 and 2016.
Measurements: Opioid-related overdose identified by International Classification of Diseases, Ninth and Tenth Revisions.
Findings: In our sample, 1386 individuals were prescribed extended-release injectable naltrexone (median filled prescriptions = 9 months), 7782 were prescribed oral naltrexone (5 months), and 40,441 were prescribed buprenorphine (19 months) at least once during follow-up. Individuals receiving buprenorphine therapy were at significantly reduced risk of opioid-related overdose compared to no treatment (adjusted hazard ratio (HR) = 0.40, 95% CI 0.35 − 0.46), while a significant association was not observed in extended-release injectable (HR = 0.74, 95% CI 0.42–1.31) or oral (HR = 0.93, 95% CI 0.71–1.22) naltrexone. We found no association with opioid overdose within four weeks of discontinuation of any medication.
Conclusion: Among commercially-insured patients who initiate medications for opioid use disorder, buprenorphine, but not naltrexone, was associated with lower risk of overdose during active treatment compared to post-discontinuation. More research is needed to understand the benefits and risks unique to each treatment option to better tailor therapies to patients with opioid use disorder.

1. Introduction

Opioid use is epidemic in the US, with overdose deaths increasing nearly 28% from 2015 to 2016, and emergency medicine systems across the country facing a growing burden of overdoses (Vivolo-Kantor et al., 2018). Expanding access to evidence-based medications for opioid use disorder (MOUDs) is a central tool to combat the epidemic (O'Donnell et al., 2017). Oral naltrexone, extended-release injectable naltrexone (XR-NTX), and buprenorphine are three Food and Drug Administration (FDA)-approved MOUDs available in office-based settings in the United States. Buprenorphine, a partial opioid agonist, dosed daily and absorbed sublingually or oral mucosally, is the most widely used of the three (Volkow et al., 2014). Oral naltrexone is dosed daily and XR-NTX is dosed monthly. They are opioid antagonists that provide a treatment option that does not generate physiologic dependence and may therefore be more acceptable to individuals and institutions not interested in receiving or offering in agonist therapy (U.S. Food and Drug Administration, 2010). Methadone has been used to treat opioid use

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https://doi.org/10.1016/j.drugalcdep.2019.02.031
Received 15 October 2018; Received in revised form 11 February 2019; Accepted 13 February 2019
Available online 03 May 2019

disorder (OUD) since the late 1960s. However, methadone for OUD is only available through federally and state-regulated clinics where treatment is typically not covered by commercial insurance, even though it is cost-saving (McCarty et al., 2010).

The comparative effectiveness of buprenorphine and naltrexone in the real world remains uncertain. Recently, two randomized-controlled trials have provided evidence of the efficacy of XR-NTX and buprenorphine to prevent opioid relapse when initiated in specific settings such as inpatient or residential detoxification programs (Tanum et al., 2017; Lee et al., 2017). When considering comparative effectiveness of buprenorphine and naltrexone in an "as treated" manner, both studies found similar efficacy. In intention to treat analyses of the X:BOT trial, however, buprenorphine was superior to naltrexone, due to fewer individuals initiating naltrexone treatment (Lee et al., 2017). While neither of these previous trials found a difference in overdose rates, overdose was a secondary outcome with limited follow-up, and the overdose risk over an individual's treatment trajectory remains unknown. Randomized studies are important because randomization addresses issues of confounding, but rigorous inclusion and exclusion criteria and the specific treatment settings where they are conducted limit their generalizability. In addition, the standardized care provided in a clinical trial does not reflect the heterogeneity of OUD treatment in the real world.

Medical claims provide an additional tool with which to analyze MOUD outcomes. For example, a longitudinal analysis of commercial insurance claims data found that discontinuation was significantly higher among those with OUD initiated on XR-NTX compared to buprenorphine products, with over half of XR-NTX patients discontinuing after the first injection (Morgan et al., 2018; Larochelle et al., 2018). This finding is concerning given a recent analysis of adverse events reported to the FDA suggesting that discontinuation of XR-NTX may be followed by a period of elevated overdose risk, possibly due to the loss of opioid tolerance (Saucier et al., 2018). For methadone and buprenorphine, a meta-analysis demonstrated substantially elevated mortality risk in the initial four weeks after discontinuation (Sordo et al., 2017). Overdose risk during discontinuation time has not been investigated for naltrexone and questions remain, about the length of the period of elevated risk. These concerns can be assessed by analyzing medical claims data.

