ADDICTION
SSA SOCIETY FOR THE STUDY OF ADDICTION
RESEARCH REPORT
doi:10.1111/add.15392

Abuse-deterrent extended-release oxycodone and risk of opioid-related harm

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ABSTRACT

Aim To establish and quantify the association between abuse-deterrent formulation (ADF) oxycodone and 1-year risk of opioid-related harm. **Design** Propensity score-matched cohort study of electronic medical records for years 2014–18, with patients followed up for 1 year after their index health-care visit. **Setting** More than 70 million patients from 56 US health-care organizations. **Participants** Patients aged 18–64 years at index health-care visit with any indication for an oral opioid analgesic, with no past 12-month history of oral oxycodone use or substance use disorder, and who were alive at the end of the 1-year follow-up (new episode of prescription oral ADF oxycodone [OxyContin], n = 45 045; new episode of non-ADF oxycodone opioid preparation, n = 1 377 359). **Measurements** International Classification of Diseases diagnoses of any opioid-related disorder or non-fatal opioid poisoning within 1 year of the index health-care visit. Pooled odds ratios (OR) with 95% confidence intervals (95% CI). **Findings** After propensity score matching, 89 802 patients with a mean age of 44 [standard deviation (SD) = 11] years (62% women, 68% white) were included. During 1-year follow-up, 1445 diagnoses of opioid use disorder or opioid poisoning occurred in the ADF oxycodone cohort (34.8/1000 person-years) and 765 occurred in the non-ADF oxycodone cohort (18.2/1000 person-years). The odds of opioid-related adverse outcomes were increased in the ADF oxycodone cohort compared with the non-ADF oxycodone opioid cohort, including for opioid use disorders (OR = 2.02; 95% CI = 1.83, 2.23) and opioid poisoning (OR = 1.64 95% CI = 1.35, 1.99). **Conclusions** Patients with a new prescription of abuse-deterrent formulation oxycodone may be at increased risk of opioid-related harm.

Keywords Abuse-deterrent formulations, cohort study, opioid use disorders, opioids, oxycodone, pharmacoepidemiology.

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Submitted 26 May 2020; initial review completed 5 August 2020; final version accepted 23 December 2020

INTRODUCTION

Opioids are widely misused, and there is a complex interplay between use of prescription opioids and illicit opioids [1,2]. For example, it has been suggested that prescription opioids can act as a gateway to illicit opioids such as heroin and fentanyl [3]. Therefore, both medical and non-medical use of opioids contribute to the substantial public health burden arising from high opioid availability.

According to global estimates, nearly 110 000 people died from an opioid overdose, and approximately 40.5 million were dependent on opioids in 2017 [4]. The United States has the highest availability of opioid analgesics and the highest rate of opioid-related deaths of Organization for Economic Co-operation and Development (OECD) countries [5,6]. In 2016, the rate of opioid-related deaths in the United States was five times higher than the OECD average (13.1 versus 2.6 per 100 000 population, respectively). Furthermore, of the 92 million US individuals who used prescription opioids in 2016, 2.1 million (2.3%) met the criteria of an opioid use disorder [7].

To address the high opioid-related public health burden, pharmaceutical companies have developed abuse-deterrent formulations of opioid analgesics (ADFs) [8]. One such Food and Drug Administration-approved opioid is a re-formulation of the extended-release oral oxycodone product OxyContin. Some studies have reported that the introduction of ADF OxyContin was associated with a decline in OxyContin abuse potential and lower rates of OxyContin-specific abuse and overdose mortality

[8–10]. However, there is currently very limited evidence available on the real-world net effectiveness of ADF opioid analgesics in reducing the substantial morbidity and mortality related to opioid misuse. By using retrospective longitudinal data available on more than 70 million US patients with linked data on electronic medical records and pharmacy data on dispensed prescription medicines, we have examined and quantified the association between a new episode of prescription ADF oxycodone (OxyContin) and 1-year risk of opioid use disorder and opioid overdose in a large sample of patients treated with oral oxycodone.

