RESEARCH ARTICLE

Analgesic utilization in people with knee osteoarthritis: A population-based study using primary care data

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Abstract

Purpose: Osteoarthritis (OA) is a chronic painful condition that often affects large joints such as the knee. Treatment guidelines recommend paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs), and opioids. Antidepressants and anti-epileptic drugs (AEDs) are commonly prescribed for chronic noncancer pain conditions including OA, as an off-label use. This study describes analgesic utilization in patients with knee OA at population level using standard pharmaco-epidemiological methods.

Method: This was a cross-sectional study between 2000 and 2014 using data from the U.K. Clinical Practice Research Datalink (CPRD). The use of antidepressants, AEDs, opioids, NSAIDs, and paracetamol was studied in adults with knee OA using the following measures: annual number of prescriptions, defined daily doses (DDD), oral morphine equivalent dose (OMEQ), and days' supply.

Results: In total, there were 8,944,381 prescriptions prescribed for 117,637 patients with knee OA during the 15-year period. There was a steady increase in the prescribing of all drug classes, except for NSAIDs, over the study period. Opioids were the most prevalent class prescribed in every study year. Tramadol was the most commonly prescribed opioid, with the number of DDD increasing from 0.11 to 0.71 DDDs per 1000 registrants in 2000 and 2014, respectively. The largest increase in prescribing was for AEDs, where the number of prescriptions increased from 2 to 11 per 1000 CPRD registrants.

Conclusion: There was an overall increase in the prescribing of analgesics apart from NSAIDs. Opioids were the most frequently prescribed class; however, the greatest increase in prescribing between 2000 and 2014 was observed in AEDs.

KEYWORDS
analgesics, antidepressants, anti-epileptic drugs, drug utilization, osteoarthritis

INTRODUCTION

Osteoarthritis (OA) is a prevalent debilitating joint disease affecting more than 300 million people globally[1,2] that is frequently associated with joint pain and functional limitation and adversely affects physical and mental well-being, and compromises the quality of life. Additionally, OA imposes a substantial burden on social and healthcare resources.[1] OA can affect any joint; however, knees are most commonly involved and it is estimated that knee osteoarthritis (KOA) accounts for 83% of the total OA burden.[3] In England, 18.2% of people aged over 45 years (4.11 million people) have KOA, and 1.4 million of whom have severely symptomatic KOA.[4]

Management involves nonpharmacological approaches such as exercise and weight control, and pharmacological approaches including prescribing analgesics such as paracetamol, nonsteroidal anti-inflammatory

drugs (NSAID), and opioids[5] or antidepressants.[6] Although not recommended by many international guidelines, anti-epileptic drugs (AEDs) are being increasingly prescribed for chronic noncancer pain (CNCP) conditions including OA, as an off-label use.[7] Antidepressants and AEDs are centrally acting drug classes that are prescribed for neuropathic pain conditions such as diabetic nephropathy.[8] Research confirmed the involvement of complex pain mechanisms including central sensitization and neuropathic pain mechanisms in OA-related pain[9] and suggested a role of antidepressants and AEDs.

Other studies have showed that at any time, patients with OA commonly use several analgesics and for various periods of time, in their search for pain relief as currently no disease-modifying treatments are available.[10,11] However, data on prescribing prevalence and temporal changes in utilization trends of analgesics including antidepressants and AEDs in patients with KOA are sparse.

Previous drug utilization studies in patients with OA/KOA differ in the number and types of drugs included, ranging from single-class drugs, for example, opioids,[12] or prescription and OTC drugs,[13] or included drugs and nutraceuticals.[10] Additionally, data sources used to describe their utilization also varied, including national and regional surveys,[14] primary care medical records[10] or hospital records.[15] Few studies measured the annual prescription prevalence and the proportion of patients using analgesics over differing periods of time, ranging from one[16] to 22 years.[17] However, population-level data on drug utilization using standard pharmaco-epidemiological measures (eg, defined daily dose (DDD) and annual days of supply) in patients with KOA have not been comprehensively described.

In the U.K., the health care is provided through publicly funded systems in which a comprehensive range of health services is provided free at the point of use for people ordinary resident in the country. Primary care services are provided mainly by general practitioners (GPs), who also act as "gatekeepers" in providing access to secondary care.[18] People can register with the general practice near them for free and GPs are the usual first point of contact for people with symptomatic (painful) OA. Although a rise in prescribing opioids,[19] antidepressants,[20] and AEDs[21] has been shown in the U.K., data from people with specific painful conditions (eg, OA) are limited. Condition-specific drug utilization data would enable comparisons with other painful chronic conditions and inform future actions. The present study sought to describe the temporal changes in analgesic prescribing in primary care patients with KOA in the U.K. Such description of prescribing trends is most meaningful when trends are described and compared over time, particularly when knowing that in the U.K., no change

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Key points

1. There have been steady increases in the prescribing of all analgesic classes, except NSAIDs, for knee osteoarthritis between 2000 and 2014.
2. Opioids were the most frequently prescribed class; tramadol was the most frequently prescribed opioid.
3. The largest increase in prescribing was for AEDs, where prescriptions increased from 2 to 11/1000 registrants between 2000 and 2014.

