



## ORIGINAL RESEARCH

# Prevalence and Incidence Trends for Diagnosed Prescription Opioid Use Disorders in the United Kingdom

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## ABSTRACT

**Introduction:** The prevalence of prescription opioid use disorders in the US has increased markedly in parallel with increases in opioid prescribing. Whilst an increase in opioid prescribing has also occurred in the UK, it remains unknown if there have been concurrent increases in opioid use disorders. The aim of this study was to examine national trends in the prevalence and incidence of physician-diagnosed opioid use disorders in the UK.

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**Methods:** In a retrospective electronic health care database analysis using data from the UK Clinical Practice Research Datalink (CPRD), we identified persons receiving a first opioid prescription between January 1, 2008 and December 31, 2012. Persons with an opioid use disorder were identified by Read codes assigned by patients' physicians within 6 months following an opioid prescription. We calculated prevalence and incidence rates by dividing the analysis population by the total number of patients exposed (prevalence) or the total patient-years of exposure (incidence) using the 'exact' Clopper–Pearson Binomial method.

**Results:** Our analysis included 714,699 person-years of prescription opioid exposure. The 5-year period prevalence of opioid use disorders

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was 4.61 (95% CI 4.28–4.96) per 10,000 individuals, or 0.05%. The incidence rate of opioid use disorders was of 6.51 (95% CI 5.93–7.13) patients per 10,000 patient-years exposed. When examined by study year, there was no clear suggestion of a changing trend over time. When stratified by opioid drug, trends in the incidence rate during the study were either stable (i.e., codeine and tramadol), increasing (i.e., morphine) or decreasing (i.e., dihydrocodeine).

**Conclusions:** Our study demonstrates that despite the marked increase in overall opioid prescribing in the UK in the past decade, there has not been an increase in the incidence of physician-diagnosed opioid use disorders.

**Keywords:** Abuse; Clinical Practice Research Datalink (CPRD); Dependence; Incidence; Misuse; Opioids; Opioid use disorders; Prescription; Prevalence; UK

## INTRODUCTION

The increase in the prescribing of opioid analgesics for the management of pain has been paralleled by increases in adverse outcomes associated with misuse and abuse, particularly in the United States [1]. Despite increased prescribing of opioid analgesics in Europe [2], few studies have sought to investigate the extent of this relationship [3]. In a recent review of prescription opioid use disorders by Vowles et al. [4], of the 38 studies included, only two were from Europe. Because the US is not comparable to most European countries in terms of the health care system and prescription practices [5], the strength of the relationship between prescription opioid use and subsequent risk of misuse and abuse seen in the US should not be assumed to be generalizable beyond North America.

Similar to the US, the UK has seen a marked increase in opioid prescribing in the past decade, especially of the stronger opioids [6]. In contrast to the US, however, there is limited information on the relationship between prescription opioid use and the development of opioid use disorders in the UK [4, 5]. As such,

using data from the UK Clinical Practice Research Datalink (CPRD), the largest database of anonymized, longitudinal primary care records including approximately 4.4 million active patients, we aimed to describe the characteristics of patients with a diagnosis of prescription opioid use disorders and investigate the 5-year cumulative prevalence and trends in incidence rates of prescription opioid use disorders between 2008 and 2012. Additionally, we sought to examine the prevalence and incidence of opioid use disorders stratified by the different opioids available in the UK.

## METHODS

### CPRD Database

This study was conducted using data from the UK CPRD database [7, 8]. In brief, CPRD is a computerized medical records database consisting of approximately 14 million patients, 4.4 million of which are active patients, from 674 primary care practices throughout the UK which have recorded anonymized data on clinical events, referrals to specialist and secondary care clinics, prescriptions issued in primary care and lifestyle information. The CPRD population has been shown to be representative of the UK population with regard to age, sex, and geographical distribution [9]. The validity of the diagnoses recorded in CPRD have repeatedly been demonstrated in previous studies [7, 10–12]. The present study uses the following variables recorded in UK routine general practice and which are recorded and available for public-benefiting medical research from CPRD [13]: anonymized patient identification number, age, sex, smoking status, mental health status, history of alcohol and substance abuse, and prescription medication information including specific opioid drug, dispensing date, pack size, number of packs, and prescription opioid use disorder medical codes.