We used a large, nationally representative database of commercially insured individuals initiating MOUDs to evaluate overdose risk during periods on and off treatment. This retrospective cohort study described the overdose experience of individuals from the point of their initial treatment. It was designed to inform treatment decisions given three FDA-approved, evidence-based medication options at the time of treatment initiation while incorporating changes in exposure over time. MOUDs prescribed through outpatient, office-based treatment settings were buprenorphine (both mono-formulated and co-formulated with naloxone), oral naltrexone, and XR-NTX. We excluded methadone maintenance therapy because it is not reliably included in commercial claims data. We examined population rates of overdose on and off these MOUD treatments, compared the protective effects of these treatments on opioid-related overdose risk, and investigated whether overdose risk rises during the four weeks after discontinuation of these medications.

2. Methods

2.1. Design, population, and data collection

We assembled a cohort of individuals with OUD who initiated MOUD in the Truven Health Analytics MarketScan Commercial Claims Database (MarketScan) for the years 2010 − 2016. MarketScan is an insurance claims-based dataset that includes ambulatory and inpatient visits, laboratory and diagnostic testing, and outpatient pharmacy claims, from a nationally representative sample of the U.S. commercially insured population (Truven Health Analytics, 2015).

Inclusion criteria included: 1) evidence of a diagnosis of OUD based on ICD-9 or ICD-10 codes in medical claims; and 2) prescription of naltrexone or buprenorphine (Substance Abuse and Mental Health Services Administration, 2012). We chose to include mono-buprenorphine products (including transdermal buprenorphine which is not FDA-approved for treatment of OUD) both to capture those who may be prescribed mono-buprenorphine for cost or medical (such as pregnancy or sensitivity to naloxone) reasons and because we restricted our sample to OUD-diagnosed persons, so were reasonably confident that the buprenorphine was treatment for OUD (Lanier et al., 2007). We determined which ICD-9 and ICD-10 codes to include based on expert review and previous literature (Cochran et al., 2014) (Appendix Table 1 in Supplementary material). We excluded individuals who had no evidence of having OUD prior to their initial MOUD prescription to avoid including individuals who were prescribed medications for other conditions (for example, oral naltrexone is also prescribed for alcohol use disorder).

2.2. Measures

We identified overdose events based on the presence of relevant ICD-9 and ICD-10 codes (Appendix Table 1 in Supplementary material) on an inpatient or outpatient medical claim. This outcome includes overdoses for which a medical claim was made, typically meaning a patient received care for an overdose at a hospital. Thus, the outcome measure includes both individuals experiencing a non-fatal overdose, as well as those treated for a fatal overdose at a hospital. Over the course of the observation period, we measured whether an individual was currently receiving each of the three MOUD treatments (XR-NTX, oral naltrexone, and buprenorphine) in a given week (Appendix Table 2 in Supplementary material). It was possible for an individual to be prescribed different medications over the course of the study period, and we calculated the person-time accrued on each medication, and the time spent on no medication. We categorized MOUDs based on national drug codes (Micromedex Solutions, 2018) and we employed outpatient prescription drug data to determine the date on which individuals filled MOUD prescriptions and the days' supply in each prescription. We then used the date of fill and days' supply to characterize an individual's MOUD prescription coverage both in the current week and over the past four weeks in order to determine those currently prescribed MOUD as well as those who recently discontinued. We used a four-week window for recent discontinuation based on a meta-analysis of overdose risk following release from prison (and opioid detoxification) (Merrall et al., 2010). Individuals began contributing follow-up time at their initial MOUD prescription, defined as the earliest known OUD therapy in the data preceded by at least three months without any OUD medication. In the time-to-event analysis, individuals ceased contributing time when they experienced an overdose or were censored at the end date of the database (December 31, 2016), or at exit from their commercial insurance plan.

2.3. Analyses

To broadly understand usage and overdose patterns in our cohort, we first calculated the unadjusted overdose rate for each of four treatment status categories – current XR-NTX, current naltrexone, current buprenorphine, and off treatment. Our four treatment status categories reflect the natural history of OUD, which as a chronic, relapsing illness features patients moving on and off treatment over time. We calculated the total person-time in each category and the total number of opioid-related overdoses occurring in each category. For each category we calculated the incidence rate of overdose per 100 person years and associated 95% confidence interval.