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in trends of incidence of physician-diagnosed OA between 1992 and 2013 was reported.[17] Several regulatory measures were introduced in the U.K. to control the use of opioids and gabapentinoids. In June 2014, tramadol was reclassified as a schedule 3 controlled drug, and in April 2019, gabapentinoids were also reclassified as schedule 3 drugs.[22] Controlled drugs are drugs that are subject to high levels of regulation based on government decisions aiming to strengthen governance arrangements for their management and use to minimize patient harm, misuse, and criminality. There are five schedules for these drugs in the U.K.; schedule 1 contains drugs that are considered to have little or no therapeutic value and are subjective to most restrictive control. Schedule 2 and 3 contain drugs that can be prescribed and therefore legally possessed and supplied by pharmacists and doctors. In schedule 4, drugs can only be lawfully possessed under a prescription otherwise, possession is an offense. Schedule 5 contains drugs that are considered to have therapeutic value and are commonly available as over-the-counter medicines. Findings from the present study would provide baseline information to inform future research on the impact of such regulations.

METHODS

Study design and data source

This was a retrospective, cross-sectional study using data from the Clinical Practice Research Datalink-Gold (CPRD). CPRD is a large primary care longitudinal electronic medical records database that contains anonymous records of patients from general practices across the U.K. (including England, Scotland, Wales, and Northern Ireland) who have agreed at a practice level to provide data on a monthly basis.[23] As of July 2013, 674 practices contributed data to CPRD GOLD and records of more than 4.4 million active patients (alive and contribute data to CPRD)

were included. Recording of diagnosis is mandatory for every consultation, and there is no limit on the number of diagnoses entered. The database contains information on symptoms, diagnoses, prescriptions, referrals, tests, immunization, lifestyle factors, and information on medical staff.[24]

Substantial research has been undertaken to investigate the validity and completeness of CPRD data and has provided satisfactory results.[24,25] The comprehensive records of prescribing would enable reliable analyses of analgesic utilization. Further information on CPRD can be obtained from https://cprd.com/primary-care.

Study population and prescriptions

Patients with at least one medical code for KOA diagnosis recorded between January 1, 2000, and December 31, 2014, and aged 18 years or over, were included. This time period would enable the capture any changes in prescribing all five study drug classes before the introduction of new regulatory controls in 2014[26] and 2019.[22] Patients with records containing medical codes for cancer-related diagnoses recorded prior to or during the study period were not included. The total number of patients prescribed each analgesic class, and their demographic data were recorded.

Prescriptions of antidepressants, AEDs, opioids, NSAIDs, and paracetamol (Table S1) prescribed for the selected patients, were extracted from CPRD using specific drug-related product codes (which are CPRD unique codes for the drug product selected by the GP). Injections and suppository product codes were not included as these dosage forms are less likely to be prescribed in primary care for the long-term management of KOA-related pain. Buprenorphine 2 mg and 8 mg tablets were excluded too, as these are almost exclusively prescribed for the treatment of opioid dependence. Each prescription record contains information of item name and strength, prescription date, quantity, and numerical daily dose (NDD). Prescriptions were included after the latest of the two dates; the practices' up-to-standard (uts) date (date at which the practice data is deemed to be of research quality) or the patients' practice registration date.

Study measures

The following study measures were calculated in repeat cross-sectional estimates for each year. These measures were adopted from the previous published work on the utilization of analgesics in cancer and noncancer pain in the U.K.[19]

Number of analgesic prescriptions

The total number of analgesic prescriptions prescribed for patients with KOA during the 15-year study period and the number of analgesic prescriptions per 1000 CPRD registrants per year for each analgesic class was calculated. This is calculated by dividing the number of analgesic prescriptions prescribed for patients with KOA by the total number of people in the database that year (referred to as registrants hereinafter).

Defined daily dose

The quantity of each prescribed drug was multiplied by the strength (in milligrams) to calculate the amount of each prescription. For transdermal buprenorphine and fentanyl formulations, the patch strength and the duration of delivery rate of the formulations were included in the dose calculation. The annual total prescribed dose in milligrams for each drug was calculated and divided by the defined daily dose (DDD) (the daily average maintenance for a 70-kg male patient as defined by the WHO Collaborating Centre for Drug Statistics Methodology[27]) (Table S1). The result was then divided by the total number of people registered in CPRD for the year and then multiplied by 1000 and further divided by 365 to yield the mean annual number of DDDs per 1000 registrants per day.[19]

To quantify their utilization, antidepressant drugs were grouped into four subclasses as described in the British National Formulary[28]; tricyclic and related antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), and other antidepressants. AEDs were grouped into two main groups: older AEDs and newer AEDs.[29,30] The main differences between them are that the newer AEDs exhibit fewer pharmacokinetic drug–drug interactions, due to the absence of hepatic enzyme induction/inhibition properties, and have fewer adverse drug events compared with older AEDs.[31]

Oral morphine equivalent (OMEQ) doses

The dose for each opioid prescription was multiplied by the equianalgesic ratio (Table S2) of the opioid[32,33] to derive the oral morphine equivalent (OMEQ) dose. Annual OMEQ dose per day was calculated by dividing the total OMEQ dose by the total days of supply (detailed below) for each patient in a calendar year.