METHODS

Data

We used the TriNetX (TriNetX Inc., Cambridge, MA 02140, USA) proprietary patient repository and analytics platform to identify eligible patients between years 2014 and 2018 [11]. The TriNetX platform provided access to de-identified aggregate-level information on electronic health-care records (EHRs, including diagnoses, medical procedures and dispensed medications) of more than 70 million patients from 56 major US health-care organizations (HCOs). These HCOs are typically large academic medical centres that provide a range of health-care services, ranging from emergency, outpatient and inpatient care and including primary and preventative care, secondary and tertiary services. A single HCO typically has more than one facility, including main and satellite hospitals and outpatient clinics, and EHR data from all facilities within an HCO are available on the TriNetX platform. The EHR data available captures any care that a patient receives during a visit to a centre within the HCO, as well as any follow-up care that occurs at the same organization or any of its partner institutions. Because the data provided are EHR data, patients are included regardless of insurance status, including government-provided insurance, private insurance or uninsured patients. The quality of TriNetX data is ensured by and evaluated against pre-specified quality standards [12]. Data were accessed via the TriNetX website and analysed in September 2020 by using the TriNetX built-in query builder. All data processing was conducted using the TriNetX built-in proprietary algorithms. As a federated network, TriNetX received a waiver from the Western Institutional Review Board, because only de-identified aggregated-level information is received from the participating HCOs. All diagnoses were identified using the International Classification of Diseases (ICD), 10th revision, clinical modification (ICD-10-CM) codes, medical procedures using the ICD-10 Procedure Coding System (ICD-10-PCS) and dispensed outpatient prescription medications using the RxNorm codes (Supporting information, Table S1).

Design

The TriNetX analytics platform included a relatively large number of patients prescribed with opioid analgesics, which allowed us to study rare opioid-related outcomes. Patients were eligible if they were aged 18–64 years, had not used prescription oxycodone opioids during the past 12 months before index visit (new oxycodone episode), did not have a diagnosis for substance use disorder other than nicotine dependence during the past 12 months before the index visit and were alive for the subsequent 12 months after the index visit. The ADF oxycodone preparation included in this study was OxyContin and the non-ADF oxycodone opioid cohort consisted of patients who were prescribed either generic oxycodone or any of the following oxycodone brands Endocet, Oxaydo, Percocet, Roxicet or Roxicodone. These oxycodone preparations represented more than 90% of all identified oxycodone preparations in the data. We did not include discontinued opioid preparations or opioids prescribed to a small number of patients. All dispensed prescriptions were for outpatients, and patients with missing information were excluded from the analysis.

We divided the 5-year study period, from 1 January 2014 to 31 December 2018, into five separate consecutive 1-year blocks based on calendar time to partially control for potential unmeasured confounding by cohort and period effects in opioid prescribing and associated factors. Eligible patients were identified independently within each calendar year, and cohorts were defined and propensity score-matched separately for each calendar year block. Patients were followed-up for 12 months after their index visit.

We identified a total of 1 422 404 patients, of whom 45 045 were eligible for the ADF oxycodone cohort and 1 377 359 for the non-ADF oxycodone cohort. Before matching, patients in the ADF oxycodone cohort were, on average, older, had more often a history of substance use disorders or overdose by opioids or psycholeptics (hallucinogens) beyond the past 12 months before index visit, diagnoses of diseases of the musculoskeletal system and connective tissue, neoplasms, mood disorders, external causes of injury, long-term use of opiate analgesics, clinically managed pain conditions, any type of surgery, had a history of prescription opioid analgesics, naloxone, benzodiazepines, gabapentin or pregabalin than patients in the non-ADF oxycodone cohort (Supporting information, Table S2).