We then developed a Cox hazards model on a weekly timescale to predict time from MOUD initiation to first opioid related overdose as a function of medication type, both currently prescribed and recently

discontinued within the previous four weeks. Our previous work has demonstrated that significant demographic differences exist among individuals initiating one of the three medication treatments (Morgan et al., 2018), so we summarized these differences in a descriptive table and controlled for this confounding by incorporating these characteristics in the hazards model. The Cox model controlled for demographic and clinical covariates including an individual's sex, age, and region of residence (Northeast, Midwest, South, West); type of commercial insurance coverage (Preferred Provider Organization (PPO), Health Maintenance Organization (HMO), Point-of-Service (POS), other); whether they were the primary plan holder, covered as a spouse, or covered as a dependent; evidence of another substance use disorder (including alcohol, amphetamines, antidepressants, cannabis, cocaine, hallucinogens, or sedatives) identified using ICD-9 and ICD-10 diagnosis codes; polypharmacy defined as evidence of concurrent prescription of sedating and stimulating drugs (gabapentin, benzodiazepines, and others, see Appendix Table 3 in Supplementary material); and, whether an insurance claim indicated that an individual had been seen at a substance use treatment facility at any time during the observation period. This yielded the adjusted rate of opioid-related overdose for each medication type.

3. Results

The cohort included 46,846 individuals with 72,215 person-years of follow-up, an average of 1.5 years of follow-up time per person. Buprenorphine was the most commonly prescribed (N = 40,441 individuals contributing 29,628 person-years and a median length of filled prescriptions of 9 months) followed by oral naltrexone (N = 7782 individuals contributing 1617 person-years, and a median of 5 months of filled prescriptions) and injectable naltrexone (N = 1386 individuals contributing 390 person-years and a median of 9 months of filled prescriptions). Some individuals received more than one type of medication during the study period. Descriptive statistic of the cohort overall and by drug initiated are presented in Table 1. The median age of an individual in our cohort was 29 (25th percentile = 23, 75th percentile = 42), and 62% were male. In this commercially insured population, 38% were the primary insurance beneficiaries (covered through an employer-sponsored plan), 22% were covered as spouses, and 40% were the children or other dependents of the primary beneficiary. There were 1805 individuals who experienced 2755 opioid-related overdoses during the study period. Each individual in the cohort began follow-up while contributing time to current MOUD treatment, but discontinuation was common leading to 40,580 person-years of non-medication use time.

3.1. Overall overdose rates

We found 2020 opioid-related overdoses that occurred while individuals were not on treatment, leading to an unadjusted rate of 4.98 overdoses per 100 person years (95% CI, 4.79–5.22). Those identified as taking buprenorphine products based on their prescription fill date experienced 620 overdoses for a rate of 2.08 overdoses/100 PY (95% CI 1.94–2.26), which was significantly lower than the rate for those not on treatment (Fig. 1). There were fewer events and less follow-up time associated with XR-NTX and oral naltrexone. With 15 overdose events, those on XR-NTX had a rate of 3.85 overdoses per 100 PY (95% CI 2.31–6.37) and those on oral naltrexone experienced 100 events for a rate of 6.18 overdoses per 100 PY (95% CI 5.08–7.52). The overdose incidence rates for the 4-week discontinuation periods were 3.86 (95% CI 3.36–4.23), 10.46 (95% CI 6.40–17.06), and 10.96 (95% CI 8.82–13.63) overdoses per 100 person-years for buprenorphine, XR-NTX, and oral NTX, respectively. The overdose rates for those on either naltrexone product were not significantly different from the rate of those not on treatment.

3.2. Cox-adjusted overdose risk

In the Cox hazards model, we found that overdose risk varied by the type of OUD therapy prescribed after adjusting for other covariates (unadjusted results are presented in Appendix Table 4 in Supplementary material). Those currently on buprenorphine therapy were at significantly reduced risk of experiencing an overdose in that same week compared to no treatment (adjusted hazard ratio (HR) = 0.40, 95% CI 0.35 − 0.46). In comparison, current treatment with either XR-NTX or oral naltrexone was not significantly protective against overdose (HR = 0.74, 95% CI 0.42–1.31 and HR = 0.93, 95% CI 0.71–1.22, respectively) (Table 2). We did not detect a significant effect on overdose risk of recently discontinuing any of the MOUDs within the past four weeks (HR = 1.08, 95% CI 0.91–1.28 for recently discontinuing buprenorphine, HR = 1.50, 95% CI 0.83–2.73 for XR-NTX, and HR = 1.15, 95% CI 0.84–1.57 for oral naltrexone) compared to no treatment (Table 2).

Several clinical and non-clinical covariates were also predictive of experiencing an opioid-related overdose. Being prescribed a polypharmacy medication during a given week or being seen at a substance use treatment facility during the study period were both associated with an increased risk of overdose (HR = 1.52, 95% CI 1.38–1.67 and HR = 1.86, 95% CI 1.66–2.07). A concurrent diagnosis for another substance use disorder was also associated with an increased risk of overdose, including alcohol (HR = 1.33, 95% CI 1.20–1.47), cannabis (HR = 1.29, 95% CI 1.16–1.44), cocaine (HR = 1.62, 95% CI 1.45–1.82), and sedatives (HR = 1.46, 95% CI 1.31–1.63). The older an individual, the less likely he or she was to overdose (HR = 0.98 for each year of age, 95% CI 0.97 − 0.99), and being a child or other dependent of a primary beneficiary was associated with a higher risk of overdose (HR = 1.83 relative to the primary beneficiary, 95% CI 1.51–2.22) even after controlling for age. Finally, we found evidence of geographic variation in overdose risk, with patients in the Northeast (HR = 1.31, 95% CI 1.14–1.49) and Midwest (HR = 1.76, 95% CI 1.55–2.00) at a higher risk of overdose relative to individuals in the South.