Opioid dose was further classified according into four OMEQ dose ranks, ≤50, 51–≤100, 101–200, and >200 mg/day. Such dose ranking would identify the proportion of patients prescribed lower or higher doses. Previous

research showed that patients receiving higher opioid doses (OMEQ ≥ 100 mg/day) are more likely to deviate from the prescribed dose, using illicit opioids or other substances that increase risk of overdose.[34]

Days' supply

The number of "days of supply" for each prescription was calculated by dividing the quantity by the NDD. The total days of supply of prescriptions for each patient per calendar year were calculated, and any overlapping days of supply between prescriptions within a year were subtracted.

Data management

Data cleaning involved data inspection for missing information or outliers. Patient records with missing information on year of birth were excluded. Less than 0.3% of prescriptions with missing quantity or extreme values (ie, greater than two times of the 99th percentile value) were excluded from the analysis. Between 8.3% and 27.5% of the prescriptions had missing NDD (for AEDs and opioids, respectively) and were imputed using the recommended dosing information from the British National Formulary.[28] Patients were stratified into five groups according to the drug classes prescribed.

Data analysis

Descriptive statistics were used to report the study measures for each year and the percentage change between 2000 and 2014 data for each study measure was reported. Sensitivity analyses were conducted to assess the impact of NDD missing data management on the dose calculation. All analyses were carried out using Stata 15.1 (Stata Corp LLC. 2017). This research was approved by the CPRD Independent Scientific Advisory Committee (protocol number 18_170R).

RESULTS

There were 137,457 patients with a recorded diagnosis of KOA between 2000 and 2014 in CPRD. This study included 117,637 patients (85.6% of total after exclusion of those diagnosed with KOA outside uts date and those with cancer diagnoses as illustrated in Figure S1) with a mean age of 66.3 (SD 12.7) years and 58.7% (n = 69,053) were female (Table 1 and Table S3). There was a higher proportion of patients aged between 40 and 64 years old (43.9%), followed by those aged 56–80 (38.7%).

In total, there were 8,944,381 prescriptions of the five study drug classes issued for patients with KOA over the study period. The number varied according to the drug

TABLE 1 Characteristics of the study population (N = 117,637).

Characteristics	Number of patients (% from total)
Gender	
Males	48,584 (41.3%)
Females	69,053 (58.7%)
Age at OA diagnosis (years)	
Mean (±SD)	66.3 (±12.7)
Range	18–106
Age ranks (years)	
<40	2143 (2.1%)
40–64	45,678 (43.9%)
65–80	40,305 (38.7%)
>80	15,956 (15.3%)
IMD score[a]	
1 (least deprived)	14,176 (21.6%)
2	15,456 (23.5%)
3	13,842 (21.2%)
4	12,610 (19.2%)
5 (most deprived)	9696 (14.8%)
Number of patients prescribed specific analgesics over the study years[b]	
Antidepressants	53,467 (45.5%)
AEDs	15,814 (13.4%)
Opioids	93,007 (79.1%)
NSAIDs	84,750 (72.0%)
Paracetamol	82,497 (70.1%)

Abbreviations: IMD, index of multiple deprivation; SD, standard deviation.
[a]Data were available for 104,082 patients.
[b]Total exceeds 100% as some patients prescribed more than one class.

class (n = 491,881 AED and 3,120,074 opioid prescriptions) representing 5.5% and 34.9% of total analgesic prescriptions, respectively. Paracetamol prescriptions constituted 23.0% and antidepressants 22.0% of total prescriptions (Table 2).

The mean number of prescriptions per patient per year increased from 5.8 (±4.0) to 9.6 (±7.0), 8.7 (±6.2) to 9.6 (±3.4), and from 5.1(±4.4) to 7.2 (±6.7) for antidepressants, AED, and opioid prescriptions, respectively, in 2000 and 2014, representing 65.5%, 10.3%, and 41.1% increases, respectively.

The annual number of prescriptions per 1000 CPRD registrants showed an overall increase over the study period for all classes except for NSAIDs (Figure 1). Of the five studied drug classes, opioids were the most frequently prescribed class in every study year; however, the most prominent change was in AED use, with 450% increase in 2014 compared with 2000 (from two to 11 prescriptions per 1000 registrants), followed by antidepressants (from 14 to 35) and opioids (from 27 to 46) prescriptions per 1000 registrants. The number of NSAID prescriptions per 1000 CPRD registrants dropped from

TABLE 2 Analgesic prescriptions between 2000 and 2014 prescribed for patients with KOA included in the study.

