Original article

Analgesic prescribing in patients with inflammatory arthritis in England: an observational study using electronic healthcare record data

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Abstract

Objectives. International data suggest inflammatory arthritis (IA) pain management frequently involves opioid prescribing, despite little evidence of efficacy, and potential harms. We evaluated analgesic prescribing in English National Health Service-managed patients with IA.

Methods. Repeated cross-sectional analyses in the Consultations in Primary Care Archive (primary care consultation and prescription data in nine general practices from 2000 to 2015) evaluated the annual prevalence of analgesic prescriptions in: (i) IA cases (RA, PsA or axial spondyloarthritis [SpA]), and (ii) up to five age-, sex- and practice-matched controls. Analgesic prescriptions were classified into basic, opioids, gabapentinoids and oral NSAIDs, and sub-classified into chronic and intermittent ($\geq$3 and 1–2 prescriptions per calendar year, respectively).

Results. In 2000, there were 594 cases and 2652 controls, rising to 1080 cases and 4703 controls in 2015. In all years, most (65.3–78.5%) cases received analgesics, compared with fewer (37.5–41.1%) controls. Opioid prescribing in cases fell between 2000 and 2015 but remained common with 45.4% (95% CI: 42.4%, 48.4%) and 32.9% (95% CI: 29.8%, 36.0%) receiving at least 1 and $\geq$3 opioid prescriptions, respectively, in 2015. Gabapentinoid prescription prevalence in cases increased from 0% in 2000 to 9.5% (95% CI: 7.9%, 11.4%) in 2015, and oral NSAID prescription prevalence fell from 53.7% (95% CI: 49.6%, 57.8%) in 2000 to 25.0% (95% CI: 22.4%, 27.7%) in 2015. Across years, analgesic prescribing was commoner in RA than PsA/axial SpA, and 1.7–2.0 times higher in cases than controls.

Conclusions. Analgesic prescribing in IA is common. This is at variance with existing evidence of analgesic efficacy and risks, and guidelines. Interventions are needed to improve analgesic prescribing in this population.

Key words: inflammatory arthritis, pain, analgesics, opioids

CLINICAL SCIENCE

Rheumatology key messages

- Analgesic prescribing in NHS-managed patients with IA is common.
- Oral NSAID prescriptions have fallen substantially from 2000 to 2015 in patients with IA.
- Many patients with IA receive long-term opioid prescriptions.

Introduction

Inflammatory arthritis (IA) is an umbrella-term for conditions causing autoimmune joint inflammation. Its main forms—RA, PsA and axial spondyloarthritis (axial SpA)—affect 1–2% of adults in the UK [1–3]. Pain is a major problem for patients with IA, with research consistently demonstrating high pain levels, and pain reported by patients as their priority area for health improvement [4, 5]. While achieving remission from disease activity improves pain, it often fails to resolve it [6], with pain intensity scores remaining similar in cohorts of patients with RA over the last few decades despite falling disease activity [7]. There is, therefore, an urgent need to improve pain management

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for patients with IA, as exemplified in the Versus Arthritis Research Pain Roadmap, whose central vision is 'an end to pain'.

With the exception of NSAIDs in axial SpA, systematic reviews evaluating trials of analgesics in IA demonstrate little impact on pain [8, 9]. Furthermore, analgesics potentially harbour substantial harms, with a previous study attributing 18% of admissions in two large National Health Service (NHS) hospitals to adverse drug reactions from non-aspirin NSAIDs or opioids [10]. Consequently, guidelines recommend a biopsychosocial approach to IA pain management, focusing on non-drug care [11].

Despite this evidence base, international data demonstrate analgesics are widely prescribed in IA, with up to 40% of North American patients with RA being 'regular' opioid users [12–14]. Opioid prescribing is also prominent in patients with RA receiving biologics; in the Australian biologics registry, one-third of patients with RA received opioids, with only 38% opioid-naïve at 5 years [15]. Few data exist on analgesic prescribing in patients with IA managed in the English NHS. One historical evaluation of NSAID risks among patients with IA in the Norfolk Arthritis Registry reported that 81.7% were ever-NSAID users between 1990 and 2003 [16]. Another study evaluated the proportion of patients with PsA receiving analgesics at some point post-diagnosis in The Health Improvement Network primary care database: 73.3% and 23.7% had received prescription NSAIDs and opioids, respectively [17].