Propensity score matching

To balance the cohorts at baseline, we conducted propensity score matching for sex, age, race and all the above covariates. The TriNetX built-in algorithm used a 1 : 1

nearest-neighbour matching with a caliper of 0.1 standard deviations (SDs). Of the patients in the ADF oxycodone cohort, 99.7% (n = 44 901/45045) were successfully matched with a patient in the non-ADF oxycodone cohort. After matching, the two cohorts were successfully balanced for all the covariates, i.e. all standard differences were < 0.1 after propensity score-matching (Supporting information, Table S2). The purpose of propensity score-matching was to improve comparability of the treatment (ADF oxycodone) and control (non-ADF oxycodone) groups in relation to history of opioid exposure, opioid-related harm and for various other measured patient characteristics that could otherwise bias the comparison, including indications for prescribing opioid analgesics (i.e. type and nature of pain). Opioid exposure was triangulated by several diagnostic (ICD-10-CM) and medication (RxNorm) codes used for reimbursement purposes. Use of any prescription opioids was identified either by RxNorm (RxClass) code CN101 for 'opioid analgesics' or ICD-10-CM code Z79.891 for 'long-term (current) use of opiate analgesics': a code which can be assigned for patients continuously using opioid analgesics as prescribed but without signs or symptoms of misuse or addiction. We also matched specifically for use of prescription fentanyl, because it is a very high-potency opioid (RxCUI: 4337). For history of opioid-related harm, we used ICD-10-CM codes for 'opioid-related disorders' (F11.0–F11.9); for opioid poisoning/overdose, we used opioid-specific codes from 'poisoning by, adverse effect of and underdosing of narcotics and psychodysleptics (hallucinogens)' (T40.0–T40.4, T40.6); and an RxNorm code for naloxone (RxCUI: 7242), because it is indicated for treating opioid overdose and can be prescribed to individuals receiving high doses of opioids or who are otherwise known to be at risk for opioid-related harm.

Outcome measurement

Primary outcome measures were any opioid-related disorder (ICD-10-CM: F11.0–F11.9) and non-fatal opioid poisoning/overdose (ICD-10-CM: T40.0–T40.4, T40.6). We included only incident outcomes for each primary outcome, i.e. we included only patients who did not have a recorded history of the given outcome in their medical records. We excluded deaths from the analyses because we did not have information on causes of death, only information whether the patient had died in a given year.

Additional analyses

In Table 2, we examined different outcomes: other substance use disorders (i.e. excluding opioid-related disorders), alcoholic liver disease, major depressive disorder, head injury, and acute hepatitis B or C. Additionally, to identify potential residual confounding, we included type 2 diabetes mellitus, chronic obstructive pulmonary disease (COPD), and acute myocardial infarction as negative control outcomes. Furthermore, we conducted sensitivity analyses by study year (Supporting information, Table S3) to explore the potential effect of the study year, timing of outcome measurement (Supporting information, Table S4) to explore how the timing of outcome measurement affects the observed association, exposure to other opioids (Supporting information, Table S5) to explore the potential confounding by exposure to other opioids or crossing over between ADF oxycodone and non-ADF oxycodone cohorts early on during follow-up, and strength of oxycodone initially prescribed (Supporting information, Table S6) to indirectly explore the potential confounding by dose of oxycodone prescribed.

Statistical analysis

We calculated odds ratios (ORs) with 95% confidence intervals (CIs) for each of the five baseline years separately (2014–18) and used the Mantel–Haenszel method with random effects to obtain a weighted pooled OR during the 5-year study period. The analysis plan was not preregistered and therefore the findings could be considered exploratory rather than confirmatory.