4. Discussion

We conducted a real world, longitudinal analysis of 46,846 commercially insured individuals with OUD who initiated naltrexone or buprenorphine treatment. Notably, 40% of these individuals were children or other dependents of the primary beneficiary, providing a sample with a broad age range and a mix of employed adults and youth (many of whom were likely to be unemployed and/or in school). In this population, buprenorphine was the only medication significantly associated with a reduced risk of an opioid-related overdose. We did not detect a significant association with overdose from either naltrexone formulation. We did not find strong evidence of a higher risk of overdose within four weeks after discontinuation of either naltrexone or buprenorphine.

Our finding that being on naltrexone treatment was not protective against overdose may be because person-time accumulated on naltrexone was much less than that on buprenorphine. Thus, the confidence intervals around the protective effect of naltrexone were large. With additional follow-up time and greater utilization of naltrexone, we might have found a protective effect for naltrexone compared to no treatment. Given that XR-NTX is delivered as a fixed-dose, we do not expect any overdoses compared to other MOUDs, where while we know an individual picked up a prescription, daily adherence is not known. While our sample of 15 overdoses on XR-NTX precludes a detailed analysis of timing, future work investigating when overdoses on XR-NTX occur relative to dosing could inform treatment decisions and whether re-dosing earlier than 30 days may be appropriate. This is particularly important given the increasing presence of fentanyl, which may make it possible to override the blockade produced by XR-NTX, especially in the third or fourth week after dosing. Additionally, every

Table 1
Descriptive characteristics of a cohort of individuals initiating medication treatment for opioid use disorder between 2010 and 2016.

	All initiations		XR-NTX first initiations[a]		Oral naltrexone first initiations[a]		Buprenorphine first initiations[a]	
Variable	n	%	n	%	n	%	n	%
Total	46,566	100%	863	100%	6,357	100%	39,346	100%
Clinical characteristics								
Polypharmacy, ever								
Yes	38,701	82.6%	650	75.3%	5,773	90.8%	32,278	82.0%
No	7,865	16.8%	213	24.7%	584	9.2%	7,068	18.0%
Admitted to detox, ever								
Yes	8,477	18.1%	171	19.8%	1,322	20.8%	6,984	17.8%
No	38,089	81.3%	692	80.2%	5,035	79.2%	32,362	82.2%
Concurrent substance use disorder diagnosis								
Alcohol	10,490	22.4%	339	39.3%	2,970	46.7%	7,181	18.3%
Amphetamines	2,799	6.0%	98	11.4%	592	9.3%	2,109	5.4%
Cannabis	5,417	11.6%	131	15.2%	998	15.7%	4,288	10.9%
Cocaine	3,955	8.4%	117	13.6%	776	12.2%	3,062	7.8%
Hallucinogens	315	0.7%	14	1.6%	70	1.1%	231	0.6%
Sedatives	5,883	12.6%	148	17.1%	1,149	18.1%	4,586	11.7%
Non-clinical characteristics								
Age, mean (SD)	33.0	12.1	30.5	11.5	32.3	12.6	33.2	12.0
Sex								
Male	29,028	62.0%	561	65.0%	3,641	57.3%	24,826	63.1%
Female	17,538	37.4%	302	35.0%	2,716	42.7%	14,520	36.9%
Relation to primary beneficiary								
Employee	17,830	38.1%	256	29.7%	2,098	33.0%	15,476	39.3%
Spouse	10,121	21.6%	129	14.9%	1,236	19.4%	8,756	22.3%
Child	18,615	39.7%	478	55.4%	3,023	47.6%	15,114	38.4%
Region								
South	16,437	35.1%	333	38.6%	2,173	34.2%	13,931	35.4%
Midwest	9,853	21.0%	127	14.7%	1,376	21.6%	8,350	21.2%
Northeast	10,621	22.7%	245	28.4%	1,627	25.6%	8,749	22.2%
West	8,382	17.9%	147	17.0%	1,094	17.2%	7,141	18.1%
Unknown	1,273	2.7%	11	1.3%	87	1.4%	1,175	3.0%
Insurance type								
PPO	28,561	61.0%	571	66.2%	3,793	59.7%	24,197	61.5%
HMO	5,160	11.0%	67	7.8%	660	10.4%	4,433	11.3%
POS	3,122	6.7%	54	6.3%	443	7.0%	2,625	6.7%
Other	9,723	20.8%	171	19.8%	1,461	23.0%	8,091	20.6%

XR-NTX = extended-release injectable naltrexone; SD = standard deviation; PPO = Preferred Provider Organization; HMO = Health Maintenance Organization; POS = Point-of-Service.