The crucial first step towards improving NHS IA pain management is to define current practice. Our study has addressed this from the perspective of analgesic prescribing. Its primary aim was to report the annual prevalence of primary care analgesic prescriptions in patients with IA (cases), compared with patients without inflammatory rheumatic conditions (controls). Secondary aims were to (i) report the annual prevalence of long-term analgesic prescriptions and the co-prescribing of gastro-protection to cases receiving NSAID prescriptions (in line with national guidance [18, 19]), and (ii) evaluate the relationship between national initiatives for safer oral NSAID prescribing [20, 21] and changes in the annual prevalence of NSAID prescriptions.

Methods

Study design

Repeated cross-sectional analyses in cases and controls registered with practices contributing to the Consultations in Primary Care Archive (CiPCA) between 2000 and 2015 were conducted. CiPCA is a database of anonymized medical record data from nine general practices in North Staffordshire, UK. It includes records from ~200 000 patients. Practices have a research agreement with Keele University, coding clinical activity to a high standard [22]. Data quality is at least comparable to national general practice databases [23]. Of the UK population, >98% are registered with a primary care

general practitioner (GP), who acts as the gatekeeper to other NHS services, referring to secondary care if needed (who feedback information to GPs about their patients including diagnoses) and overseeing most prescriptions (including those initiated by specialists).

CiPCA received research database ethics approval from the North West – Haydock REC ref: 17/NW/0232 (date 20 April 2017). The current study was approved by the CiPCA Academic Custodianship Committee prior to commencement of data analysis.

As personally identifiable data are not extracted from practices into CiPCA (with each patient given a unique anonymised ID by EMIS Health during data extraction before data are supplied to Keele University, which means that researchers cannot identify patients) patients are not asked for consent for their data to be downloaded. Contributing practices advertise to patients that they are a research practice through leaflets and posters displayed within the practice. Patients who state they do not wish for their anonymised records to be used for research are tagged on the eleectronic computer system and their records are not included in the extraction by EMIS Health.

Subjects

Cases

In each calendar year, patients with existing diagnoses of RA, PsA or axial SpA aged ≥18 years were identified using Read codes (coded clinical terms) and for RA synthetic DMARD prescriptions. For patients with RA, the Read code list/algorithm devised by Thomas *et al.* and updated by Muller *et al.* was used (>80% sensitivity/specificity) [24, 25]. We removed Read codes for 'adult Still's disease', 'rheumatoid arthritis of DIP joint of finger', 'rheumatoid arthritis of sacro-iliac joint', 'juvenile rheumatoid arthritis—Still's disease', 'adult-onset Still's disease', and 'remitting seronegative symmetrical synovitis with pitting oedema' (representing distinct diseases or being joints not classically affected by RA). For PsA, Read codes complied by Ogdie *et al.* were used (positive predictive value of 85%) [17], substituting the code 'other psoriatic arthropathies' for 'juvenile arthritis in psoriasis'. For axial SpA, a new Read code list was devised (existing lists for identifying ankylosing spondylitis do not consider non-radiographic axial SpA). A Read code for 'ankylosing spondylitis' has a positive predictive value of 72% [26]. Read codes are provided in Supplementary Tables S1–S3 (available at *Rheumatology* online). Patients with ≥1 full calendar year of data on 1 January following their diagnosis of IA were included; only patients with full calendar years of data were included in each calendar year of analysis (allowing prescription chronicity to be evaluated).

Controls

In each calendar year, up to five birth year-, sex- and practice-matched controls for each case were identified. Controls were patients without RA, PsA, axial SpA and other major inflammatory rheumatic conditions comprising

gout, SLE and vasculitis (defined as never having Read codes for these conditions; Read code lists are shown in Supplementary Tables S4–S6, available at *Rheumatology* online). Controls needed to have a full calendar year of data available for the calendar year in which they were included in the analysis.