FINDINGS

After propensity score-matching, we included 89 802 patients. Of these patients, 62% were women, 68% white, and their mean age was 44 years (SD = 11) at index visit (Supporting information, Table S2). During the 1-year follow-up, 1445 incident diagnoses of opioid use disorder or opioid poisoning occurred in the ADF oxycodone cohort (34.8/1000 person-years) and 765 occurred in the non-ADF oxycodone cohort (18.2/1000 person-years). Overall, patients in the ADF oxycodone cohort were approximately twice as likely (OR = 1.95; 95% CI = 1.78, 2.13) to receive a diagnosis for opioid use disorder or opioid poisoning within a year of the initial prescription than patients in the non-ADF oxycodone opioid cohort (Table 1). The odds of all opioid-related outcomes were increased by at least 1.6-fold in the ADF oxycodone cohort compared to the non-ADF oxycodone cohort, including for any opioid use disorder (OR = 2.02; 95% CI = 1.83, 2.23) and non-fatal opioid poisoning (OR = 1.64; 95% CI = 1.35, 1.99). Unmatched models yielded comparable results, but with higher ORs (Table 1).

Additional analyses showed that patients in the ADF oxycodone cohort were not more likely to receive incident diagnoses for various individual substance use disorder diagnoses, acute hepatitis B or C, alcoholic liver disease, head injury or major depressive disorder during the 1-year

Table 1 One-year incidence of outcomes directly attributable to opioid use before and after matching.

	ADF oxycodone			*Non-ADF oxycodone*				
	Patients	*Cases*	*IR/1000*	*Patients*	*Cases*	*IR/1000*	*OR*	*95% CI*
Before matching								
Opioid use disorder	42 237	1201	28.4	1 363 000	11 101	8.1	3.56	3.13, 4.05
Opioid poisoning	44 030	503	11.4	1 370 054	4467	3.3	3.51	2.85, 4.32
Opioid use disorder or opioid poisoning	41 528	1455	35.0	1 357 054	14 252	10.5	3.44	3.06, 3.86
After matching								
Opioid use disorder	42 178	1189	28.2	42 564	602	14.1	2.02	1.83, 2.23
Opioid poisoning	43 919	495	11.3	44 080	300	6.8	1.64	1.35, 1.99
Opioid use disorder or opioid poisoning	41 477	1445	34.8	42 028	765	18.2	1.95	1.78, 2.13

Pooled odds ratios (OR) with 95% confidence intervals (95% CI) and incidence rates (IR) per 1000 person-years for years 2014–18. Patients aged 18–64 years at index visit and alive for 12 months after index visit. Cohorts matched for age at index visit; sex; race; substance use disorders; poisoning by, adverse effect of and underdosing of narcotics and psychodysleptics (hallucinogens); mood disorders; diseases of the musculoskeletal system and connective tissue; neoplasms; pain, not elsewhere classified; surgery; external causes of injury; use of opioid analgesics; long-term use of opiate analgesics; use of fentanyl; benzodiazepines; gabapentin; pregabalin; naloxone. ADF = abuse-deterrent formulation.

Table 2 One-year incidence of comparative outcomes.

	ADF oxycodone			*Non-ADF oxycodone*				
	Patients	*Cases*	*IR/1000*	*Patients*	*Cases*	*IR/1000*	*OR*	*95% CI*
Other substance use disorders								
Alcohol	42 916	396	9.2	43 177	465	10.8	0.86	0.75, 0.98
Cannabis	43 496	443	10.2	43 713	394	9.0	1.13	0.97, 1.32
Sedative, hypnotic or anxiolytic	44 540	139	3.1	44 588	109	2.4	1.28	0.99, 1.64
Cocaine	44 434	127	2.8	44 475	120	2.7	1.06	0.82, 1.36
Other stimulants	44 504	136	3.0	44 545	141	3.2	0.96	0.67, 1.39
Hallucinogens	44 857	40	0.9	44 856	40	0.9	1.00	0.43, 2.30
Nicotine dependence	34 611	1088	31.4	35 413	1206	34.0	0.92	0.82, 1.02
Inhalants	44 034	145	3.3	44 117	114	2.6	1.21	0.90, 1.62
Other psychoactive substances	43 315	483	11.1	43 479	393	9.0	1.19	0.94, 1.49
Other outcomes potentially associated with opioid use								
Acute hepatitis B or C	44 702	52	1.2	44 704	50	1.1	1.04	0.71, 1.53
Alcoholic liver disease	44 482	89	2.0	44 648	96	2.1	0.93	0.70, 1.24
Head injury	40 941	977	23.9	39 866	1011	25.3	0.94	0.83, 1.06
Major depressive disorder, single episode	36 048	1700	47.1	37 006	1628	44.0	1.09	0.96, 1.23
Negative control outcomes								
Type 2 diabetes mellitus	38 384	726	18.9	38 761	778	20.1	0.94	0.85, 1.04
COPD	41 883	560	13.4	42 241	566	13.4	1.00	0.89, 1.12
Acute myocardial infarction	44 231	199	4.5	44 097	201	4.6	0.99	0.81, 1.20

