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Original article

Initial analgesic prescriptions for osteoarthritis in the United Kingdom, 2000–2016

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Abstract

Objectives. To examine trends in the initial prescription of commonly-prescribed analgesics and patient- as well as practice-level factors related to their selection in incident OA.

Methods. Patients consulting with incident clinical OA between 2000–2016 were identified within The Health Improvement Network in the United Kingdom (UK) general practice. Excluded were patients who had history of cancer or were prescribed the analgesics of interest within 6 months before diagnosis of OA. Initial analgesic prescription included oral non-selective NSAID, oral selective cyclooxygenase-2 inhibitor, topical NSAID, paracetamol, topical salicylate or oral/transdermal opioid within 1 month after OA diagnosis.

Results. ~44% of patients with incident OA ($n = 125\ 696$) were prescribed one of these analgesics. Incidence of oral NSAID prescriptions decreased whereas other analgesic prescriptions, including oral opioid prescriptions, increased (all P-for-trend < 0.001). Patients with a history of gastrointestinal disease were more likely to receive topical NSAIDs, paracetamol or oral/transdermal opioids. Only 38% of patients with history of gastrointestinal disease and 21% of patients without it had co-prescription of gastroprotective agent with oral NSAIDs. Oral/transdermal opioid prescription was higher among the elderly (≥65 years), women, obesity, current smoker, and patients with gastrointestinal, cardiovascular or chronic kidney disease. Prescription of oral opioids increased with social deprivation (P-for-trend < 0.05) and was highest in Scotland, whereas transdermal opioid prescription was highest in Northern Ireland (all P-for-homogeneity-test < 0.05).

Conclusion. The initial prescription pattern of analgesics for OA has changed over time in the UK. Co-prescription of gastroprotective agents with oral NSAIDs remains suboptimal, even among those with prior gastrointestinal disease.

Key words: non-steroidal anti-inflammatory drug, opioid, osteoarthritis, United Kingdom

Introduction

Pain is a key reason for patients with clinical OA to seek medical care and is an important antecedent to disability [1, 2]. The National Institute for Health and Care Excellence (NICE) OA guideline recommends that core interventions are non-pharmacological, but that local and systemic analgesics should also be considered, if required, as adjunctive treatments for pain relief [3]. In addition, topical NSAIDs and oral paracetamol should be considered ahead of oral non-selective NSAID (ns-NSAIDs), selective cyclooxygenase-2 (COX-2) inhibitors and opioids [3]. However, whether general practitioners (GPs), who manage the vast majority of patients with OA, follow NICE guidance and what factors influence patterns of their initial prescription remain unclear.

While topical NSAIDs give similar levels of pain relief to oral NSAIDs [4–6], the latter were associated with increased risks of gastrointestinal (GI) and cardiovascular (CV) events [7, 8]. To our knowledge, no study has

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CLINICAL SCIENCE

Rheumatology key messages

- Initial prescription of oral NSAID decreased whereas oral opioids increased in UK primary care.
- Co-prescription of gastroprotective agents with oral NSAIDs remains suboptimal.

reported that initial prescription of topical NSAIDs is more common than that of oral NSAIDs. In addition, there is increasing evidence that paracetamol is not more clinically effective than placebo for OA-related pain, and its risk of GI adverse events is similar to that of oral NSAIDs [9–13]; however, it is unclear whether the initial prescription of paracetamol has changed in practice. Finally, oral opioids, especially weaker opioids, have been widely used among patients with OA [14, 15], and their prescription rose markedly among incident OA patients in the UK from 1992 to 2013 [16]. Recently, we reported oral tramadol, a weaker opioid, was associated with a higher risk of all-cause mortality than oral NSAIDs [14], suggesting that weaker opioids may not be as safe as generally perceived [17]. Despite increasing concerns over opioids in recent years, it is unknown whether the increasing trend of opioid prescription has continued and, if it does, what factors are attributable to such an increase among OA patients.

Knowledge of the secular trend and factors affecting such a trend would allow us to identify the gaps between the prescribing practice of GPs and recommended guidelines. This information should help us to develop more effective approaches to disseminate treatment guidelines, and to make appropriate policy interventions to optimize analgesic use. The aims of this study were to examine: the secular trend of initial prescriptions of commonly prescribed analgesics in patients with incident OA from 2000–2016 in UK primary care; and the patient-level factors [year of OA diagnosis, age, sex, BMI, drinking status, smoking status, GI disease, CV disease, chronic kidney disease (CKD) and socioeconomic deprivation index] and practice-level factors (practice size and location) that associate with initial prescription of each of these analgesics.

Methods

Data source

The Health Improvement Network (THIN) is an electronic medical record database derived from the records of GP practices in the United Kingdom (UK). THIN contains medical records for ~17 million patients from 790 general practices. The vast majority of individuals in the UK, regardless of health status, are registered with a GP. THIN uses the Read classification system to code diagnoses and the Multilex classification system based on a drug dictionary in British National Formulary and Anatomical Therapeutic Chemical code formats to code medications. Previous studies have demonstrated the patient population within THIN is representative of the UK population [18], and THIN data were valid for use in clinical and epidemiological research [19].

Study population

Eligible participants consisted of patients who were registered with the general practice for at least one year before the first diagnosis of clinical OA, aged 50 years or more, had no history of cancer, and were not prescribed any one of analgesics under the current study six months prior to the diagnosis of OA. The study observation period was between January 2000 and December 2016. The date of OA diagnosis was defined as the date of the first Read code for OA. This study was approved by the THIN Scientific Review Committee (19THIN050) and received approval from the medical ethical committee at Xiangya Hospital (2018091077), with waiver of informed consent.