[a] This table presents descriptive characteristics upon entry into the cohort – the first initiation. The stratified count of medications is lower than the total number of individuals prescribed a given medication over the entire study period (reported in the results, e.g. 863 persons initiating XR-NTX vs. 1386 persons contributing XR-NTX person time over the course of the study) as some individuals switched medications after discontinuing the initial medication.

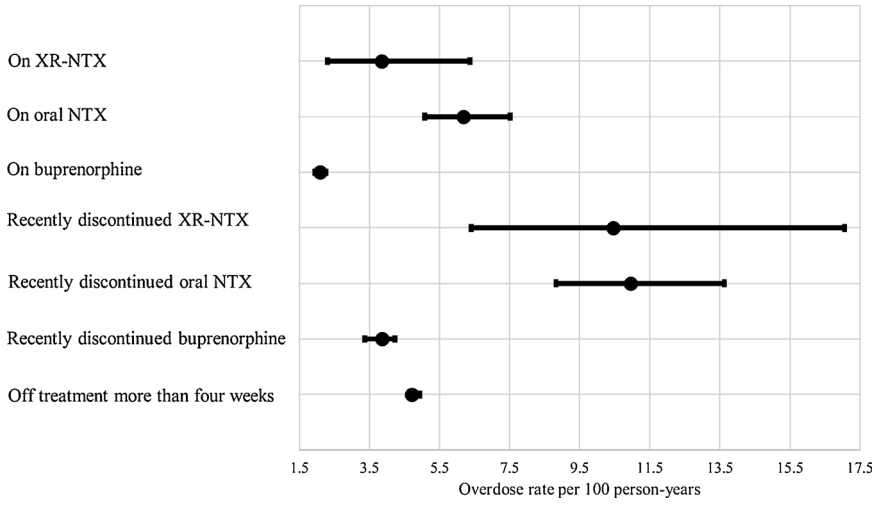

Fig. 1. Unadjusted overdose rates are calculated for time on and off treatment as overdose events per 100-person years. There were 1,683 overdoses during 35,776 person-years spent off treatment (not counting the first four weeks after MOUD discontinuation) for a rate of 4.70 per 100-person years (95% CI 4.48-4.93). There were 15 overdoses observed while on XR-NTX, 100 while on oral NTX, and 620 while on buprenorphine during 390, 1,617, and 29,628 person-years, respectively, resulting in overdose rates of 3.85 per 100 person-years (95% CI 2.31-6.37) while on XR-NTX, 6.18 per 100-person years while on oral naltrexone (95% CI 5.08-7.52), and 2.09 per 100-person years while on buprenorphine. In the first four weeks after MOUD discontinuation, there were 16 overdoses among those discontinuing XR-NTX, 81 among those discontinuing oral NTX, and 200 among those discontinuing buprenorphine over 153, 739, and 5,188 person-years, respectively, resulting in overdoses rates of 10.46 per 100 person-years after discontinuing XR-NTX (95% CI 6.40-17.06), 10.96 per 100 person-years after discontinuing oral NTX (95% CI 8.82-13.63), and 3.86 after discontinuing buprenorphine (95% CI 3.36-4.23). MOUD = medications for opioid use disorder; XR-NTX = extended-release injectable naltrexone; NTX = naltrexone; CI = confidence interval.

Table 2
Modeling the effect of MOUD on overdose in a given week.