Study drug class	Total no. of prescriptions per analgesic class over study years	Analgesic prescriptions per 1000 CPRD registrants (people registered in CPRD for the year)		
		2000	**2014**	**% change**
Antidepressants	1,967,660	14.0	35.4	152.8
AEDs	491,881	2.6	11.6	450
Opioids	3,120,074	27.5	46.5	69.5
NSAIDs	1,302,060	17.5	7.4	−57.7
Paracetamol	2,062,706	20.5	31.2	52.2

Abbreviation: KOA, knee osteoarthritis.
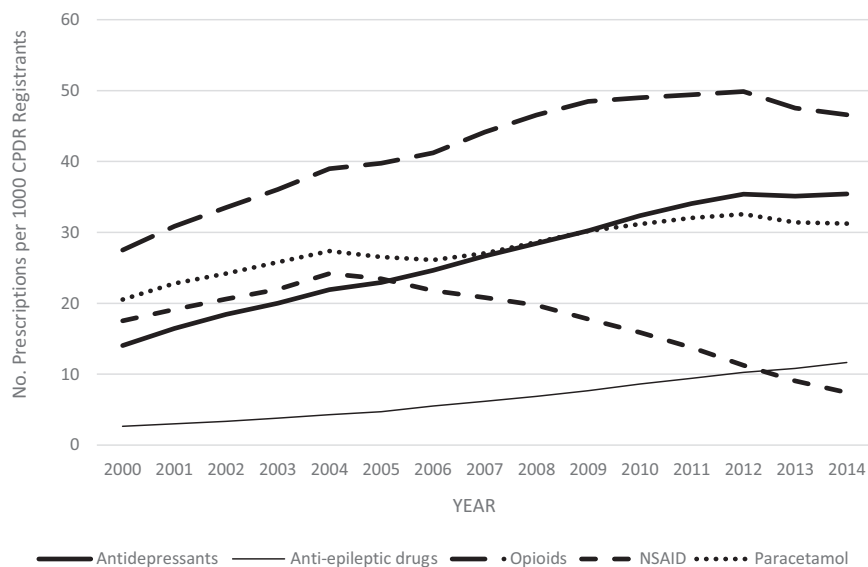
FIGURE 1 Number of prescriptions per 1000 CPRD registrants over the study period.

17 to 7 (58.8% drop) between 2000 to 2014 (Figure 1 and Table 2).

Defined daily doses (DDD) of study drug classes

Of all five analgesic classes, paracetamol had the highest mean annual DDD (between 0.79 to 1.40 per 1000 registrants per day) followed by opioids, which ranged from 0.16 to 0.22 per 1000 registrants per day in 2000 and 2014 respectively (Figure 2).

Within antidepressants, the number of DDDs per 1000 registrants for SSRIs and other antidepressant subclasses increased throughout the study period, from 0.09 to 0.32 and from 0.02 to 0.07 DDDs per patient per day in 2000 and 2014, respectively (Figure 3). In contrast to the older AEDs, the mean annual DDD per 1000 CPRD registrants for newer AEDs showed a sharp rise over the study period (from 0.0009 in 2000 to 0.02435 DDD per 1000 registrants in 2014) (Figure 4). Among the newer AEDs, gabapentinoids (gabapentin and pregabalin) demonstrated a progressive increase (from 0.005 to 0.247 DDD/1000 CPRD registrants) between 2000 and 2014, particularly from 2004 (Figure S2).

Considering individual opioids, the most prominent change was the increase in the number of DDDs of tramadol (0.11 DDDs in 2000 to 0.71 in 2014) (545.4% increase) (Figure 5). There were also substantial increases in prescribing prevalence of morphine and oxycodone was also prominent, with an increase from 0.01 to 0.1 and from 0.006 to 0.06 DDDs per 1000 registrants per day, respectively.