Assessment of analgesic prescription

We included seven broad categories of commonly prescribed analgesics, specifically: (i) oral ns-NSAIDs; (ii) oral COX-2 inhibitors; (iii) topical NSAIDs; (iv) paracetamol; (v) topical salicylate; (vi) oral opioids; and (vii) transdermal opioids (Supplementary Table S1, available at *Rheumatology* online). We defined initial prescription of each of these analgesics as a prescription occurring within 30 days after the date of diagnosis of incident clinical OA. If the prescription of analgesic changed or more than one analgesic was prescribed at the same time within 30 days after OA diagnosis, they were considered separately.

Assessment of possible factors for analgesic prescriptions

The patient-level factors of interest were year of OA diagnosis, age (<65 and ≥65 years old), sex, BMI (normal weight: <25 kg/m^2; overweight: ≥25 to <30 kg/m^2; and obesity: ≥30 kg/m^2), drinking status (none, past and current), smoking status (none, past and current), history of common GI diseases (i.e. peptic ulcer, gastroesophageal reflux disease and gastritis) [20], history of major CV diseases (i.e. myocardial infarction, stroke, peripheral vascular disease and heart failure) [21], history of moderate-to-severe CKD (i.e. CKD stage 3–5) [22], and Townsend Deprivation Index [a socioeconomic deprivation index, ranging from 1 (least deprived) to 5 (most deprived)] [23]. The practice-level factors included practice size (i.e. the number of people registered with the practice) [24] and practice location (i.e. England, Northern Ireland, Scotland or Wales).

Statistical analysis

We divided the date of initial analgesic prescription into four periods (2000–2003, 2004–2007, 2008–2011 and 2012–2016) and described the characteristics of participants for each period.

We calculated the annual incidence of initial prescriptions of each of the seven broad categories of analgesics as well as individual analgesic within 30 days after incident clinical OA diagnosis and described each of their secular trend, respectively. We compared the incidence of initial prescription of each category of analgesics among four periods described above (reference period: 2000–2003) using generalized linear mixed effect model (SAS: PROC GLIMMIX), which accounted for correlation among prescriptions of medications within a practice level. We performed the site-specific analyses to assess whether the secular trend differed among patients with knee OA only, hip OA only, hand OA only or multiple-site OA (i.e. knee and hip OA, knee and hand OA, hip and hand OA, and knee, hip and hand OA). To test the robustness of findings, we conducted sensitivity analyses by excluding patients accompanied with fever, trauma or surgery in the 30 days after OA diagnosis. We took the same approach to assess the relation of each of the patient-level and practice-level factors to the incidence of initial prescription of analgesic (e.g. the comparator was people without initial prescription of oral ns-NSAIDs when the outcome was initial prescription of oral ns-NSAIDs), including age (<65 or ≥ 65 years old), sex, BMI (normal weight, overweight or obesity), drinking status (non, past or current), smoking status (non, past or current), GI disease (present or absent), CV disease (present or absent), CKD (present or absent), socioeconomic deprivation index (1–5), practice size (quartiles), and practice location (England, Northern Ireland, Scotland or Wales). For each factor, we used a causal diagram to guide the selection of potential confounders (Supplemental Fig. S1, available at *Rheumatology* online).

Finally, we estimated the proportion of co-prescription of initial oral ns-NSAIDs or COX-2 inhibitors with proton pump inhibitors (PPIs) or histamine-2 receptor antagonist (H2RA) among incident OA patients with and without a history of GI disease, respectively. In this analysis, co-prescription of PPI or H2RA was defined as any prescription ordered within 60 days (days' supply + 30-day grace period) [20] prior to or on the same date of initial ns-NSAID or COX-2 inhibitor prescription.

All *P*-values were two-sided and $P < 0.05$ was considered statistically significant for all tests. All statistical analyses were conducted using SAS v9.4.

Results

During the study period, 366 707 subjects aged 50 years or older were diagnosed with incident clinical OA. We excluded from the analysis 47 346 patients with a history of cancer and 35 925 with a prescription of the analgesics of the interests in the six months before the OA diagnosis. Of the remaining ($n = 283\ 436$), 125 696 were initially prescribed at least one of the seven analgesic groups of interest. The characteristics of incident OA cases are shown in Table 1.

Secular trends in initial analgesic prescription

As shown in Fig. 1A and Table 2, the incidence of initial prescription of oral ns-NSAIDs decreased by almost 50%, from 31.7% in 2000 to 16.0% in 2016 (Supplementary Table S2, available at *Rheumatology* online). The incidence of prescription of oral COX-2 inhibitors increased from 2000–2004 and then declined sharply afterwards. Topical NSAID prescription almost tripled during the study period from 4.7% in 2000 to 12.8% in 2016 and was more noticeable after 2008 when NICE guidelines recommended it for the initial pain management of OA. Paracetamol prescription increased from 8.0% in 2000 to 14.4% in 2011, and then decreased to 10.7% in 2016. Oral opioid prescription increased during the study period from 3.8% in 2000 to 9.0% in 2013, and there was no indication that such a trend had changed recently. Initial prescription of either topical salicylate or transdermal opioids was low ($\sim$1%). The findings did not change materially in the site-specific analyses (Supplementary Tables S3–S6, available at *Rheumatology* online) and sensitivity analyses excluding patients accompanied with fever, trauma or surgery in the 30 days after OA diagnosis (Supplementary Table S7, available at *Rheumatology* online).