Analgesic classification

We used the hierarchical analgesic classification scheme developed by Bedson *et al.* [21]. Devised using consensus methods involving 25 GPs, this comprises five analgesic groups of increasing potency, and a separate unclassifiable strength group (oral NSAIDs). Group 1 comprises basic analgesics (e.g. paracetamol); groups 2–5 comprise opioids and compound medications containing opioids of increasing strength (weak, moderate, strong, very strong); and group 6 comprises oral NSAIDs. For this study, we included an additional group 7, comprising oral gabapentinoids (pregabalin/gabapentin).

Prescription chronicity

To understand the burden of long-term prescribing, cases and controls receiving opioid prescriptions were classified as receiving (i) 'chronic' prescriptions if they received ≥3 prescriptions in a calendar year (assuming a 28-day supply per prescription [13], and consistent with existing definitions of long-term opioid therapy [27, 28]), or (ii) 'intermittent' prescriptions, if they received 1–2 prescriptions in each calendar year. This was repeated for basic analgesics, oral NSAID and gabapentinoid prescriptions.

Analgesic prescription prevalence

The annual prevalence of analgesic prescriptions was calculated. The numerator was the number of people receiving ≥1 analgesic prescription in a calendar year. The denominator was the number of people contributing data within that calendar year. Annual prevalence was reported for any analgesic or analgesic subgroups separately. Annual prevalence was further reported by (i) IA subtypes and (ii) age groups (<40, 40–70, >70 years) and gender. Approximate ages were calculated, subtracting patient birth year from the current calendar year (to preserve anonymization, day and month of birth data were unavailable). Annual prevalence of chronic and intermittent analgesic prescriptions was also reported.

Other prescription prevalence

The proportion of people prescribed an oral NSAID also co-prescribed gastro-protection (proton pump inhibitor and/or H2-receptor antagonist) and the annual prevalence of synthetic DMARD prescriptions were calculated in each calendar year in cases. Additionally, the proportion of NSAID prescriptions in which gastro-protection was co-prescribed on the same date was calculated in cases in each calendar year. Biologic prescribing data were unavailable (prescribed through secondary care, unlike analgesics, which are mainly GP-prescribed).

Relationship between trends in oral NSAID prescribing and national initiatives

We used joinpoint regression to identify calendar years where a marked change (the 'joinpoint') in the trend in the annual prevalence of oral NSAID prescriptions occurred [29]. Permutation tests (Monte Carlo methods) determined the minimum number of joinpoints providing an adequate fit to the data. A significance level of 5% was used to assess the need for additional joinpoints, starting from zero and up to a maximum of two joinpoints (15 calendar years). The annual percentage change (representing the percentage change in prescribing prevalence/year) was estimated for each time period separated by identified joinpoints. Time points were compared with dates of Medical Healthcare Regulatory Authority (MHRA) interventions to deliver safer NSAID prescribing, which started in 2004 [20].

Statistical program

Analyses were conducted using R (version 4.1.0; R Foundation for Statistical Computing, Vienna, Austria) and the National Cancer Institute's joinpoint regression programme (version 4.9.0; USA) [30].

Results

Patients

The number of cases and controls increased yearly from 594 cases and 2652 controls in 2000 to 1080 cases and 4703 controls in 2015. The increase in cases reflects the fact that each calendar year includes prevalent and incident cases (the latter from the preceding calendar year) and many cases remained registered for the majority or whole of the study period (Supplementary Figs S1 and S2, available at *Rheumatology* online). The increase in cases is in line with the expected annual incidence of IA (15–35 per 100 000) [31].

In all years, more were female (annual proportions ranging 56.4–58.7% in cases, and 58.6–60.6% in controls). Mean age increased over time, from 59.3 (95% CI: 58.2, 60.4) years in 2000 to 62.1 (95% CI: 61.2, 62.9) years in 2015 in cases, and 60.5 (95% CI: 60.0, 61.0) years in 2000 to 63.0 (95% CI: 62.6, 63.4) years in 2015 in controls. The minor differences in mean age or gender of cases and controls reflects the fact that across years, matching controls could not be obtained for 7.9–14.6% of cases (Supplementary Table S7, available at *Rheumatology* online).