Annual OMEQ doses

The mean OMEQ over the study period was 63.26 ± 21.96 mg/day, and there was an increasing trend throughout, from 32.6 mg in 2000 to 71.7 mg in 2014 (119.9% increase) (Figure 6). Patients with KOA were predominantly prescribed low doses of opioids (≤ 50 mg/day); however, there was a continuous rise in the proportion of patients who were prescribed higher OMEQ doses (≥ 50 mg/day), including those who used 51–100 mg and 101 to 200 mg per day from 0.38% to 1.75% (361% increase) and from 0.38% to 0.79% (108% increase), respectively, which was associated with a small decrease in the proportion of patients who used low dose ranks (Figure S3).
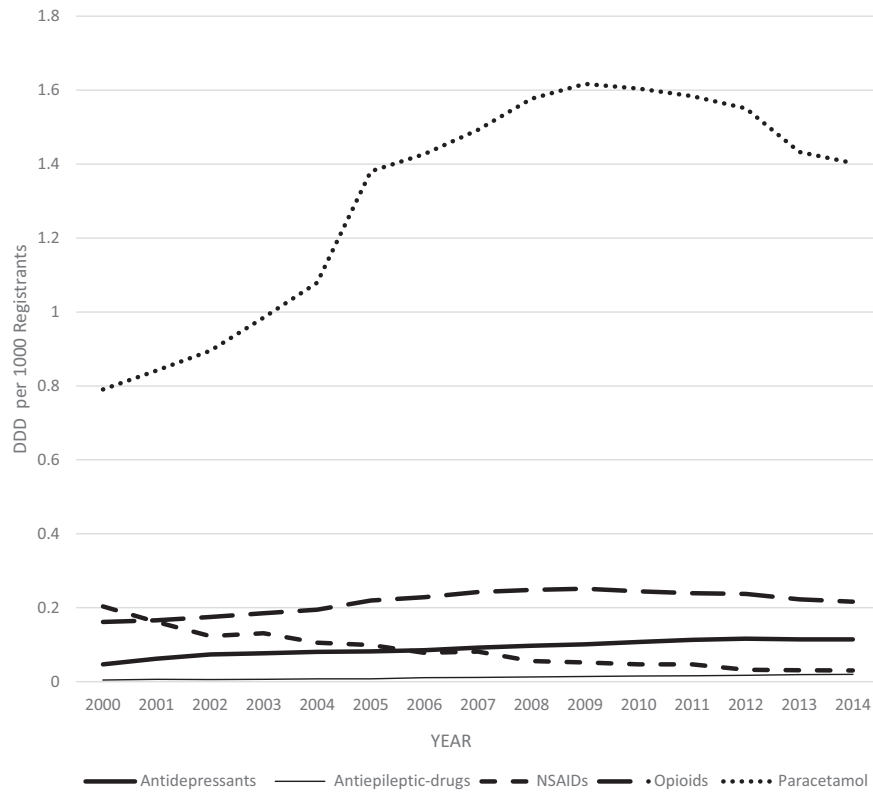
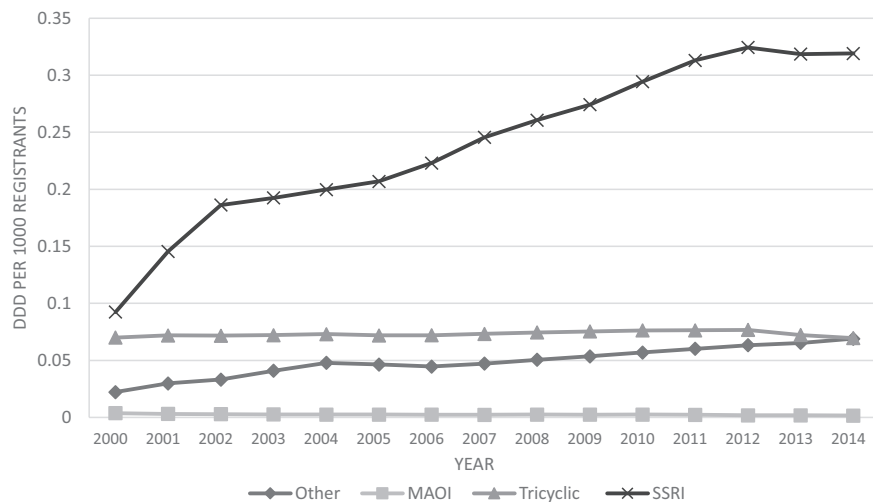**FIGURE 2**   Mean annual DDD per 1000 registrants, all study drug classes.

FIGURE 3   Mean annual DDD per 1000 Registrants for antidepressants.

Annual days' supply

The mean annual days' supply per patient during the study period was longer for antidepressants compared with the remaining classes (167.2 and 186.9 days in 2000 and 2014) (Table S4). The mean number of annual days' supply per patient for opioids and paracetamol increased by 29.7% and 29.0%, more than the other classes (antidepressants 11.8%, NSAIDs 16.2%). However, there was a decrease in AEDs days' supply

from 91.1 (SD 10.1) to 73.4 (SD 8.91) days, representing a 19.4% decrease.

DISCUSSION

Main findings

There were steady increases in the prescribing of all studied drug classes, except NSAIDs. Opioids were the
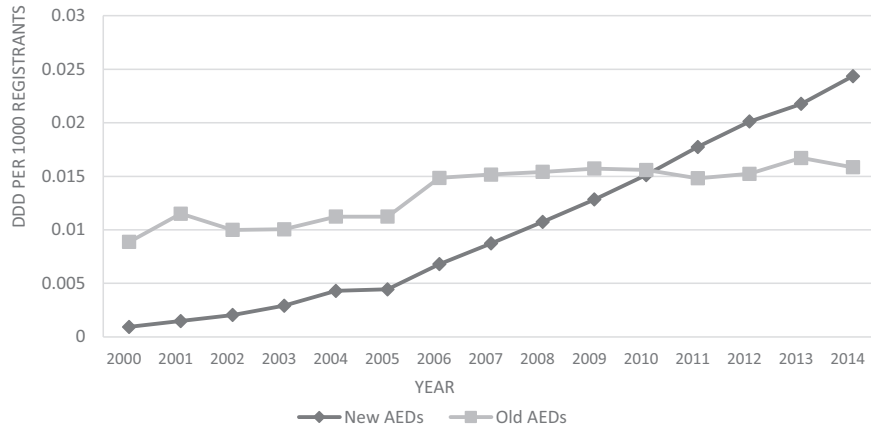
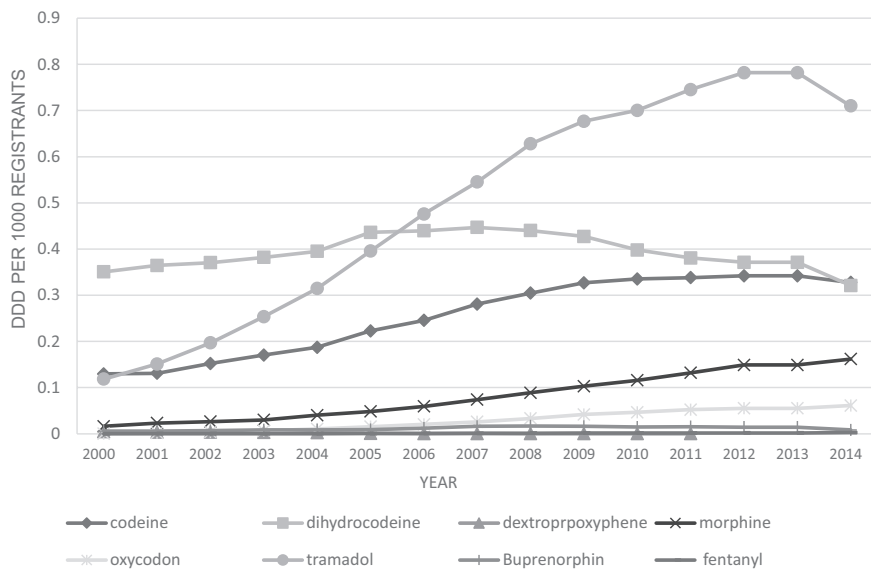**FIGURE 4** Mean annual DDD per 1000 registrants for antiepileptic drugs (AEDs).