Secular trends in initial prescription of each individual analgesic also differed. Of note, initial prescription of oral naproxen increased by 2.7-fold, whereas prescription of ibuprofen or diclofenac decreased rapidly (Fig. 1B, Supplementary Table S8, available at *Rheumatology* online). Only two COX-2 inhibitors (i.e. celecoxib and etoricoxib) were still in the market after 2007 and their prescriptions remained low ($<1\%$) (Fig. 1C, Supplementary Table S9, available at *Rheumatology* online). The most commonly prescribed topical NSAID was ibuprofen (Fig. 1D, Supplementary Table S10, available at *Rheumatology* online). Tramadol was one of the most commonly prescribed opioids and its prescription increased from 1.3% in 2000 to 5.0% in 2013, and then levelled off (Fig. 1E, Supplementary Table S11, available at *Rheumatology* online).

Patient-level factors for initial prescription of analgesics

As shown in Table 3, older age (≥ 65 years), female sex, and history of GI disease or CKD were associated with a lower incidence of oral ns-NSAIDs prescription but a higher incidence of other six analgesics prescriptions than their counterparts. Patients with obesity had a higher incidence of oral ns-NSAIDs, oral COX-2 inhibitors, oral paracetamol, oral opioids and transdermal opioids prescriptions, but a lower incidence of topical

Table 1 Characteristics of included participants with incident OA (2000–2016)

Characteristics	2000–2003 (*n* = 62 429)	2004–2007 (*n* = 78 277)	2008–2011 (*n* = 73 211)	2012–2016 (*n* = 69 519)
Age, mean (S.D.), yr	66.8 (10.0)	66.6 (9.8)	66.2 (9.7)	65.8 (9.6)
Women, %	62.0	61.0	60.0	59.0
BMI[a], %				
Normal weight	32.9	30.0	27.7	26.1
Overweight	40.9	39.8	38.9	37.9
Obesity	26.2	30.2	33.4	36.0
Drinking status, %				
None	19.7	20.3	19.4	18.4
Past	1.5	2.2	2.6	3.1
Current	78.8	77.5	78.0	78.5
Smoking status, %				
None	57.7	55.0	54.4	55.3
Past	23.4	29.6	31.8	31.8
Current	18.9	15.4	13.8	12.9
Gastrointestinal disease[b], %	40.6	39.7	38.4	36.1
Cardiovascular disease[c], %	22.5	18.7	14.8	11.2
Chronic kidney disease,[d] %	20.3	20.5	16.7	11.9
Socioeconomic deprivation index,[e] mean (S.D)	2.6 (1.3)	2.6 (1.3)	2.6 (1.3)	2.6 (1.3)
Practice size,[f] mean (S.D.)	601 (308.9)	553 (300.3)	537 (303.1)	535 (304.0)
Practice location				
England, %	79.0	73.9	70.2	60.7
Northern Ireland, %	2.8	2.8	3.6	4.2
Scotland, %	9.4	11.9	16.3	21.1
Wales, %	8.8	10.4	9.9	14.0

[a]BMI status was defined as normal weight $<25\,kg/m^2$, overweight ≥ 25 to $<30\,kg/m^2$ and obesity $\geq 30\,kg/m^2$. [b]Gastrointestinal diseases include ulcer disease, gastroesophageal reflux disease and gastritis disease. [c]Cardiovascular diseases include myocardial infarction, stroke, peripheral vascular disease and congestive heart failure. [d]Chronic kidney disease was defined as chronic kidney disease stage 3–5 (i.e. moderate-to-severe chronic kidney disease). [e]The socioeconomic deprivation index (i.e. Townsend Deprivation Index) ranged from 1 (least deprived) to 5 (most deprived). [f]The number of patients registered with a general practitioner. *n*: number of participants; yr: years.