Pooled odds ratios (OR) with 95% confidence intervals (95% CI) and incidence rates (IR) per 1000 person-years for years 2014–18. Patients aged 18–64 years at index visit and alive for 12 months after index visit. Cohorts matched for age at index visit; sex; race; substance use disorders; poisoning by, adverse effect of and underdosing of narcotics and psychodysleptics (hallucinogens); mood disorders; diseases of the musculoskeletal system and connective tissue; neoplasms; pain, not elsewhere classified; surgery; external causes of injury; use of opioid analgesics; long-term use of opiate analgesics; use of fentanyl; benzodiazepines; gabapentin; pregabalin; naloxone. ADF = abuse-deterrent formulation; COPD = chronic obstructive pulmonary disease.

follow-up compared to patients in the non-ADF oxycodone cohort. However, because the increased ORs for cannabis; sedative, hypnotic or anxiolytics; inhalants, and other psychoactive substances were each borderline statistically significant, we estimated a model where these outcomes were combined. This combined outcome showed that patients in the ADF oxycodone cohort had a higher odds of experiencing these outcomes than patients in the non-ADF oxycodone cohort (OR = 1.19; 95% CI = 1.05, 1.34). No residual confounding was detected when we examined associations between ADF oxycodone and physical health outcomes (i.e. the negative control outcomes), including type 2 diabetes mellitus, chronic obstructive pulmonary disease or acute myocardial infarction (Table 2).

Sensitivity analyses showed that the ORs for opioid-related outcomes were relatively homogeneous across study years (Supporting information, Table S3), i.e. no meaningful heterogeneity of effect was observed across study years (e.g. for opioid poisoning, for which heterogeneity was largest, measures of heterogeneity were: $\tau^2 = 0.02$; $I^2 = 42\%$; $\chi^2 = 6.92$, degrees of freedom = 4, $P = 0.14$). Sensitivity analyses by timing of outcome measurement showed that the ADF oxycodone cohort already had significantly higher odds for opioid-related outcomes 1 month after the index visit, and that this difference remained relatively constant over time until the end of follow-up at 12 months after the index visit (Supporting information, Table S4). Controlling for potential confounding by recent exposure to other opioids, by including only patients who did not have prescriptions for any opioid analgesics 6 months before the index visit and who did not cross over from their initial oxycodone cohort (ADF versus non-ADF) within 3 months of the index visit, showed that patients in the ADF oxycodone cohort were approximately three times as likely (OR = 2.96, 95% CI = 2.46, 3.55) to experience opioid-related harm within 12 months compared to patients who were initially in the non-ADF oxycodone cohort (Supporting information, Table S5). Because a single dose of OxyContin of > 40 mg strength is indicated only for patients with established opioid tolerance, we excluded patients who were initially prescribed with oxycodone preparations of 40–80 mg strength. These results showed that patients in the ADF oxycodone (OxyContin) cohort were still approximately twice as likely to experience opioid-related harm (OR = 1.86, 95% CI = 1.69, 2.03) compared to patients in the non-ADF oxycodone cohort (Supporting information, Table S6).