In all years, the most frequent IA diagnosis was RA (52.9–60.9%), then axial SpA (28.6–31.0%) and PsA (10.4–16.1%). Among cases, 46.5–51.9% in each year received synthetic DMARDs (68.8–73.8% RA; 5.9–9.4% axial SpA; 37.7–47.7% PsA).

Fɪɢ. 1 Annual prevalence of analgesic prescriptions in cases and controls
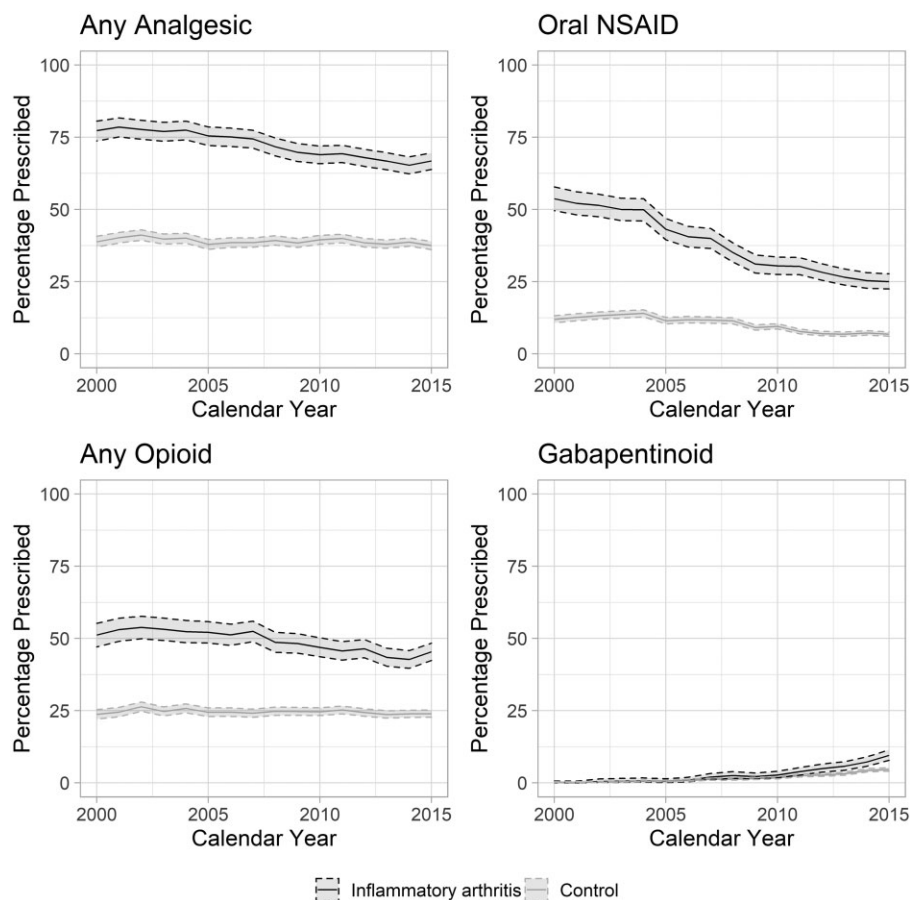
Annual prevalence of analgesic prescriptions with 95% CIs plotted in each calendar year. 'Inflammatory arthritis' comprises patients with RA, PsA and axial spondyloarthritis. 'Controls' comprise up to five age-, sex- and practice-matched patients without inflammatory rheumatic conditions for each patient with inflammatory arthritis in each calendar year.

Annual analgesic prescription prevalence

Any analgesic
In all years the majority of cases received an analgesic prescription, falling slightly over time (Fig. 1; Supplementary Table S8, available at *Rheumatology* online). In 2000, 77.3% (95% CI: 73.7%, 80.6%) received an analgesic prescription, peaking at 78.5% (95% CI: 75.1%, 81.7%) in 2001, and gradually falling to 66.8% (95% CI: 63.9%, 69.6%) in 2015. In all years, substantially more cases received an analgesic prescription than controls, with prescription prevalence 1.7–2.0 times higher. In all years, analgesic prescriptions were commoner in RA than in axial SpA/PsA (Fig. 2).