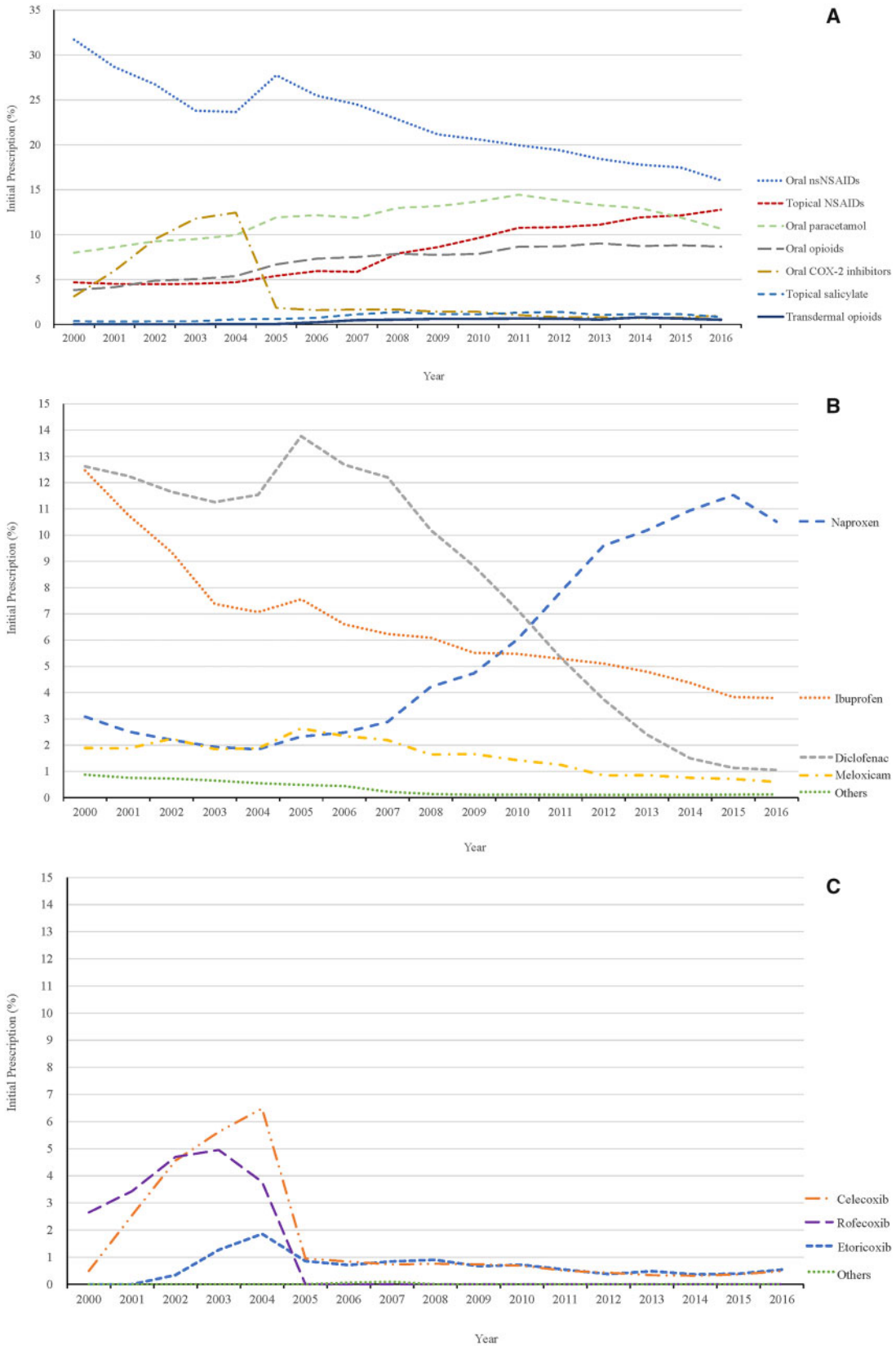
NSAIDs and topical salicylate prescriptions. Current alcohol drinkers were more likely to initially receive oral ns-NSAIDs but were less likely to receive the other six analgesics. Patients with current smoking were more likely to initially receive oral ns-NSAIDs, oral COX-2 inhibitors, oral paracetamol, oral opioids and transdermal opioids. Although the proportion of co-prescription of PPI or H2RA with oral ns-NSAID or COX-2 inhibitors increased significantly from 2000 (17.5%) to 2016 (67.1%) among patients with history of GI disease, still approximately one-third of patients were not co-prescribed PPI or H2RA with ns-NSAID or COX-2 inhibitor in the most recent year (Supplementary Table S12, available at *Rheumatology* online). The proportion of co-prescription of PPI or H2RA with oral ns-NSAID or COX-2 inhibitor among subjects without GI disease was even lower (ranging from 4.5% in 2000 to 51.0% in 2016). (Supplementary Table S13, available at *Rheumatology* online). Patients with CV disease were less likely to initially receive oral ns-NSAIDs or oral COX-2 inhibitors but were more likely to receive the other five analgesics. Initial prescription of topical NSAIDs, paracetamol or oral opioids was more common in the deprived areas (all *P* for trend <0.001); however, no such pattern was observed for other types of analgesics (Table 3).

Practice-level factors for initial prescription of analgesics

As shown in Table 4, no apparent association was observed between practice size and prescription of each type of analgesic. However, incidence of initial prescription of analgesics varied greatly according to practice location (Fig. 2). Compared with England, GPs in Northern Ireland were more likely to initiate NSAIDs and transdermal opioids but less likely to prescribe paracetamol and topical salicylate, GPs in Scotland tended to prescribe more oral opioids, and those in Wales prescribed more transdermal opioids and less topical salicylate (all *P* for test of homogeneity <0.05).

Most associations identified above still held in the recent years, i.e. 2012–2016 (Supplementary Tables S14

Fig. 1 Initial prescription of commonly prescribed analgesics among patients with incident clinical OA



(**A**) Seven broad categories of commonly prescribed analgesics. (**B**) Individual oral ns-NSAID. (**C**) Individual oral COX-2 inhibitor. (**D**) Individual topical NSAID. (**E**) Individual oral opioid. ns-NSAIDs: non-selective NSAIDs; COX-2: cyclooxygenase-2.

FIG. 1 (continued)

and Table S15, available at *Rheumatology* online). However, there was no substantial difference in initial prescription of oral ns-NSAIDs in men *vs* women and oral opioids among those <65 years *vs* those ≥65 years. The initial prescription of oral COX-2 inhibitors in older age (≥65 years) was lower than those aged <65 years.

Discussion

We observed that the incidence of initial prescription of oral NSAIDs in patients with incident OA decreased whereas the incidence of prescription of topical NSAIDs, paracetamol and oral/transdermal opioids increased over the study period. Co-prescription of gastroprotective agents with oral NSAIDs was low, even among the patients with a history of GI disease. There was large geographic variability in initial prescription of opioids, with oral opioids being prescribed more often in Scotland and transdermal opioids more often in Northern Ireland. Finally, the initial prescription of oral opioids was much higher in the deprived areas.