DISCUSSION

We examined the association between a new episode of ADF oxycodone (OxyContin) prescription and opioid-related harm over the subsequent year in 89 802 patients aged 18–64 years in the US prescribed with oxycodone-based opioids. Patients in the ADF oxycodone cohort were significantly more likely to experience opioid-related incident harm within 12 months of the initial prescription compared to patients with a new prescription of non-ADF oxycodone opioids (34.8 versus 18.2 cases per 1000 person-years, respectively). The results showed consistently that patients prescribed with ADF oxycodone were approximately twice as likely to experience opioid-related harm as were patients in the non-ADF oxycodone cohort, when taking into account various sources of confounding. Despite previous research reporting that the introduction of ADF oxycodone was associated with reduced rates of oxycodone-specific abuse and mortality [8–10], our results show that patients with ADF oxycodone prescriptions were not at reduced risk of opioid-related net harm. However, it is possible that the observed association could, at least partly, be explained by clinical selection into treatment pathways rather than ADF oxycodone itself, i.e. that ADF oxycodone (OxyContin) may have been prescribed more frequently to high-risk patients. This initial safety signal should be confirmed in other patient populations.

The 12-month incidence of opioid use disorder in our data was 2.8% in the ADF oxycodone cohort and 1.4% in the non-ADF oxycodone group. This finding is in line with a recent meta-analysis which reported a pooled incidence of 4.7% (95% CI = 2.1–10.4) among more than 310 000 patients using prescription opioids [13]. A previous study of 2 million US adults who had a past-year opioid use disorder between years 2015 and 2017 showed that 75% of these individuals had another co-occurring substance use disorder, such as nicotine dependence, alcohol use disorder, cannabis use disorder or a disorder related to the use of sedatives or hypnotics [14]. Furthermore, Blanco *et al*. found that history of any other substance use disorder increased the risk of opioid use disorder by threefold compared to no history of substance use disorder [15], and Liang *et al*. found that those who used cannabis for non-medical purposes were 2.5-fold more likely to develop opioid use disorder compared to cannabis non-users [16]. We found that, compared to patients in the non-ADF oxycodone cohort, patients who were prescribed ADF oxycodone had more frequently a history of substance use disorders. After matching, these patients were not more likely to experience incident substance use related harm, other than related to opioid use, during the 1-year follow-up than patients in the non-ADF oxycodone cohort when these diagnostic groups were analysed separately. However, a combined outcome of substance use disorders for cannabis; sedatives, hypnotics or anxiolytics; inhalants; and other psychoactive substances showed that patients in the ADF oxycodone cohort were more likely to experience these incident outcomes. This finding is in line with the previous research suggesting a generalized vulnerability to substance use disorders among those experiencing opioid-related harm [14–17].

Future research should aim to establish the underlying mechanisms for our findings, but there are several potential explanations that should be considered. First, it is possible that in our data with real-world clinical selection to treatment pathways, patients with known or suspected risk of substance use disorders [18,19] may have been selected to receive ADF oxycodone over other non-ADF oxycodone opioids because ADF oxycodone was assumed to have a reduced risk of abuse. This interpretation seems plausible, because we found that the odds of incident opioid use disorder was already increased 1 month after index visit and remained relatively constant over time until the

end of follow-up. Second, ADF opioids can only deter specific routes of abuse (e.g. injecting or snorting) and high-risk patients in the ADF oxycodone cohort may have changed their route of abuse based on this information [20,21]. Third, high-risk patients with drug-seeking behaviour in the ADF oxycodone cohort may have more frequently moved to other opioids of abuse, including heroin or fentanyl [20]. Fourth, the results may reflect the risk difference between extended- and immediate-release opioid formulations [21]. All in all, however, our results show that ADF oxycodone was initially prescribed more frequently to patients with high underlying risk for opioid-related harm than was non-ADF oxycodone. It is therefore important to more clearly understand the actual clinical rationale physicians use to prescribe ADF opioids.