This article is based on previously conducted studies, and does not involve any new studies of human subjects performed by any of the authors. Our study protocol was approved by the Independent Scientific Advisory Committee

(ISAC) for Medicines and Healthcare Products Regulatory Agency (MHRA) database research (ISAC Protocol No.: 14\_033R). For all observational research undertaken using anonymized CPRD data, ethical approval is granted by the National Research Ethics Service Committee (NRES).

### Definitions of Problematic Opioid Use Disorders and Opioid Exposure Duration

A list of medical codes (Read codes) specific for problematic opioid use disorders was created prior to study initiation. Read codes provide a hierarchical clinical coding system used in primary care in the UK for the purpose of reporting, research, decision-making, and to allow data to be shared reliably between different computer systems. Following processing and quality checking, these codes are then added to the CPRD database.

For this study, an opioid use disorder was identified by Read codes assigned by patients' physicians. Read codes identified as indicative of an opioid use disorder are provided in Table 1. Cases were included in this study if they were ascribed an opioid use disorder Read code within 6 months following an opioid prescription. If a patient was ascribed an opioid use disorder Read code but did not receive an opioid prescription in the previous 6 months, then they did not contribute to this study so as to reduce the likelihood of including potential cases resulting from illicit opioid use.

The prescription opioids available in the UK, and included in this study, categorized by opioid strength, were: codeine, dihydrocodeine, metazolinol, tramadol (weak opioids) and buprenorphine, diamorphine, dipipanone, fentanyl, hydromorphone, methadone, morphine, oxycodone, papaveretum, pentazocine, pethidine, and tapentadol (strong opioids).

Duration of opioid exposure (calculated in days) was estimated based on each prescription date and the quantity of opioid prescribed, as recorded in the CPRD database. Long-term opioid use was defined as a patient having  $\geq 3$  consecutive opioid prescriptions within any 6-month period during the duration of the study.

### Study Population

Persons receiving a first opioid prescription between January 1, 2008 and December 31, 2012 were eligible for inclusion in these analyses ( $n = 1,613,465$ ) (Fig. 1). We excluded patients who during the study period received an opioid prescription used for the purpose of substitution therapy (i.e., patients prescribed methadone powder or solution formulation, naltrexone, or buprenorphine oral or sublingual tablets of doses  $>1$ – $<8$  mg;  $n = 4021$ ) (Fig. 1). We also excluded patients ( $n = 59,137$ ) who received a first opioid prescription  $\leq 6$  months prior to the end of the study (i.e., December 31, 2012) to ensure sufficient follow-up for all persons. Following all exclusions, 1,550,307 patients were eligible for these analyses, 715 of which were identified as having been diagnosed with an opioid use disorder between January 1, 2008 and December 31, 2012. Of these 715 patients, hereon termed '*diagnosed patients*', we then identified a subgroup of "true" '*incident cases*', that is—patients who developed an opioid use disorder during the study and who had an available healthcare record  $\geq 6$  months prior to the start of the study with no evidence of a history of opioid use disorders ( $n = 465$ ).

### Statistical Analysis

Descriptive characteristics were summarized for: (1) the total population prescribed opioids who did not develop an opioid use disorder ( $n = 1,549,592$ ), (2) all *diagnosed patients* ( $n = 715$ ) and (3) *incident cases* ( $n = 465$ ) using means with SDs, medians with interquartile ranges (IQR), or frequencies.