To date, there is a paucity of data on secular trends in initial prescription of analgesics among patients with OA. Using data from the Clinical Practice Research Datalink, Yu and colleagues reported that oral NSAID prescription fell from 2004 to 2013 in the UK [16]. Our results were corroborated with theirs and demonstrated

Table 2 Association between year with initial analgesic prescription among patients with incident OA[a] (2000–2016)

Types of analgesic	2000–2003 (*n* = 62 429)	2004–2007 (*n* = 78 277)	2008–2011 (*n* = 73 211)	2012–2016 (*n* = 69 519)	*P* for trend
Oral ns-NSAIDs					
%	27.3	25.4	21.2	18.0	
RR[b] (95% CI)	1.00 (reference)	0.88 (0.86, 0.91)	0.68 (0.66, 0.70)	0.56 (0.54, 0.58)	<0.001
Oral COX-2 inhibitors					
%	8.1	4.4	1.4	0.8	
RR[b] (95% CI)	1.00 (reference)	0.48 (0.46, 0.51)	0.15 (0.14, 0.16)	0.09 (0.08, 0.10)	<0.001
Topical NSAIDs					
%	4.5	5.5	9.5	11.7	
RR[b] (95% CI)	1.00 (reference)	1.23 (1.17, 1.30)	2.27 (2.16, 2.38)	3.03 (2.89, 3.19)	<0.001
Oral paracetamol					
%	8.9	11.5	13.5	12.7	
RR[b] (95% CI)	1.00 (reference)	1.33 (1.28, 1.38)	1.69 (1.63, 1.76)	1.58 (1.52, 1.65)	<0.001
Topical salicylate					
%	0.3	0.8	1.2	1.1	
RR[b] (95% CI)	1.00 (reference)	2.12 (1.80, 2.51)	3.86 (3.29, 4.53)	3.75 (3.18, 4.42)	<0.001
Oral opioids					
%	4.5	6.7	8.0	8.8	
RR[b] (95% CI)	1.00 (reference)	1.43 (1.36, 1.51)	1.78 (1.69, 1.87)	1.97 (1.87, 2.07)	<0.001
Transdermal opioids					
%	0.0	0.2	0.6	0.6	
RR[b] (95% CI)	—	1.00 (reference)	3.40 (2.79, 4.15)	3.30 (2.69, 4.06)	<0.001

[a]Incidence was estimated as the percentage of incident OA patients who received an initial analgesic prescription within 30 days after OA diagnosis, among those who had not used analgesic (defined as those who satisfied the above criteria and also had been continuously enrolled for at least one year and had no recorded analgesic prescription during those 6 months). [b]Adjusted for age, sex, Townsend Deprivation Index, and practice location. *n*: number of participants; ns-NSAIDs: non-selective NSAIDs; COX-2: cyclooxygenase-2; RR: risk ratio.

that such a trend still exists. Our findings that older patients (≥65 years), women and patients with a history of GI disease, CV disease or CKD were less likely to be prescribed oral ns-NSAIDs but more often given topical analgesics indicated that most GPs' initial prescription of analgesic was in accordance with NICE guidelines [3]. Interestingly, although several studies have found a relatively high risk of GI diseases from naproxen use [25–27] we observed a substantial increase in its prescription during the study period. While CV risk from naproxen seems relatively low [28], its potential GI should not be neglected.

Although the proportion of co-prescription of PPI or H2RA with oral NSAIDs has been increasing during the study period, approximately one-third of incident OA patients with a history of GI disease in 2016 were not co-prescribed with a gastroprotective medication, and such figure was even lower among those without history of GI disease (Supplemental Table S7, available at *Rheumatology* online). Considering that addition of a PPI to both oral ns-NSAID or COX-2 inhibitor was highly cost effective [29], a continuing education is required to improve such clinical practice.

Our study indicates that initial prescription of topical NSAIDs has been increasing during the past decades, especially among older patients, women and those with comorbidity. Such a trend was more noticeable after 2008 when the NICE guideline recommended topical NSAIDs as first-line analgesic for pain management of OA, suggesting that some GPs were following this recommendation [3]. Nevertheless, among incident OA patients who were initially prescribed analgesics in the last five years, less than a third were initially prescribed topical NSAIDs. Thus, for most OA patients, topical NSAIDs are still not prescribed ahead of other analgesics under the study despite their similar pain-relief effect but far greater safety [4–6, 30–32].

Our finding of a relatively high incidence of paracetamol prescription, especially in OA patients with a history of GI disease, is of potential concern. Although the incidence of paracetamol prescription slightly decreased between 2012 and 2016, possibly reflecting GPs' responses to the 2014 NICE guideline questioning the risk-benefit ratio of paracetamol for OA-related pain management [3], further reduction of paracetamol prescription may be warranted.

In line with one previous report [16], our study showed that initial prescription of opioids, especially tramadol, has been increasing in the UK, particularly among elderly, women and those living in deprived areas. Such a pattern may reflect a generally perceived notion that tramadol is more effective for pain relief and has fewer side effects compared with oral NSAIDs. However, results from several recently published studies show

Table 3 Association between patient-level predictors with initial analgesic prescription among patients with incident OA (2000–2016)