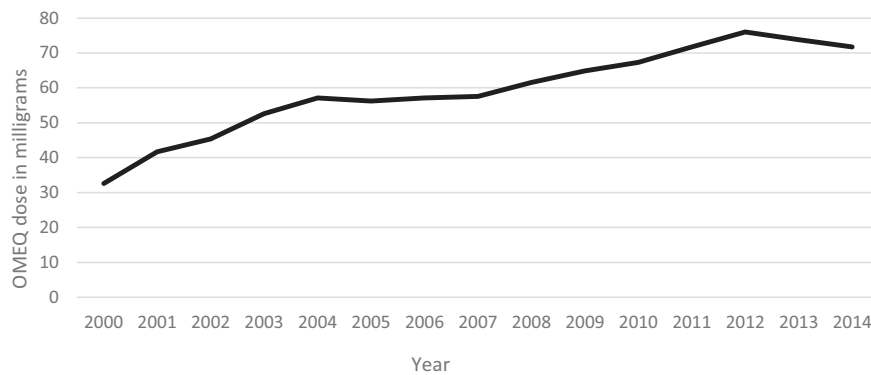**FIGURE 5** Mean annual DDD per 1000 registrants for individual opioids.

FIGURE 6 Mean daily oral morphine equivalent (OMEQ) dose in each study year.

most frequently prescribed analgesic class and tramadol was the most frequently prescribed opioid, for which the DDD per 1000 CPRD registrants increased from 0.11 to 0.71 in 2000 and 2014, respectively. The most prominent increase was found in AED prescribing, where the number of prescriptions increased from 2 to 11 per 1000 CPRD registrants. However, there was a decrease in the number of NSAID prescriptions between 2004 and 2014,

with the numbers dropping from 17.5 to 7.4 and 0.2 to 0.03 for prescriptions and DDDs per 1000 CPRD registrants, respectively.

Comparison with analgesic prescribing studies

Findings from the present study were consistent with those from prior research. An overall increase in antidepressant prescriptions was reported in five European countries (Spain, Germany, Denmark, Netherlands, and the U.K.) using seven different electronic health record (EHR) databases (including CPRD) between 2001 and 2009.[35] Antidepressant prescribing in the U.K. showed a slightly increasing trend from 836 to 1000 users per 10,000 person-years during the study period.[35] In a different study including 1,280,995 prescriptions for 350,398 CPRD registrants, antidepressant prescribing increased from 61.9 per 1000 person-years (PY) in 1995 to 129.9 per 1000 PY in 2011.[36]

The rate of patients newly treated with gabapentin has tripled between 2007 and 2017 from 230 to 679 per 100,000 persons per year, and for pregabalin from 128 to 379 for patients without epilepsy in the U.K.[7] Similarly, a 55-fold rise in gabapentin among patients without a seizure disorder (from 0.2 to 11.1 per 1000 persons) was observed, compared with only a twofold increase from 21.6 to 41.3 per 1000 persons for patients with epilepsy in Canada.[37] A dramatic increase in the incidence of new AED users was observed from 2005 to 2006 in a population-based study in Italy, where the cumulative incidence increased from 9.4 (95% CI 8.9, 9.9) to 15.5 (95% CI 14.8, 16.1) from 2003 to 2006.[29]

In patients with OA, an increase in the number of gabapentinoids prescriptions was reported in a recent population-based study using data from the CPRD.[38] The study found a substantial rise in the incidence of gabapentinoid prescribing from 9.5 (95% CI: 9.0, 10.1) to 28.0 (27.2, 28.8) people first prescribed gabapentinoids per 1000 person-years from 2005 to 2014. Gabapentin and pregabalin were classified as controlled drugs in the U.K. in April 2019 meaning that there are greater controls on the prescribing and dispensing of gabapentinoids, pharmacists must dispense the drugs within 28 days of the prescription being written.[22]