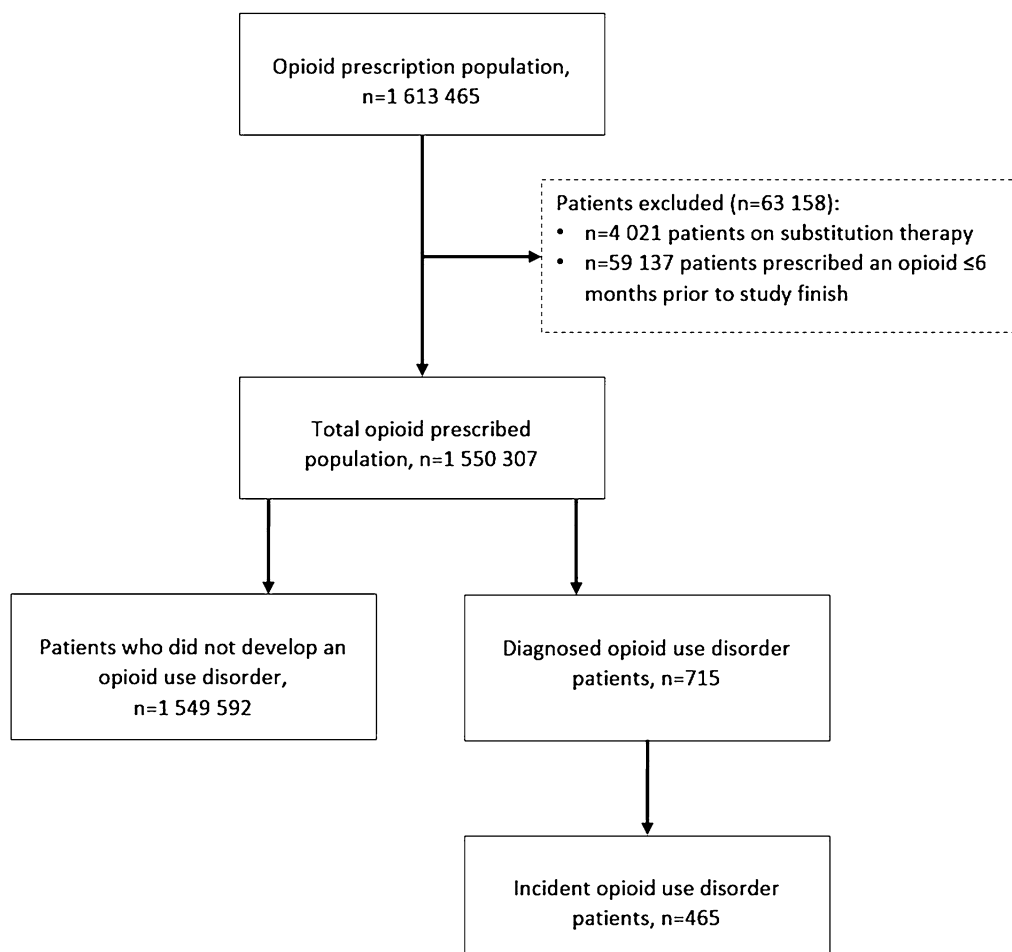
We calculated the 5-year period prevalence for *diagnosed patients* by dividing the total number of patients identified during the study (i.e.,  $n = 715$ ) by the total number of patients prescribed an opioid (i.e.,  $n = 1,550,307$ ). We also calculated the 5-year period prevalence stratified by opioid drug using the corresponding number of exposed patients as the denominator. For ease of comparison with other studies, prevalence was expressed as the number of diagnosed patients per 10,000 patients exposed.