Oral NSAIDs
Substantial reductions in the annual prevalence of oral NSAID prescriptions were observed over time in cases, and to a lesser extent in controls (Fig. 1). In 2000, 53.7% (95% CI: 49.6%, 57.8%) of cases and 11.9% (95% CI: 10.7%, 13.2%) of controls received an oral NSAID prescription, falling to 25.0% (95% CI: 22.4%, 27.7%) of

cases, and 6.8% (95% CI: 6.1%, 7.5%) of controls in 2015. In all years, substantially more cases received an oral NSAID prescription than controls, with prescription prevalence being 3.1–4.5 times higher. Similar oral NSAID prescribing was seen in RA and PsA, with a lower prevalence in axial SpA (Fig. 2).

Opioids
Minor reductions in the annual prevalence of opioid prescriptions were observed over time in cases but not controls (Fig. 1). In 2000, 51.2% (95% CI: 47.1%, 55.3%) of cases received an opioid prescription, falling to 45.4% (95% CI: 42.4%, 48.4%) in 2015. In all years, more cases received an opioid than controls (prescription prevalence 1.8–2.1 times higher). Opioid prescribing was commoner in RA than PsA/axial SpA (Fig. 2).

Similar trends in the annual prevalence of weak/moderate strength opioid prescriptions were seen in cases and controls (Fig. 3), with the prevalence of weak opioid prescriptions rising, peaking in 2006 (29.2% [95% CI: 26.0%, 32.6%] of cases), then falling. The prevalence of

Fɪɢ. 2 Annual prevalence of analgesic prescriptions by inflammatory arthritis sub-types
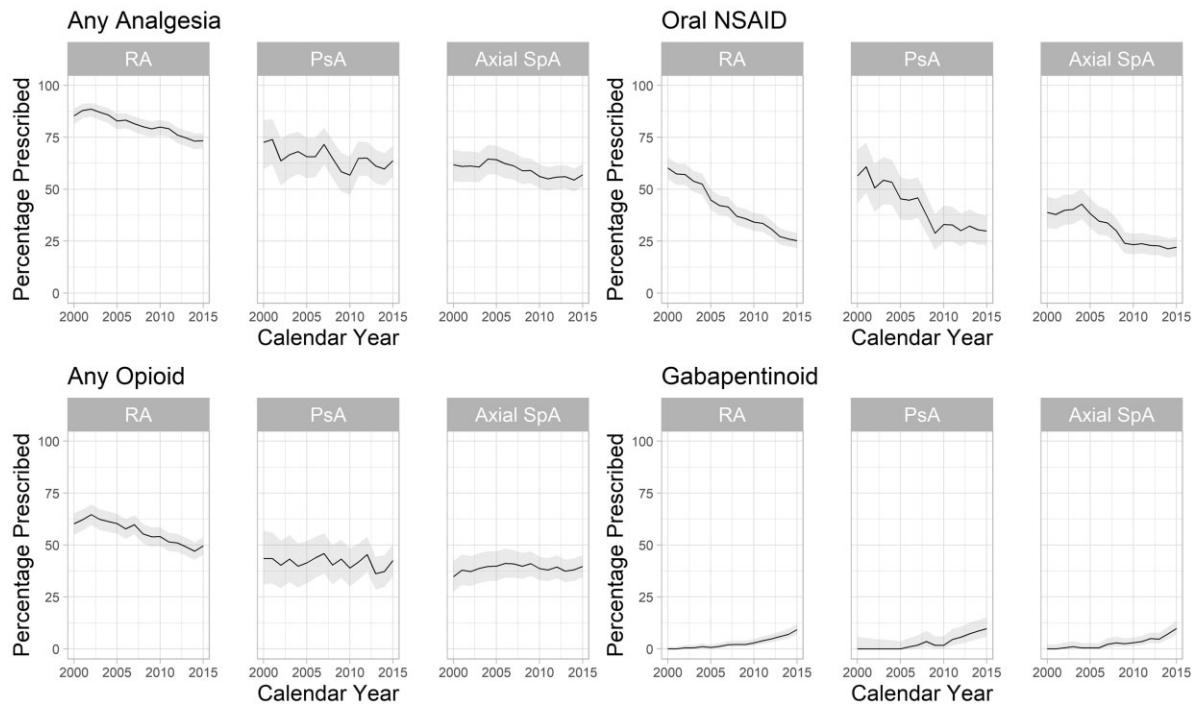
Annual prevalence of analgesic prescriptions with 95% CIs plotted in each calendar year.