Parameter	Adjusted hazard ratio	95% confidence interval		p-value
Treatment				
XR-NTX	0.74	0.42-	1.31	0.31
Oral naltrexone	0.93	0.71-	1.22	0.60
Buprenorphine	0.40	0.35-	0.46	< 0.01
Discontinued XR-NTX within 4 weeks	1.50	0.83-	2.73	0.18
Discontinued oral naltrexone within 4 weeks	1.15	0.84-	1.57	0.38
Discontinued buprenorphine within 4 weeks	1.08	0.91-	1.28	0.36
No MOUDs within 4 weeks	*Reference*			
Clinical characteristics				
Polypharmacy				
Yes	1.52	1.38-	1.67	< 0.01
No	*Reference*			
Seen at a substance use treatment facility				
Yes	1.86	1.66-	2.07	< 0.01
No	*Reference*			
Concurrent substance use disorder diagnosis				
Alcohol	1.33	1.20-	1.47	< 0.01
Amphetamines	1.00	0.87-	1.14	0.97
Cannabis	1.29	1.16-	1.44	< 0.01
Cocaine	1.62	1.45-	1.82	< 0.01
Hallucinogens	1.04	0.77-	1.41	0.79
Sedatives	1.46	1.31-	1.63	< 0.01
Non-clinical characteristics				
Age (in years)	0.98	0.97-	0.99	< 0.01
Sex				
Male	*Reference*			
Female	0.95	0.86-	1.05	0.28
Relation to primary beneficiary				
Employee	*Reference*			
Spouse	1.15	0.95-	1.38	0.15
Child	1.83	1.51-	2.22	< 0.01
Region				
South	*Reference*			
Midwest	1.76	1.55-	2.00	< 0.01
Northeast	1.31	1.15-	1.49	< 0.01
West	1.04	0.89-	1.21	0.64
Unknown	0.68	0.42-	1.13	0.14
Insurance type				
PPO	*Reference*			
HMO	1.11	0.96-	1.28	0.16
POS	0.96	0.79-	1.15	0.64
Other	1.07	0.95-	1.20	0.28

MOUD = medications for opioid use disorder; XR-NTX = extended-release injectable naltrexone; PPO = Preferred Provider Organization; HMO = Health Maintenance Organization; POS = Point-of-Service.

individual entered the cohort with initiation of MOUD treatment in order to understand the treatment and overdose experience of those starting MOUDs. We compared the protective effect of each treatment to being off treatment, but off treatment in this setting was different from individuals who use opioids and are naïve to MOUD treatment. For example, even if individuals discontinue medication, the experience of treatment may confer benefits that reduce future overdose risk such as risk reduction education from the provider, though these benefits have not been demonstrated clearly in other studies. Individuals with OUD who are not seeking treatment may have an even higher overdose risk.

There is a concern about a potentially higher overdose risk following discontinuation of XR-NTX due to a loss of tolerance that is not present for those discontinuing opioid agonists such as buprenorphine (Morgan et al., 2018). We addressed this concern in the analysis by including time-varying indicators of whether an individual had been on an MOUD within the previous four weeks. We did not find conclusive evidence of elevated risk in this period, though the confidence intervals around these estimates were wide. Additionally, there is uncertainty regarding the duration of this elevated risk. The medication guide for XR-NTX, explicitly warns about this "rebound risk" of overdose, but does not describe a particular period of risk (Saucier et al., 2018). This risk may also be present for oral naltrexone, which is cleared from the system after just 24 h and may leave patients with low opioid tolerance. As in our previous work, we found a substantial group of individuals prescribed oral naltrexone, given a systematic review that determined oral naltrexone provides no benefit over placebo (Minozzi et al., 2011). Oral naltrexone may an attractive option for providers who may not have the staff or resources to provide injections or for patients who prefer taking an oral antagonist. More evidence is required to fully understand why patients are treated with oral naltrexone. We believe the risk after discontinuation warrants further study as it is a concern unique to naltrexone, and is particularly important as interventions beginning in controlled settings, such as correctional facilities or substance use treatment facilities, are considered.

We identified several other variables associated with overdose that are important when considering a comprehensive approach to the opioid crisis. First, our ability to examine polypharmacy is a strength of the analysis, and our finding that polypharmacy is significantly associated with an elevated risk of overdose suggests that a deeper analysis of the mechanism of this effect – including the types of polypharmacy and the duration of prescriptions – may be warranted and would complement the existing literature detailing the risk posed by polypharmacy (Kim et al., 2017; Turner and Liang, 2015; Park et al., 2015). Next, we find that concomitant substance use disorders predict higher overdose risk, including cannabis use disorder. Other research has found that expansion of cannabis access through medicalization is associated with a *decrease* in opioid-related overdose mortality (Bachhuber et al., 2014), and future research should explore the relationship between cannabis use as a substitute for opioids for chronic pain, development of cannabis use disorder, and opioid-related overdose. Our finding that dependent status is associated with an increased risk of opioid-related overdose, independent of age, is not an effect widely studied and suggests that there may be another group of emerging adults at higher risk of overdose who have lost insurance coverage after aging out of parental coverage. This finding warrants consideration of how insurers support families of dependents with OUD, including dependents who may need to transition from parental coverage to Medicaid in their late twenties. Finally, while we were not able to identify the substances linked to each overdose event, the higher overdose risk in the Northeast and Midwest compared to the South may be partially attributable to the greater penetration of fentanyl in specific illicit opioid markets (Gladden et al., 2016).