**Table 1** Read codes used to identify opioid use disorders, CPRD: 2008–2012

Read codes	Description
E255. Nondependent opioid abuse	
E2550	Nondependent opioid abuse, unspecified
E2551	Nondependent opioid abuse, continuous
E2552	Nondependent opioid abuse, episodic
E255z	Nondependent opioid abuse NOS
E248. Combined opioid with other drug dependence	
E2480	Combined opioid with other drug dependence, unspecified
E2481	Combined opioid with other drug dependence, continuous
E2482	Combined opioid with other drug dependence, episodic
E2483	Combined opioid with other drug dependence in remission
E248z	Combined opioid with other drug dependence NOS
E240. Opioid type drug dependence	
E2400	Unspecified opioid dependence
E2401	Continuous opioid dependence
E2402	Episodic opioid dependence
E240z	Opioid drug dependence NOS (disorder)
Eu11. [X] Mental and behavioral disorders due to use of opioids	
Eu110	[X] Mental and behavioral disorders due to use of opioids: acute intoxication
Eu111	[X] Mental and behavioral disorders due to use of opioids: harmful use
Eu112	[X] Mental and behavioral disorders due to use of opioids: dependence syndrome
Eu113	[X] Mental and behavioral disorders due to use of opioids: withdrawal state
Eu114	[X] Mental and behavioral disorders due to use of opioids: withdrawal state with delirium
Eu115	[X] Mental and behavioral disorders due to use of opioids: psychotic disorder
Eu116	[X] Mental and behavioral disorders due to use of opioids: amnesic syndrome
Eu117	[X] Mental and behavioral disorders due to use of opioids: residual and late-onset psychotic disorder
Eu11y	[X] Mental and behavioral disorders due to use of opioids: other mental and behavioral disorders
Eu11z	[X] Mental and behavioral disorders due to use of opioids: unspecified mental and behavioral disorder

The 5-year incidence rate of opioid use disorders, for all opioid drugs combined, was calculated for *incident cases* by dividing the total number of *incident cases* (i.e.,  $n = 465$ ) by the related total number of years of exposure to prescription opioids specific to *incident cases* (i.e.,  $n = 714,699$  person-years), expressed as the

number of patients per 10,000 patient-years exposed. For the denominator, any time gaps in opioid prescriptions were subtracted from the number of patient-days exposed and expressed in patient-years. We additionally repeated the incidence rate calculation for *diagnosed patients* (i.e.,  $n = 715$ ) since all patients were assigned a

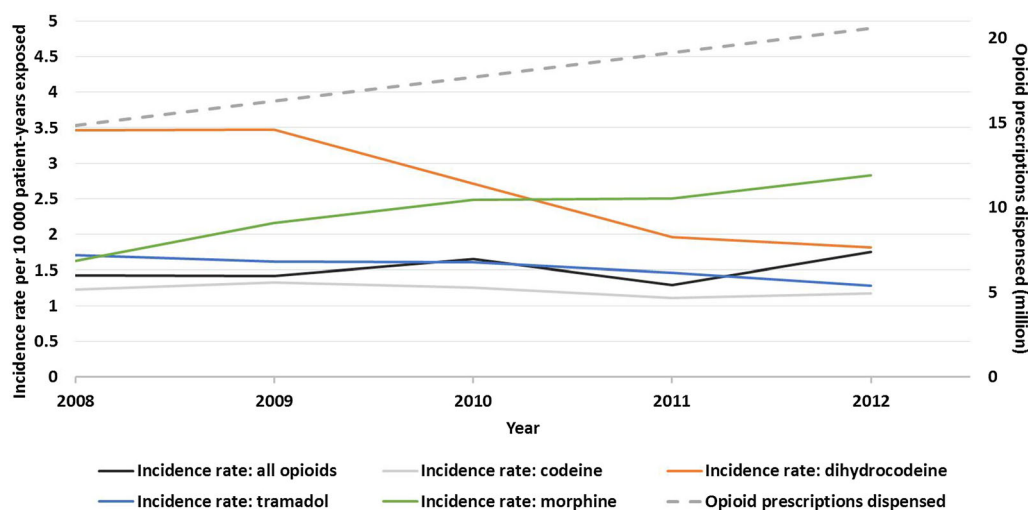


**Fig. 1** Flow diagram of persons prescribed opioids, diagnosed opioid use disorder patients, and incident cases, CPRD: 2008–2012