The increase in opioid prescribing found in the present study reflects an overall increase in the utilization of opioids in the U.K. generally, as reported in several studies in the U.K.[19,39,40] and other countries.[12,41,42] In patients with newly diagnosed OA, opioid prescriptions increase from 0.1% to 1.9% between 1993 and 2013 has been reported.[17] Similarly, a significant increase in opioid prescribing between 2003 and 2009 was found in the United States in a sample of 1387 Medicare Current Beneficiary Survey participants.[12] A total of 31% of patients with KOA received opioids in 2003 compared with 40% in 2009 (OR 1.5, 95% CI 1.1, 2.0 for 2009 compared with

2003).[12] Additionally, the proportion of opioid users in a cohort of Australian patients with KOA during the year prior to total knee replacement (TKR) increased from 37.4% to 48.6% ($p < 0.0001$) from 2001 to 2012 (n = 1205 and 1087).[42]

The rise in opioid prescribing in the present study was particularly noticeable from 2005 onward. This could be explained by the availability of several new strong opioid formulations in the U.K. around that time, including the buprenorphine 7-day patch and the fentanyl 12 mcg/h patch that were both licensed in 2005. Additionally, the global withdrawal of the COX-2 inhibitor rofecoxib in 2004 was associated with increased opioid prescribing.[43] Consistent with findings from the present study, increased tramadol utilization has been reported with the number of daily defined doses in England increasing from approximately 5.9 million in 2005 to 11.1 million in 2012.[26] Subsequently, in 2014 tramadol was classified as a schedule 3 controlled drug based on advice from the U.K.'s Advisory Council on the Misuse of Drugs, due to concerns about safety and the potential risk of misuse. It is worth mentioning that the subtle decline in prescribing certain opioids (eg, buprenorphine) observed in 2012 was in line with data reported internationally.[44]

The present study found a gradual increase in the proportion of patients using higher OMEQ dose ranks, which may be interpreted as an increased proportion of strong opioid users within the cohort. The proportion of patients using strong opioids (oxycodone) increased from 0.1 to 1.2 per 100 patients with OA, and the proportion of strong opioid users doubled from 0.1 to 0.2 per 100 patients with OA in the U.K. from 1993 to 2013.[17] Similarly, Bedson, in 2013, reported the doubling of strong opioid prescriptions from 545 to 1035 users per 10,000 registered population.[43] Additionally, a decrease in weak opioid users in Scotland was reported between 1995 and 2010, with a large increase in the proportion of strong opioid users from 0.2% in 1995 to 3.6% in 2010.[39]

In the U.K., there was a drop in COX-2 users from 12.1% to 0.6%, and NSAID users from 27% to 12.5%, from 2004 and 2013,[17] and from 41% to 31% from 2003 to 2009 in another study in the United States[12] and from 76% to 50.3% from 2001 to 2012 in Australia.[42] In 2004, the U.K. Medicine and Healthcare product Regulatory Agency (MHRA) issued a safety directive advising the avoidance of COX-2 inhibitors, due to increased risk of cardiovascular side effects such as myocardial infarction and stroke.[45] The directive was further extended to include cautionary use of nonselective NSAIDs, due to increased risk of thrombotic events, and all prescribers were advised to keep doses to the minimum effective level and to tailor doses according to patients' risk profiles.[46,47] There was a rapid decrease in the proportion of patients being newly prescribed COX-2 and NSAIDs following the issuance of this MHRA guidance,[43] also replicated in the present study.

The present study reported an increase in the prescriptions of paracetamol, which was consistent with findings on analgesic use 1 year prior to TKR. The study found that the overall prevalence of paracetamol prescriptions in Australia increased by 9.3% between 2001 and 2012.[42]

Among all drug classes, antidepressants had the longest days' supply per year, followed by NSAIDs, with a gradual increase trend over the study period. Long-term prescribing of antidepressants was found to be the main reason behind the increase in antidepressant prescribing in the U.K.,[36,48] probably indicating better adherence to depression management guidelines.[49]

AEDs and paracetamol had the lowest mean annual days' supply per year (roughly decreased to 2.5 months for AEDs in 2014), which indicates a poor retention despite the observed increased prescribing. In fact, the increased prescribing of AEDs was probably for off-label indications as an adoption of a multimodal approach as seen for other classes of analgesics (eg, antidepressants) in an effort to mitigate opioid over prescribing. However, the poor retention of AEDs could be a reflection of treatment discontinuation due to lack of efficacy and/or undesirable side effect profiles.[50] The risk of adverse drug effects appears to be particularly prevalent when combined with other CNS system depressants including opioids. Patients with prolonged use of concomitant gabapentin and opioids were significantly more likely to experience an all-cause or drug-related hospital inpatient stay particularly for altered mental status or respiratory depression.[51]

In 2014, those who used opioids, had used them for almost 3 months, and that represented around 30% increase from 2000 (from 66.9 ± 92.6 to 86.8 ± 112.6 in 2000 and 2014). This finding may be of particular importance since long-term opioid use has been associated with serious adverse events including major trauma and overdose[52].