	Oral ns-NSAIDs	Oral COX-2	Topical NSAIDs	Oral paracetamol	Topical salicylate	Oral opioids	Transdermal opioids
Age,[a] RR (95% CI)							
< 65 years	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
≥ 65 years	0.74 (0.72, 0.75)	1.15 (1.11, 1.21)	1.91 (1.85, 1.97)	2.71 (2.64, 2.79)	2.25 (2.05, 2.47)	1.07 (1.04, 1.10)	2.00 (1.74, 2.31)
Sex,[b] RR (95% CI)							
Men	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Women	0.94 (0.93, 0.96)	1.31 (1.25, 1.37)	1.29 (1.25, 1.33)	1.26 (1.23, 1.30)	1.38 (1.26, 1.51)	1.23 (1.19, 1.27)	1.90 (1.63, 2.21)
BMI,[c] RR (95% CI)							
Normal weight	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Overweight	1.14 (1.11, 1.17)	1.20 (1.03, 1.40)	0.95 (0.92, 0.99)	1.02 (0.99, 1.06)	0.90 (0.81, 1.01)	1.08 (1.03, 1.13)	1.07 (0.88, 1.29)
Obesity	1.27 (1.23, 1.30)	1.27 (1.09, 1.48)	0.93 (0.89, 0.97)	1.15 (1.11, 1.19)	0.94 (0.83, 1.05)	1.61 (1.54, 1.68)	1.51 (1.25, 1.81)
P for trend	<0.001	<0.001	0.002	<0.001	0.453	<0.001	<0.001
Drinking status,[d] RR (95% CI)							
None	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Past	0.97 (0.90, 1.04)	0.98 (0.83, 1.18)	0.95 (0.86, 1.05)	1.08 (0.99, 1.17)	0.89 (0.67, 1.16)	1.37 (1.25, 1.49)	0.83 (0.57, 1.23)
Current	1.07 (1.04, 1.10)	0.93 (0.88, 0.99)	0.80 (0.77, 0.84)	0.75 (0.73, 0.78)	0.69 (0.62, 0.77)	0.73 (0.70, 0.76)	0.57 (0.49, 0.67)
P for trend	<0.001	0.022	0.035	0.181	<0.001	0.425	0.014
Smoking status,[e] RR (95% CI)							
None	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Past	0.99 (0.97, 1.01)	1.05 (0.99, 1.12)	1.06 (1.02, 1.10)	1.07 (1.04, 1.11)	1.14 (1.03, 1.26)	1.35 (1.30, 1.40)	1.32 (1.12, 1.56)
Current	1.14 (1.11, 1.18)	1.15 (1.08, 1.24)	0.97 (0.92, 1.02)	1.07 (1.03, 1.12)	0.89 (0.76, 1.04)	1.72 (1.65, 1.81)	1.79 (1.47, 2.19)
P for trend	<0.001	<0.001	0.767	<0.001	0.899	<0.001	<0.001
GI disease,[f] RR (95% CI)							
Without	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
With	0.82 (0.80, 0.84)	1.32 (1.26, 1.39)	1.23 (1.19, 1.27)	1.16 (1.13, 1.19)	1.04 (0.95, 1.14)	1.44 (1.39, 1.49)	1.44 (1.24, 1.66)
CV disease,[g] RR (95% CI)							
Without	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
With	0.79 (0.77, 0.82)	0.91 (0.86, 0.98)	1.14 (1.10, 1.20)	1.32 (1.27, 1.36)	1.25 (1.11, 1.41)	1.36 (1.30, 1.42)	1.37 (1.14, 1.65)
CKD,[h] RR (95% CI)							
Without	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
With	0.90 (0.87, 0.93)	1.03 (0.97, 1.10)	1.04 (1.00, 1.09)	1.24 (1.20, 1.28)	1.28 (1.14, 1.43)	1.17 (1.12, 1.23)	1.43 (1.21, 1.70)
TDI,[i] RR (95% CI)							
1	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
2	1.03 (0.97, 1.07)	1.02 (0.96, 1.09)	1.05 (1.01, 1.10)	1.13 (1.08, 1.17)	1.09 (0.96, 1.24)	1.18 (1.12, 1.24)	1.09 (0.96, 1.24)
3	1.06 (0.98, 1.14)	1.06 (0.98, 1.14)	1.13 (1.08, 1.19)	1.32 (1.27, 1.38)	1.04 (0.91, 1.19)	1.44 (1.36, 1.51)	1.30 (0.96, 1.63)

(continued)

Table 3 Continued

	Oral ns-NSAIDs	Oral COX-2	Topical NSAIDs	Oral paracetamol	Topical salicylate	Oral opioids	Transdermal opioids
4	1.05 (0.99, 1.10)	1.09 (0.99, 1.20)	1.27 (1.21, 1.34)	1.52 (1.46, 1.59)	1.17 (0.94, 1.39)	1.77 (1.68, 1.86)	1.45 (0.98, 1.91)
5	1.07 (0.98, 1.15)	1.07 (0.99, 1.16)	1.35 (1.28, 1.43)	1.70 (1.62, 1.79)	1.25 (0.97, 1.53)	2.01 (1.90, 2.13)	1.46 (0.96, 1.94)
P for trend	0.217	0.171	<0.001	<0.001	0.214	<0.001	0.107

[a]Adjusted for sex, year, Townsend Deprivation Index, and practice location. [b]Adjusted for age, year, Townsend Deprivation Index, and practice location. [c]Adjusted for age, sex, year, Townsend Deprivation Index, practice location, smoking status and drinking status. [d]Adjusted for age, sex, year, Townsend Deprivation Index, practice location, BMI and smoking status. [e]Adjusted for age, sex, year, Townsend Deprivation Index, practice location, BMI and drinking status. [f]Adjusted for age, sex, year, Townsend Deprivation Index, practice location, BMI, smoking status, drinking status, CV disease and CKD. [g]Adjusted for age, sex, year, Townsend Deprivation Index, practice location, BMI, smoking status, drinking status, GI disease and CKD. [h]Adjusted for age, sex, year, Townsend Deprivation Index, practice location, BMI, smoking status, drinking status, GI disease and CV disease. [i]Townsend Deprivation Index ranged from 1 (least deprived) to 5 (most deprived); adjusted for age, sex, year and practice location. ns-NSAIDs: non-selective NSAIDs; COX-2: cyclooxygenase-2; RR: risk ratio; GI: gastrointestinal; CV: cardiovascular; CKD: chronic kidney disease; TDI: Townsend Deprivation Index.