‘new/first’ opioid use disorder code during the study irrespective of a previous history of opioid use disorders; the denominator for this calculation was the total number of patient-years exposed for all patients (i.e.,  $n = 729,556$  person-years). In further analyses, we calculated incidence rates stratified by study year (i.e.,  $n = 5$  years) and opioid drug (i.e.,  $n = 16$ ) for *diagnosed patients* as one group to maximize study power. Consistent with the ISAC policy for MHRA database research using CPRD data [14], we do not present results for specific opioid drugs with  $\leq 5$  patients diagnosed with an opioid use disorder. Consequently, we did not calculate incidence rates and 95% confidence intervals (CIs) to determine trends for buprenorphine, oxycodone, fentanyl,

metazolinol, diamorphine, dipipanone, hydro-morphone, methadone, papaveretum, pentazocine, pethidine, and tapentadol. An individual’s contribution to patient-years of exposure (calculated in days and expressed in years) ceased at the date of diagnosis of an opioid use disorder, December 31, 2012, the date of death or the date the participant left the general practice and no longer contributed data to CPRD, whichever came first. Estimates for incidence and prevalence, and their corresponding 95% CIs, were calculated using the ‘exact’ Clopper–Pearson Binomial method.

To examine prescription opioid use in further detail, we also described: (1) the median duration from first opioid prescription to being diagnosed with an opioid use disorder, (2) the



**Fig. 2** Trends in prescription opioid use disorders, UK: 2008–2012. Data for all opioids combined is displayed for *incident cases* only (i.e.,  $n = 465$ ) whereas, to maximize study power due to small numbers, all other data is

displayed for *diagnosed patients* as one group (i.e.,  $n = 715$ ). Data source for opioid prescriptions dispensed is available from the Health and Social Care Information Centre [19]

most frequently prescribed opioid drugs at first prescription, (3) the opioid drugs which were most frequently prescribed in the 6-months prior to a diagnosis of an opioid use disorder, (4) concomitant prescription of benzodiazepines, and (5) long-term prescription opioid use. Finally, we described the frequency of use of the prescription opioid use disorder diagnostic codes. Data were expressed using means with SDs, medians with interquartile ranges (IQR) or frequencies.

All analyses were conducted using SAS 9.3 (SAS Institute Inc., Cary, NC, USA). Microsoft Excel was used in the production of Fig. 2.

## RESULTS

### Study Population

From January 1, 2008 to December 31, 2012, a total of 1,550,307 individuals received at least one opioid prescription and had a mean duration of opioid exposure of 0.47 years, culminating in 729,556 person-years of opioid exposure during the 5-year study. Of these, 715 individuals were identified as having an opioid

use disorder (*diagnosed patients*), 465 of which were identified as *incident cases*. Compared to individuals who received an opioid prescription but who did not develop an opioid use disorder, *diagnosed patients* were more likely to be younger, male and to have a history of smoking and alcohol- and substance-abuse disorders. The baseline characteristics of *incident cases* were not dissimilar to *diagnosed patients* as one group (Table 2), except for the percentage of men and the percentage of ‘other substance abuse (including alcohol)’, both of which were lower among *incident cases*.

### Prevalence

The 5-year period prevalence of opioid use disorders among *diagnosed patients* was 4.61 (95% CI 4.28–4.96) per 10,000 individuals prescribed an opioid, or 0.05%. The prevalence of opioid use disorders was highest among men and those aged 25–34 years and lowest among women and those age 55 years or older (Table 3). When stratified by opioid drug, the 5-year period prevalence (per 10,000 patients exposed) among *diagnosed patients* was highest for oxycodone (14.29; 95% CI 10.06–19.69) followed

**Table 2** Characteristics of persons prescribed opioids, diagnosed opioid use disorder patients, and incident cases, CPRD: 2008–2012