Our nationally representative data represent the largest population studied for MOUDs and overdose risk we are aware of to date, but there are several important limitations. First, we were unable to evaluate associations with overdose fatalities, as we cannot identify whether or not an overdose was fatal. We found that 7% of individuals exited the data within 30 days of an overdose which represents the upper limit of fatal overdose. However, individuals also exited the dataset when they dis-enrolled from an employer sponsored insurance plan, as may happen from loss of employment after relapse to active drug use. Second, these data included only individuals with commercial insurance and exclude vulnerable populations such as those incarcerated, covered by public insurance, or uninsured. These are vulnerable populations should examined in future research to assess whether our findings are replicated. We did identify an added risk among dependents, who are likely to be youth or emerging adults who are either unemployed or employed in a position that allows them to be eligible for and prefer dependent coverage. Third, we relied on administrative claims to identify OUD and overdose, which are not as detailed as medical records. Neither administrative claims nor medical records can identify undiagnosed OUD, nor overdoses that are reversed by friends or family who do not contact an emergency medical provider. In the

population of commercially insured, methadone treatment for OUD is not reliably counted in claims data. Fourth, we do not track the number of treatment attempts after initiation, so our estimate of the effect of treatment includes both individuals engaging in that treatment for the first time and those returning to treatment after discontinuation. However, we believe this captures the realistic experience of individuals with a chronic, relapsing condition engaging in treatment and discontinuation over time. Finally, we could not control for the effects of non-medication treatments, such as counseling or residential treatment, as these are not reliably recorded in our commercial outpatient claims database, as is typical of claims data. Similarly, while we can identify whether an individual visited a substance use treatment facility within the study period, we did not have access to additional information about the services provided such as length of stay.

In commercially-insured populations, fewer than one fifth of individuals diagnosed with OUD are prescribed MOUDs (Morgan et al., 2018). It is therefore important to expand the number of effective treatment options for individuals struggling with OUD. While choice is important and having options for antagonist therapy will likely expand the pool of individuals receiving treatment, this study raises the question as to whether all MOUD options are equally effective at preventing overdoses. The relatively small sample of individuals on XR-NTX in our cohort makes estimating the associations between overdose and XR-NTX treatment and discontinuation challenging, but the lack of clear evidence of a protective effect of naltrexone compared to no therapy among those previously treated with MOUDs, is useful information for patients and prescribers. Increased access and use of MOUDs is critical to addressing the opioid overdose epidemic. This access needs to be coupled with a clear understanding of the risks and benefits of each MOUD in order to tailor treatment to an individual patient's needs.

Role of funding source

This study was funded in part by the National Institute on Drug Abuse (P30DA040500 and R01DA046527). Funder had no role in design or conduct of the study.

Contributions

JRM, AYW, and BPL conceived of the topic. JRM performed all statistical analyses. All authors contributed to substantial editing of the manuscript. All authors approved the final article.

Conflict of interest

Authors have no conflicts to declare.

Acknowledgments

The authors would like to thanks CHERISH reviewers Sean Murphy and Brandon Aden for their helpful comments.

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.2019.02.031.

References

Bachhuber, M.A., Saloner, B., Cunningham, C.O., Barry, C.L., 2014. Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999–2010. JAMA Intern. Med. 174, 1668–1673.

Cochran, B.N., Flentje, A., Heck, N.C., Van Den Bos, J., Perlman, D., Torres, J., Valuck, T., Carter, J., 2014. Factors predicting development of opioid use disorders among individuals who receive an initial opioid prescription: mathematical modeling using a database of commercially-insured individuals. Drug Alcohol Depend. 138, 202–208.

Gladden, R.M., Martinez, P., Seth, P., 2016. Fentanyl law enforcement submissions and increases in synthetic opioid-involved overdose deaths – 27 states, 2013–2014. MMWR Morb. Mortal. Wkly. Rep. 65, 837–843.

Kim, T.W., Walley, A.Y., Heeren, T.C., Patts, G.J., Ventura, A.S., Lerner, G.B., Mauricio, N., Saitz, R., 2017. Polypharmacy and risk of non-fatal overdose for patients with HIV infection and substance dependence. J. Subst. Abuse Treat. 81, 1–10.

Lanier, R.K., Umbricht, A., Harrison, J.A., Nuwayser, E.S., Bigelow, G.E., 2007. Evaluation of a transdermal buprenorphine formulation in opioid detoxification. Addiction 102, 1648–1656.

Larochelle, M.R., Bernson, D., Land, T., Stopka, T.J., Wang, N., Xuan, Z., Bagley, S.M., Liebschutz, J.M., Walley, A.Y., 2018. Medication for opioid use disorder after nonfatal opioid overdose and association with mortality: a cohort study. Ann. Intern. Med. 169, 137–145.