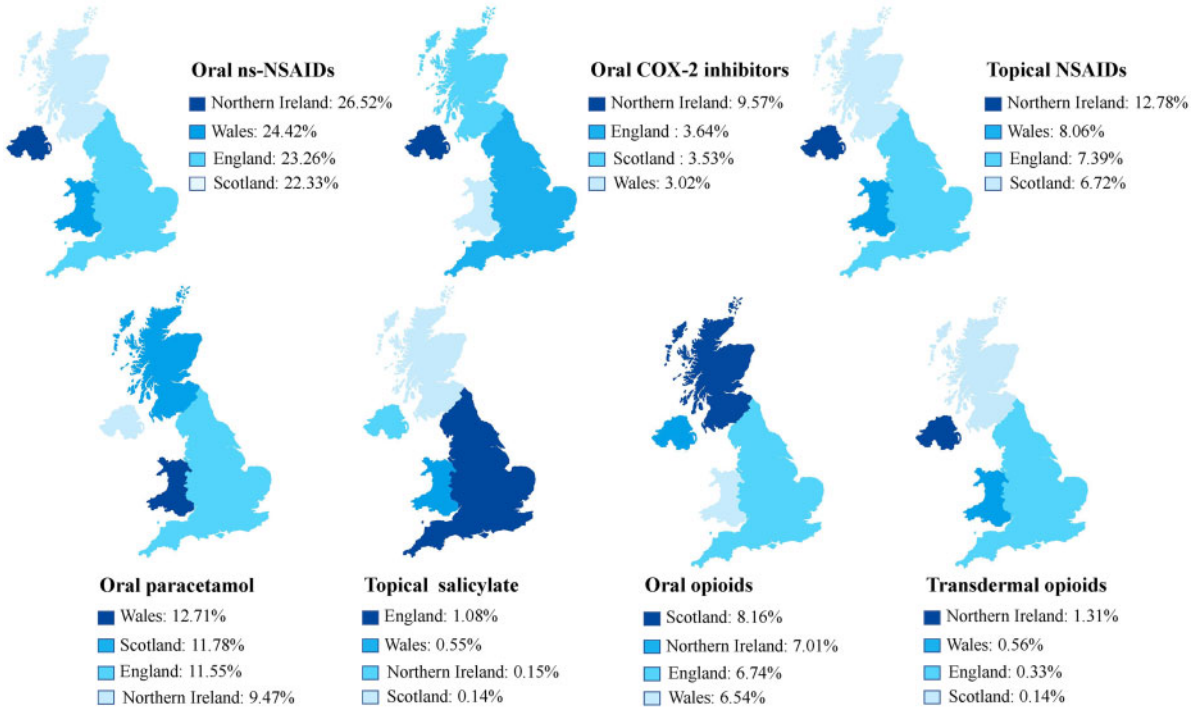
that tramadol does not provide better pain relief for patients with OA [33], but associates with a higher risk of all-cause mortality than commonly used oral NSAIDs [14]. Thus, a re-evaluation of its risk-benefit ratio in OA treatment is warranted.

We also found apparent geographic variation in initial analgesic prescription. Notably, oral opioids were more often prescribed initially in Scotland than other regions of the UK. This finding was substantiated by a recent report that drug-related death rates in Scotland were the highest in Europe [34]. Interestingly, OA treatment guidelines appear to vary among the regions in the UK. The NICE guideline, which officially only serves England, recommends that topical NSAIDs and/or oral paracetamol be considered ahead of opioids [3], whereas the Scottish Intercollegiate Guidelines Network (SIGN) guideline recommends that strong opioids should be considered as an option for pain relief for patients with OA [35]. This may, in part, explain the higher incidence of initial prescription of oral opioids in Scotland.

Limitations

Our study has several limitations. First, we only studied seven categories of commonly prescribed analgesics among patients with incident OA. Other analgesics, such as topical capsaicin, may also be used for the management of OA pain. The trend and impact of other analgesics, although less commonly prescribed, should be examined in future studies. Second, medications prescribed by GPs may not equate with what patients take. For instance, patients may not hand in their prescriptions, or may not take the medication according to instruction. Third and very importantly, administrative data lack information concerning over-the-counter medications (e.g. paracetamol and topical NSAIDs) so we cannot determine whether incident OA patients had already tried over-the-counter analgesics before they consulted their GPs. This might partially explain why some GPs initially prescribed opioids, as patients may already have tried over-the-counter paracetamol and topical NSAIDs but obtained insufficient relief. However, we limited the initiation period within 30 days after the first diagnosis, which may minimize this bias. In addition, the differences in prescription patterns between patients <60 years and those ≥60 years are influenced by costs, rather than by clinical factors, as GPs may be more likely to prescribe topical NSAIDs and paracetamol for the elderly simply because they are allowed free prescriptions after the age of 60. Fourth, in such an indirect database study we could not determine with any certainty the precise rationale for the analgesic prescription or comment on the inappropriateness of the analgesic choice. However, we only included patients with incident OA and assessed prescriptions within 30 days after OA diagnosis, and excluded people with a history of cancer or who had received prescriptions of the analgesics of interest within six months prior to diagnosis of OA. Therefore, it would seem very likely that analgesics prescribed during this time period were for management of

Fig. 2 Association between practice location with initial analgesic prescription among patients with incident clinical OA



ns-NSAIDs: non-selective NSAIDs; COX-2: cyclooxygenase-2.