	Patients without an opioid use disorder ( <i>n</i> = 1,549,592)	Diagnosed patients ( <i>n</i> = 715)	Incident cases ( <i>n</i> = 465)
Age at first opioid prescription, years			
Mean (SD)	53.8 (19.9)	38.6 (12.6)	39.2 (13.8)
Sex, <i>n</i> (%)			
Male	635 888 (41.0)	401 (56.1)	233 (50.1)
Female	913 679 (59.0)	314 (43.9)	232 (49.9)
Unknown	25 (<0.1)	0 (0.0)	0 (0.0)
Smoking status, <i>n</i> (%)			
Current smoker	799 115 (51.6)	522 (73.0)	333 (71.6)
Previous smoker	497 273 (32.1)	118 (16.5)	92 (19.8)
Never smoker	105 592 (6.8)	14 (2.0)	11 (2.4)
Unknown	147 612 (9.5)	61 (8.5)	29 (6.2)
Previous substance and alcohol abuse, <i>n</i> (%)			
Alcohol	49 695 (3.2)	118 (16.5)	69 (14.8)
Other substances (including alcohol)	63 590 (4.1)	307 (42.9)	137 (29.5)
Mental health diagnoses, <i>n</i> (%) <sup>a</sup>			
All mental health disorders <sup>b</sup>	288 343 (18.6)	472 (66.0)	346 (74.4)
Mood affective disorders	149 888 (9.7)	203 (28.4)	153 (32.9)
Anxiety (neurotic, stress-related and somatoform disorders)	110 590 (7.1)	189 (26.4)	132 (28.4)
Behavioral syndromes associated with physiological disturbances and physical factors	20 586 (1.3)	56 (7.8)	44 (9.5)
Schizophrenia, schizotypal and delusional disorders	5 196 (0.3)	19 (2.7)	12 (2.6)
Behavioral and emotional disorders (onset usually occurring in childhood/adolescence)	2 083 (0.1)	5 (0.7)	5 (1.1)

<sup>a</sup> Patients can contribute to multiple categories

<sup>b</sup> All mental health disorders are comprised of: mood affective disorders; anxiety (neurotic, stress-related and somatoform disorders); behavioral syndromes associated with physiological disturbances and physical factors; schizophrenia, schizotypal, and delusional disorders; and behavioral and emotional disorders (onset usually occurring in childhood/adolescence)

by fentanyl (8.26; 95% CI 5.49–11.93), buprenorphine (7.98; 95% CI 5.80–10.71), morphine (6.94; 95% CI 5.37–8.83), dihydrocodeine (6.76; 95% CI 5.95–7.64), tramadol (4.32; 95% CI 3.69–5.03), and codeine (2.56; 95% CI 2.29–2.87).

**Table 3** 5-year period prevalence and incidence rates of physician-diagnosed opioid use disorders in CPRD: 2008–2012

	Prevalence [per 10,000 patients exposed (95% CI)] <sup>a</sup>	Incidence [per 10,000 patient-years exposed (95% CI)] <sup>b</sup>
Overall	4.61 (4.28, 4.96)	9.80 (9.10, 10.55)
Age group at index		
<18 years	–	–
18–24 years	7.65 (5.98, 9.63)	66.82 (52.32, 84.07)
25–34 years	13.82 (12.14, 15.65)	68.02 (59.81, 77.03)
35–44 years	8.68 (7.52, 9.96)	24.92 (21.60, 28.59)
45–54 years	4.23 (3.46, 5.12)	8.99 (7.35, 10.88)
55–64 years	2.22 (1.68, 2.87)	3.64 (2.76, 4.72)
65–74 years	0.93 (0.59, 1.41)	1.40 (0.88, 2.12)
75–84 years	–	–
≥85 years	–	–
Sex		
Male	6.30 (5.70, 6.95)	14.72 (13.31, 16.23)
Female	3.44 (3.07, 3.84)	6.87 (6.13, 7.67)

All results are for the *diagnosed patients* i.e.,  $n = 715$

<sup>a</sup> Numerator: number of diagnosed patients during study period, denominator: total number of patients with a prescription opioid during study period

<sup>b</sup> Numerator: number of *incident cases* during study period, denominator: years of exposure to prescription opioids during the study period specific to *incident cases* i.e., 714,699 person-years. Total years of exposure to prescription opioids was calculated in days but reported in whole years

– Robust prevalence and incidence rates, and their corresponding 95% CIs, could not be estimated due to too few cases (i.e., <5 cases)