moderate opioid prescriptions fell substantially between 2000 and 2007 in cases (27.6% [95% CI: 24.0%, 31.4%] to 9.0% [95% CI: 7.1%, 11.2%]), and to a lesser extent in controls, before becoming relatively static. The annual prevalence of strong opioid prescriptions was relatively static in cases between 2000 and 2005, and 2008 and 2015, with an increase observed in between; in controls the annual prevalence of strong opioid prescriptions gradually increased over time. The annual prevalence of very strong opioid prescriptions gradually increased over time in cases and controls.

Gabapentinoids

Between 2000 and 2006 the annual prevalence of gabapentinoid prescriptions was very low (<1% of cases and controls in each year). In 2007 it gradually rose from 2.0% (95% CI: 1.2%, 3.3%) to 9.5% (95% CI: 7.9%, 11.4%) in 2015 in cases, and 1.2% (95% CI: 0.9%, 1.6%) to 4.7% (95% CI: 4.1%, 5.3%) in 2015 in controls. From 2007 onwards the annual prevalence of gabapentinoid prescriptions was consistently higher (1.5–2.0 times) in cases than controls. Prescribing was similar across IA subtypes.

Annual prevalence of chronic prescriptions

Basic analgesics

Chronic basic analgesic prescriptions were commoner in cases than controls. They increased slightly over time in cases and controls from 16.8% (95% CI: 13.5, 20.4) and 8.6% (7.2%, 10.0%), respectively, in 2000 to 22.7%

(95% CI: 19.9%, 25.6%) and 12.6% (95% CI: 11.4%, 13.7%), respectively, in 2015 (Fig. 4 and Supplementary Table S9, available at *Rheumatology* online). Intermittent basic analgesic prescriptions were stable in both cases and controls.

Oral NSAIDs

Chronic NSAID prescriptions were common in cases in 2000, with 44.8% (95% CI: 40.6%, 49.1%) receiving ≥3 NSAID prescriptions, falling over time to 17.9% (95% CI: 15.4%, 20.5%) in 2015 (Fig. 4). Intermittent NSAID prescriptions were relatively static; never NSAID prescribing increased. Few controls received NSAID prescriptions, although chronic NSAID prescribing also fell slightly over time.

Opioids

Chronic opioid prescriptions were common in cases in 2000, with 40.7% (95% 36.5%, 45.0%) receiving ≥3 opioid prescriptions (Fig. 4). While chronic opioid prescribing decreased gradually over time, the reduction was less than that observed with NSAIDs, with 32.9% (95% CI: 29.8%, 36.0%) receiving ≥3 opioid prescriptions in 2015. As with NSAIDs, intermittent opioid prescribing prevalence was relatively static, and never opioid prescribing prevalence increased. Substantially fewer controls received chronic opioid prescriptions than cases, with similar levels of intermittent opioid prescribing observed (Fig. 4). Chronic and intermittent opioid prescribing prevalence was relatively static over the 15 years in controls.