Lee, J.D., Nunes Jr, E.V., Novo, P., Bachrach, K., Bailey, G.L., Bhatt, S., Farkas, S., Fishman, M., Gautheir, P., Hodgkins, C.C., King, J., Lindblad, R., Liu, D., Matthews, A.G., May, J., Peavy, K.M., Ross, S., Salazar, D., Schkolnik, P., Shmueli-Blumberg, D., Stablein, D., Subramaniam, G., Rotosen, J., 2017. Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial. Lancet 391, 309–318.

McCarty, D., Perrin, N.A., Green, C.A., Polen, M.R., Leo, M.C., Lynch, F., 2010. Methadone maintenance and the cost and utilization of health care among individuals dependent on opioids in a commercial health plan. Drug Alcohol Depend. 111, 235–240.

Merrall, E.L.C., Kariminia, A., Binswanger, I.A., Hobbs, M.S., Farrell, M., Marsden, J., Hutchinson, S.J., Bird, S.M., 2010. Meta-analysis of drug-related deaths soon after release from prison. Addiction 105, 1545–1554.

Micromedex Solutions, 2018. Drug Topics Red Book. online [Internet]. Available from: (Accessed 24 April 2019). http://www.micromedexsolutions.com.

Minozzi, S., Amato, L., Vecchi, S., Davoli, M., Kirchmayer, U., Verster, A., 2011. Oral naltrexone maintenance treatment for opioid dependence. Cochrane Database Syst. Rev., CD001333.

Morgan, J.R., Schackman, B.R., Leff, J.A., Linas, B.P., Walley, A.Y., 2018. Injectable naltrexone, oral naltrexone, and buprenorphine utilization and discontinuation among individuals treated for opioid use disorder in a United States commercially insured population. J. Subst. Abuse Treat. 85, 90–96.

O'Donnell, J.K., Halpin, J., Mattson, C.L., Goldberger, B.A., Gladden, R.M., 2017. Deaths involving fentanyl, fentanyl analogs, and U-47700-10 States, July-December 2016. MMWR Morb. Mortal. Wkly. Rep. 66, 1197–1202.

Park, T.W., Saitz, R., Ganoczy, D., Ilgen, M.A., Bohnert, A.S., 2015. Benzodiazepine prescribing patterns and deaths from drug overdose among US veterans receiving opioid analgesics: case-cohort study. BMJ 350, h2698.

Saucier, R., Wolfe, D., Dasgupta, N., 2018. Review of case narratives from fatal overdoses associated with injectable naltrexone for opioid dependence. Drug Saf. 41, 981–988.

Sordo, L., Barrio, G., Bravo, M.J., Indave, B.I., Degenhardt, L., Wiessing, L., Ferri, M., Pastor-Barriuso, R., 2017. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. BMJ 357, j1550.

Substance Abuse and Mental Health Services Administration, 2012. An introduction to extended-release injectable naltrexone for the treatment of people with opioid dependence. SAMHSA Advisory 11, 1–8. Accessed April 24, 2019. https://store.samhsa.gov/file/23403/download?token=p6-zsGOg.

Tanum, L., Solli, K.K., Latif, Z.E., Benth, J.S., Opheim, A., Sharma-Haase, K., Krajci, P., Kunøe, N., 2017. Effectiveness of injectable extended-release naltrexone vs daily buprenorphine-naloxone for opioid dependence: a randomized clinical noninferiority trial. JAMA Psychiatry 74, 1197–1205.

Truven Health Analytics, 2015. Truven Health MarketScan® Commercial Claims and Encounters User Guide: Data Year 2014 Edition.

Turner, B.J., Liang, Y., 2015. Drug overdose in a retrospective cohort with non-cancer pain treated with opioids, antidepressants, and/or sedative-hypnotics: interactions with mental health disorders. J. Gen. Intern. Med. 30, 1081–1096.

U.S. Food and Drug Administration (USFDA), 2010. FDA Approves Injectable Drug to Treat Opioid-Dependent Patients [Internet]. (Accessed 24 April 2019). http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm229109.htm.

Vivolo-Kantor, A.M., Seth, P., Gladden, R.M., Mattson, C.L., Baldwin, G.T., Kite-Powell, A., Coletta, M.A., 2018. Vital signs: trends in emergency department visits for suspected opioid overdoses - United States, July 2016-September 2017. MMWR Morb. Mortal. Wkly. Rep. 67, 279–285.

Volkow, N.D., Frieden, T.R., Hyde, P.S., Cha, S.S., 2014. Medication-assisted therapies–tackling the opioid-overdose epidemic. N. Engl. J. Med. 370, 2063–2066.