### Incidence and Trends in Incidence

A total of 465 patients were identified as *incident cases*, equating to an incidence rate of 6.51 (95% CI 5.93–7.13) patients per 10,000 patient-years exposed during the 5-year study duration. When examined by study year, there was no clear evidence of a changing trend over time (Fig. 2). If all *diagnosed patients* were considered as *incident cases*, the 5-year incidence rate as one group would be 9.80 (95% CI 9.10–10.55) per 10,000 patient-years exposed. Similar to the findings for prevalence, the incidence rate of opioid use disorders, for all *diagnosed patients*, was highest among men and those aged 25–34 years and lowest among women and those age 55 years or older (Table 3). When examined

by study year for *diagnosed patients* as one group, there was a suggestion of a declining trend in the incidence of opioid use disorders over time [2.60 (95% CI 2.23–3.02) per 10,000 patient-years exposed in 2008 vs. 2.01 (95% CI 1.66–2.42) per 10,000 patient-years exposed in 2012]. As shown in Fig. 2, when stratified by opioid drug, trends in the incidence rate during the study were either stable (i.e., codeine and tramadol), increasing (i.e., morphine) or decreasing (i.e., dihydrocodeine).

### Prescription Patterns

The median duration from first opioid prescription to being diagnosed with an opioid use disorder was 0.6 (IQR 0.2–1.9) years for



*diagnosed patients* and 1.1 (IQR 0.3–2.5) years for *incident cases*. The most frequently first prescribed opioid drug was codeine (40.6%) followed by dihydrocodeine (32.0%), tramadol (15.9%), buprenorphine (4.5%), morphine (4.3%), oxycodone (2.5%), and fentanyl (1.5%). Consistent with this, the opioid drug which was most frequently prescribed in the 6 months prior to a diagnosis of an opioid use disorder was codeine (43.4%) followed by dihydrocodeine (35.8%), tramadol (23.2%), morphine (9.2%), buprenorphine (6.2%), oxycodone (5.2%), and fentanyl (3.9%). Among *diagnosed patients*, a total of 185 (25.9%) were concomitantly prescribed benzodiazepines and 593 (82.9%) were long-term prescription opioid users. Among patients without a diagnosis of an opioid use disorder, 37.8% were identified as being long-term prescription opioid users.

### Opioid Use Disorder Diagnostic Coding

The most frequently ascribed prescription opioid use disorder diagnosis codes during the study were Eu11 (Mental and behavioral disorders due to use of opioids) (68.7%) and E240 (opioid type dependence) (31.3%).

## DISCUSSION

In this large population-based cohort study of prescription opioid users followed for up to 5 years, we found that the prevalence of opioid use disorders was low at 0.05% and that there was no obvious change in the incidence of newly diagnosed opioid use disorders over the duration of the study. These findings challenge the long-standing belief that increases in prescribing of opioids necessitates an increase in the incidence of problematic opioid use disorders. Our findings also demonstrate that it is the most commonly first-prescribed opioids, and not necessarily the more potent opioids, which are most frequently associated with an opioid use disorder in the 6 months leading up to diagnosis of an opioid use disorder.

As far as we are aware, this is the first nationally representative medical records database study which has sought to investigate the

association between opioid use and risk of subsequent opioid use disorders in the UK. A recent systematic review of rates of opioid misuse, abuse, and addiction in chronic pain included a total of 38 studies conducted mostly in the primary care setting or pain clinics [4]. Across most of the calculations, rates of misuse averaged between 21% and 29% (range 95% CI 13%–38%). Of note, the majority of the included studies were not database studies and the definitions used for misuse were not consistent across studies. Furthermore, out of the 38 included studies, only two were from Europe (UK and Denmark), and neither of these studies included rates for misuse or abuse; only one of the 38 studies included an estimate of opioid abuse. A study using UK death data from the Office for National Statistics has shown an increasing trend in the number of deaths attributable to opioids from 2001 to 2011 [15]. However, the results in this study were expressed as absolute number of deaths and did not account for increases in opioid prescribing over the same duration. Furthermore, using mortality data as a proxy for rates of misuse/abuse is problematic given that many other factors other than misuse/abuse are known to influence risk of opioid overdose and death, e.g., opioid dose, co-prescription with benzodiazepines, time to administration of an opioid antagonist (i.e., naloxone) and response time by emergency services. A recent study has shown that the prevalence of past-year misuse/abuse of prescription opioids in Great Britain was 6.2% [16]. The high prevalence of opioid misuse/abuse found in that study should however be interpreted with caution since the participants were not drawn from a representative nationwide database but were purposely pre-selected for problematic use, i.e., they were aged 12–49 years, likely to use tobacco and marijuana, and were recruited from needle exchanges, homeless shelters, and parks.