Fɪɢ. 3 Annual prevalence of opioid prescriptions in cases and controls
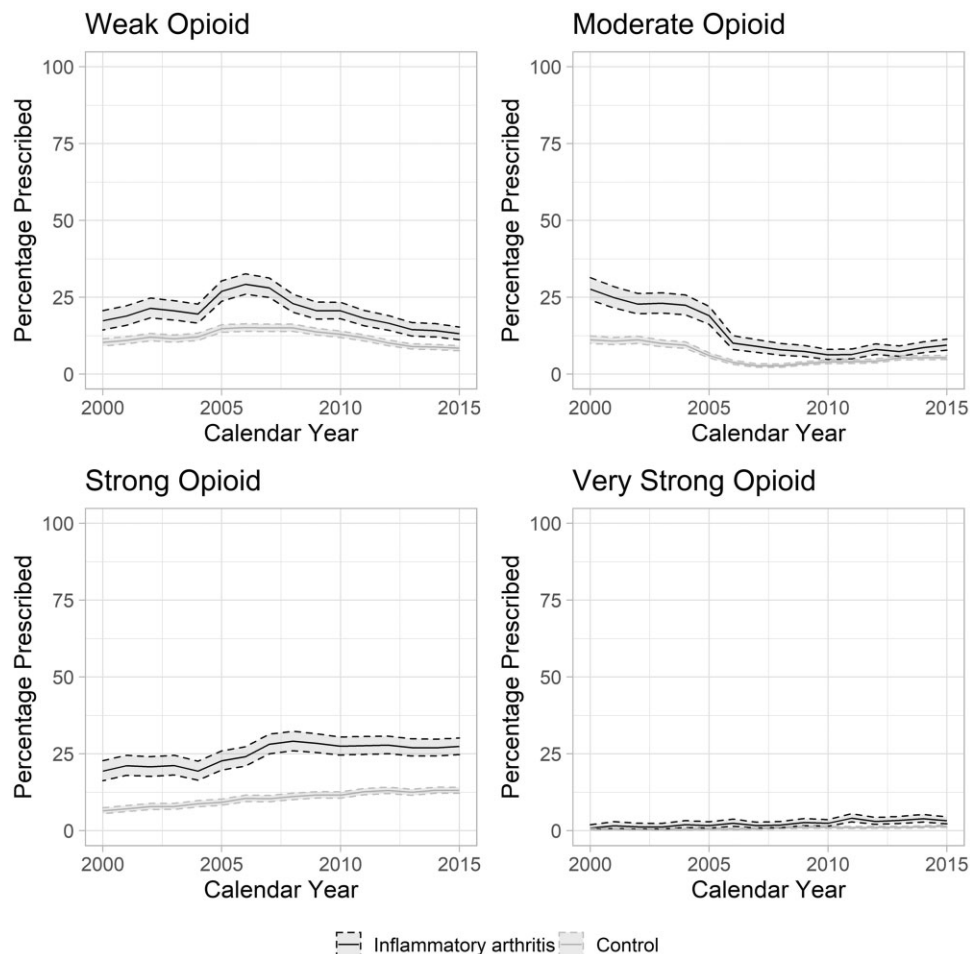
Annual prevalence of opioid prescriptions with 95% CIs plotted in each calendar year. 'Inflammatory arthritis' comprises patients with rheumatoid arthritis, PsA and axial spondyloarthritis. 'Controls' comprises up to five age-, sex- and practice-matched patients without inflammatory rheumatic conditions for each patient with inflammatory arthritis in each calendar year. Opioid strength classified using the approach developed by Bedson *et al*. [21].

Gabapentinoids
Chronic gabapentinoid prescriptions were commoner than intermittent prescriptions and both increased over time in cases and controls (Fig. 4). In 2015, 5.9% (95% CI: 4.4%, 7.6%) and 3.3% (95% CI: 2.8%, 3.9%) of cases and controls received chronic gabapentinoid prescriptions, respectively.