OA-related pain. Fifth, we were unable to examine the association between availability of analgesics as a practice-level factor and trend of initial analgesic prescription in the present study as these data are not available in the THIN database. Sixth, THIN is a consultation-based database where only people who had consulted their GPs were included in this analysis. Unlike other diseases, such as CV diseases, a proportion of people with OA do not seek for care primarily for OA and some of them may have been identified through the consultation for other diseases. Incident OA was defined as the first Read code recorded in THIN database that could lead to the underdiagnosis of OA and affect the estimate of initial analgesic prescriptions. Lastly, the current study only described the trends of initial analgesic prescriptions for OA in UK till 2016; further studies with concurrent data are needed to assess whether the trends uncovered in the present study are still continuing.

Clinical implications

In our study, ~10% of initial prescriptions among patients with incident OA were for paracetamol. Although the NICE OA guideline recommends paracetamol as the first line analgesic in pain management [3], more evidence has accumulated on its inefficacy and risk of GI events [9–13]. Thus, concerns have been raised by professional organisations, including NICE, regarding its appropriateness as a systemic analgesic for OA. In addition, a noticeable incidence of the initial prescription of analgesics seemed to not accord with current guidelines from regulatory agencies (i.e. NICE OA guidelines) [3]. Therefore, developing more effective dissemination and education programs of pain management according to NICE guidelines appears to be needed for primary care physicians.

Conclusion

The initial prescription of analgesics for OA has shifted in the UK. Prescription of oral NSAIDs has reduced, but for other analgesics, including oral opioids, prescription has increased. Oral opioids are prescribed more often in women, elderly, obesity, current alcohol drinkers, current smokers, those with GI, CV or renal co-morbidities, and those living in the socially deprived areas and in Scotland. Co-prescription of gastroprotective agents with oral NSAIDs remains suboptimal, even in those with prior GI disease.

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Y.Z. and G.L. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. G.L. and Y.Z. contributed equally. C.Z. is first author. All authors have

TABLE 4 Association between practice-level predictors with initial analgesic prescription among patients with incident OA (2000–2016)

	Oral ns-NSAIDs	Oral COX-2	Topical NSAIDs	Oral paracetamol	Topical salicylate	Oral opioids	Transdermal opioids
Practice size,[a] RR (95% CI)							
≤ 10,618 (*n*=197)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
10 619–17 002 (*n*=198)	1.00 (0.91, 1.10)	0.91 (0.74, 1.12)	1.08 (0.94, 1.23)	0.97 (0.87, 1.08)	1.02 (0.66, 1.56)	1.05 (0.93, 1.18)	0.82 (0.58, 1.14)
17 003–25 586 (*n*=198)	0.95 (0.87, 1.05)	0.83 (0.68, 1.02)	1.06 (0.93, 1.21)	1.04 (0.94, 1.15)	0.83 (0.55, 1.26)	1.06 (0.94, 1.19)	0.78 (0.50, 1.06)
≥ 25 587 (*n*=197)	0.97 (0.89, 1.07)	0.95 (0.77, 1.16)	1.08 (0.95, 1.23)	0.90 (0.81, 1.01)	0.80 (0.54, 1.21)	0.91 (0.81, 1.03)	0.72 (0.42, 1.02)
P for trend	0.618	0.347	0.296	0.359	0.537	0.294	0.263
Practice location,[b] RR (95% CI)							
England (*n*=515)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Northern Ireland (*n*=43)	1.14 (0.99, 1.31)	2.63 (1.96, 3.52)	1.73 (1.43, 2.10)	0.82 (0.70, 0.97)	0.14 (0.06, 0.33)	1.04 (0.87, 1.25)	3.96 (2.67, 5.88)
Scotland (*n*=145)	0.96 (0.89, 1.04)	0.97 (0.73,1.24)	0.91 (0.81, 1.01)	1.02 (0.93, 1.11)	0.13 (0.08, 0.20)	1.21 (1.09, 1.33)	0.41 (0.29, 0.58)
Wales (*n*=87)	1.05 (0.95, 1.17)	0.83 (0.65, 1.07)	1.09 (0.94, 1.26)	1.10 (0.97, 1.24)	0.51 (0.32, 0.80)	0.97 (0.84, 1.11)	1.70 (1.22, 2.37)
P for homogeneity test[c]	0.059	0.003	<0.001	0.032	0.019	0.009	<0.001

[a]The number of patients registered with practice; adjusted for age, sex, year, Townsend Deprivation Index and practice location. [b]Adjusted for age, sex, year and Townsend Deprivation Index. [c]*P*-value was for test of homogeneity. *n*: number of general practitioners; ns-NSAIDs: non-selective NSAIDs; COX-2: cyclooxygenase-2; RR: risk ratio.

read, provided critical feedback on intellectual content and approved the final manuscript. Concept and design: Y.Z., G.L., W.Z. and C.Z. Acquisition, analysis, or interpretation of data: all authors. Drafting of the manuscript: C.Z. and W.Z. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: J.W. and X.L. Obtained funding: C.M., G.L., C.Z. and J.W. Administrative, technical or material support: Y.Z. and G.L. Supervision: G.L., Y.Z. and W.Z. THIN is a registered trademark of Cegedim SA in the United Kingdom and other countries. Reference made to the THIN database is intended to be descriptive of the data asset licensed by IQVIA. This work uses de-identified data provided by patients as a part of their routine primary care. The lead author affirms that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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