In analyses stratified by opioid drug, we found that the relation between opioid use disorders and prescriptions of codeine and tramadol remained stable, whereas there was an increasing trend for morphine and a decreasing trend related to dihydrocodeine. In a previous study examining a cohort of new opioid users who

started treatment with weak opioids (i.e., codeine, tramadol, and dextropropoxyphene), Skurtveit et al. [17] found that 0.08% of patients went on to develop prescription patterns indicative of an opioid use disorder. This is consistent with our observation for morphine which, despite being highlighted as being associated with an increasing incidence during the study, was 0.05%. Skurtveit et al. did not examine associations with more potent opioids or morphine, which limits direct comparison with our findings [17]. We were not able to examine for trends in opioid use disorders for buprenorphine, oxycodone, fentanyl, metazolinol, diamorphine, dipipanone, hydromorphone, methadone, papaveretum, pentazocine, pethidine, and tapentadol due to too few cases. This is important because whilst our findings suggest that there is unlikely to be an abuse problem with these specific opioids at this time, it is not to say that this will not change in the future. This highlights the importance for ongoing surveillance of this important public health issue.

Important strengths of our study include use of a large representative population database with up to 5 years of follow-up data and diagnosis of opioid use disorders by family physicians. Additionally, use of a publicly available medical records database, inclusion of an in-depth statistical analysis strategy, and inclusion of a participant flow diagram, means that our findings can be replicated and repeated in future analyses to determine trends in opioid use disorders over extended durations of time.

There are a number of limitations of our study which warrant discussion. First, whilst a number of validation studies have demonstrated the high validity of the diagnoses codes recorded in CPRD, reporting strong measures of sensitivity and specificity [7, 10–12], this has not been undertaken for the codes related to problematic opioid use disorders. Secondly, data on medications given during hospitalization, medications provided in specialist care, and medications provided by a hospital following patient discharge are not recorded in patients' medical records. The likely impact of this will have been an underestimation of drug use and, potentially, an underestimation of the extent of opioid use disorders. Nevertheless,

under the assumption that these factors did not change during the study period, an examination of annual incidence rates does allow an accurate estimation of changes in trends over time even if the absolute number of patients is not estimated with precision. Thirdly, although we excluded patients who received an opioid prescription used for the purpose of substitution therapy, some of the opioid use disorder cases in our study may have received a diagnosis of an opioid use disorder based on illicit opioid use. This would, however, have led rather to an overestimation of prevalence and incidence. Finally, the possibility of significant under-diagnosis by patient's physicians does mean that future research using alternative data sources is needed, such as the research being conducted by the RADARs group in the US who recently examined prescription opioid misuse and abuse using multiple data sources in a complimentary analysis approach e.g., drug-diversion investigations, poison centers and substance-abuse treatment centers [18].

## CONCLUSIONS

In conclusion, despite the marked increase in overall opioid prescribing in the UK in the past decade, especially of the stronger opioids, this has not led to an increase in the incidence of diagnosed opioid use disorders. Given the potential for under-reporting of prescription opioid use disorders in CPRD, and the likely important influence that differing prescribing patterns and health care systems might play in determining the development of opioid use disorders, future longitudinal studies using different data sources across Europe are needed to further our understanding of this important public health issue.

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**Data Availability.** The dataset analyzed during the current study is available from the UK Medicines and Healthcare Products Regulatory Agency (MHRA) at: <https://www.cprd.com/dataAccess/>.

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