Methodological considerations

Because we used retrospective data, we did not have control over treatment allocation. The results should thus be replicated prospectively. We did not have information on the primary opioid of abuse at the time of diagnosis, which limits our interpretation on the role of specific opioids. We did not have information on dose, duration of treatment or adherence, which may have confounded the observed associations. Given that only approximately one-third of those with opioid use disorder manage to maintain long-term abstinence [22], and that we did not have information on lifetime prevalence of opioid use disorders, we probably included a mix of patients with true incidence events and those with more distal history of opioid use disorders. Our results thus reflect both incident and relapse cases. By matching for various indications of opioid analgesics we aimed to control for confounding by indication, but it is possible that some residual confounding by indication remained in the models because we did not have the diagnoses for which the opioids were prescribed. We controlled for history of substance use disorders and mental health, but it is possible that there is residual confounding by unmeasured risk factors not captured by the covariates included in the models. We were able to include a large number of patients from various major US health-care organizations, but these HCOs cannot be considered as representative of all US health-care organizations, and therefore differences in factors such as patient characteristics, data quality and treatment policies with opioid analgesics across HCOs may have affected the results. Also, if patients received treatment from HCOs not participating in the TriNetX before or after the index visit, this may have introduced bias due to misclassification in exposure status or loss to follow-up for the outcomes. Because we used medical records to identify opioid-related outcomes, we only identified patients receiving treatment for these conditions. This has probably underestimated the number of patients experiencing the outcome. We focused upon new treatment episodes with ADF oxycodone to reduce bias from exposure to oxycodone before the index visit, but also because the short-term abuse potential of ADF oxycodone preparation used in this study (OxyContin) has been widely discussed in the literature [8–10]. Therefore, the association may be different among patients with recent history of oxycodone prescriptions. However, earlier research among US patients on long-term opioid analgesic therapy shows that patients rarely use immediate- and extended-release opioid preparations concurrently or switch between these two preparations over the course of a treatment period [21]. This suggests that history of oxycodone prescriptions is probably not a marked source of confounding in this study. All in all, along with the study design used to control for potential sources of bias (eligibility criteria and propensity score matching), the observed association was consistent and robust among the various additional analyses, suggesting that the association was not markedly affected by the sources of bias explored.

CONCLUSIONS

These results suggest that patients with a new prescription of ADF oxycodone may be at increased risk of opioid-related harm. In clinical practice, the term 'abuse-deterrent' could be misleading in relation to actual risk of opioid-related harm, and prescribing ADF opioids does not substitute for the close monitoring of early signs of abuse among individuals receiving these opioid preparations. Clinical guidelines should be updated for recommendations on prescribing ADF opioids [23,24]. Further research is warranted to investigate the mechanism of the observed association, and to replicate these findings in other populations.

Declaration of interests

S.L. is an employee of TriNetX Inc. T.P., J.S., P.D.Q. and S.F. have no competing interests to declare.

Acknowledgements

TP and SF were granted free access to the TriNetX Analytics network for the purposes of psychiatric research, and with no constraints on the analyses performed or the decision to publish.

Author contributions

Tapio Paljarvi: Conceptualization; formal analysis; methodology. **John Strang:** Conceptualization; methodology. **Patrick Quinn:** Conceptualization; methodology. **Sierra Luciano:** Data curation; formal analysis; methodology; resources; validation. **Seena Fazel:** Conceptualization; funding acquisition; methodology; supervision.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 Medical codes used in defining the cohorts, in propensity score matching, and in defining the outcomes.

Table S2 Characteristics of patients before and after matching.

Table S3 One-year incidence of outcomes directly attributable to opioid use by study year after matching.

Table S4 One-year incidence of outcomes directly attributable to opioid use after matching, by timing of outcome measurement.

Table S5 One-year incidence of outcomes directly attributable to opioid use after matching. Patients who did not use any opioid analgesics six months prior index visit and did not cross over between cohorts for three months post index visit.

Table S6 One-year incidence of outcomes directly attributable to opioid use after matching for patients for whom the strength of oxycodone initially prescribed at index visit was less than 40 mg.