Strengths and limitations

The use of the CPRD, a primary care database with data on patients broadly representative of the U.K. population, enabled a detailed description of trends of drug utilization at a population level and maximized the external validity of this research.[24] Conclusions on utilization trends are generalizable across the U.K. and other countries (with health systems similar to those of the U.K., where, eg, management of KOA takes place in primary care). Prevalence was estimated using the whole population of patients with KOA, and measured annually over a prolonged period (15 years). This minimized the possibility of obtaining differing results if another timeframe had been chosen (eg, if only selected years were studied). A 15-year study period allowed a large observation window, where changes in prescribing for patients with KOA could be tracked.

Unlike previous drug utilization studies,[10] the present study quantified the use of several drug classes which are either recommended by clinical guidelines or are being used in clinical practice for KOA-related pain. Typically, drug utilization studies in patients with OA focus on opioids, nonopioids, or both.[10,12,53] However, the present study included a wider range of drugs for OA pain and, hence, enabled assessing the changes over time in prescribing the first- and second-line analgesics (paracetamol, NSAIDs, and opioids, respectively), in addition to other centrally acting KOA pain treatments (antidepressants and AEDs).

However, there are some limitations which must be considered. Firstly, the analysis was made using prescriptions generated in primary care, and it is assumed that the prescribed drugs were dispensed and actually taken by patients, which may overestimate overall drug utilization as research has shown that up to 50% of patients do not comply with their long-term therapies.[54] Nevertheless, prescribing data are one of the main data sources for drug utilization and pharmacoepidemiology studies. Drugs prescribed and dispensed in hospitals are not recorded in the CPRD; however, this is also not likely to form a major proportion of analgesic use, because KOA is primarily managed in general practice in the U.K.

Secondly, there is the potential for underestimation of NSAID and paracetamol utilization, as these agents are widely accessed through over-the-counter (OTC) purchases, hence are not completely recorded in CPRD. However, most of the patients with KOA who were identified in this research were aged over 60 years old, thus qualifying for free prescriptions in the U.K.,[55] hence they are likely only to have a very small proportion of their analgesics not prescribed by GPs.

Findings of this study describe the use of AEDs and other analgesics in people with a diagnosis of KOA. The recording of KOA diagnosis depends on the presence of what are considered more important morbidities, for example, MI or stroke.

That is, OA is likely to be recorded if it is the primary complaint and in the absence of more acute diagnoses.[56] Given that, it is less likely that other more pressing pain conditions (eg, spine-related stenosis/radiculopathy) were present in these patients.

Findings suggest an overall increased prevalence of analgesic prescribing in patients with KOA and indicate a need for regular monitoring. The raise in opioids use is of particular concern as problematic use of opioids by older adults (including those with KOA) is associated with a number of pertinent adverse effects, including sedation, cognitive impairment, falls, fractures, and constipation.[57] The successful management of KOA involves the integration of both nonpharmacological management (such as advice on exercise and weight loss support, and education on self-management) and medicines.[5] Hence, it is important

to ensure that core educational and lifestyle measures recommended by clinical guidelines,[5] are optimized when such an increase in analgesic prescribing has been observed. Previous research showed that while GPs' attitudes and beliefs on the importance of exercise for chronic knee pain (CKP) attributable to KOA were positive overall, only 11% of the GPs recommended exercise in accordance with recommendations.[58] The most reported barriers in using exercise for CKP were a lack of sufficient consultation time, reported by 51% of the 835 GPs; lack of expertise (training), reported by 41%; and the perception that patients prefer other management modalities, reported by 36%.[59] These barriers and the subsequent limited uptake of core treatment (exercise and weight loss) and self-management measures may in part explain the increasing prevalence of analgesic prescribing in primary care. Additionally, the overall increase in prescribing could have stemmed from the inclusion of patients with diagnostic Read codes for KOA as a study population, who are likely to be prescribed analgesics within 2 weeks after diagnosis compared with those with symptoms-based Read codes (eg, knee pain-related Read codes). With the increase in the prescribing prevalence of newer AEDs, particularly gabapentinoids, in this study, great emphasis must be placed on education to raise awareness through information campaigns, and training of practitioners and patients on the risks associated with their use, especially when used concomitantly with opioids. The insufficiency of evidence of opioid effectiveness for long-term use or in high doses needs to be highlighted to patients during reviews.

CONCLUSION

This study described changes in the prescribing of a range of analgesics commonly prescribed for patients with KOA over a 15-year period. There was an overall increase in the number of prescriptions and the mean number of DDDs of antidepressants, AEDs, opioids, and paracetamol throughout the study period. In contrast, the prevalence of NSAID prescribing showed a decreasing trend from 2005 onward. The increased prescribing for most of the studied drug classes, particularly opioids and AEDs, warrants further investigation into drug exposure and outcomes for individual patients to optimize safety of analgesic use in this patient population.

AUTHOR CONTRIBUTIONS

AT initiated and developed the research questions, accessed the research data, conducted data management, data analysis, and led on drafting the manuscript. RDK and SG advised on the study design and data analysis. All of the authors contributed to the interpretation of the data, critically revised the manuscript, and approved the final version submitted for publication.

CONFLICT OF INTEREST STATEMENT
The authors declare no competing interest.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are owned by the CPRD and may be available subject to data sharing regulations of the CPRD.

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SUPPORTING INFORMATION

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

Appendix S1