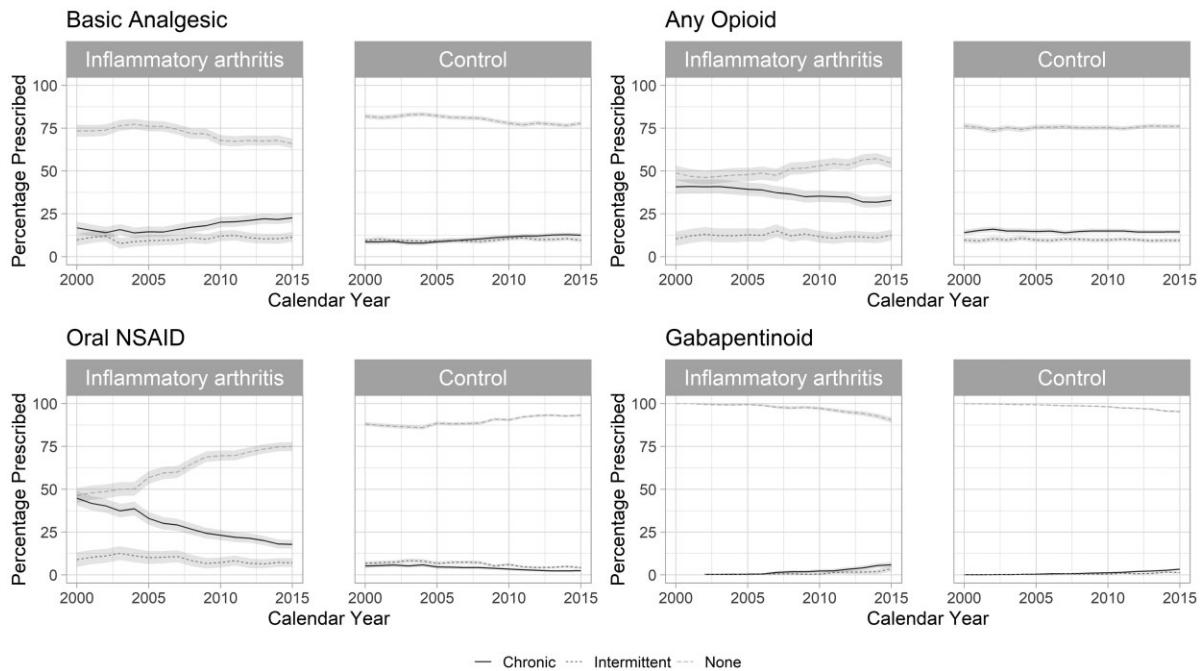### Annual prevalence of analgesic prescriptions by age and gender

Age
The annual prevalence of analgesic prescriptions increased with age in cases (Supplementary Table S8, available at *Rheumatology* online). In those aged <40 years, the annual prevalence of any analgesic prescription ranged from 49.2% (95% CI: 36.4%, 62.1%) to 70.3% (95% CI: 57.6%, 81.1%); in those aged 40–70 years it ranged from 61.8% (95% CI: 58.0%, 65.5%)

to 79.1% (95% CI: 74.9%, 82.9%); in those aged >70 it ranged from 75.5% (95% CI: 70.5%, 80.1%) to 91.2% (85.4%, 95.2%). Similar patterns were seen in controls.

Prescribing patterns for oral NSAIDs by age changed over time in cases (Fig. 5). In 2000, the annual prevalence of oral NSAID prescriptions was higher in cases aged >70 (51.1% [95% CI: 42.4%, 59.7%]) and aged 40–70 (56.2% [95% CI: 51.2%, 61.2%]) than those aged <40 (43.4% [95% CI: 31.4%, 56.7%]). However, over time oral NSAID prescribing fell more in those aged >70, compared with younger age groups, such that in 2015 the annual prevalence of oral NSAID prescriptions in those aged >70, 40–70 and <40 years was 8.7% (95% CI: 5.8%, 12.3%), 31.4% (95% CI: 27.9%, 35.0%) and 37.5% (95% CI: 26.4%, 49.7%), respectively. Changes in oral NSAID prescribing patterns were not seen over time in controls; while the annual prevalence of NSAID prescriptions fell in all age categories over 15 years, this was

Fɪɢ. 4 Annual prevalence of chronic and intermittent analgesic prescriptions in inflammatory arthritis cases and controls

Annual prevalence of prescriptions with 95% CIs plotted in each calendar year. "Inflammatory arthritis" comprises patients with rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis. "Controls" comprises up to five age, sex, and practice-matched patients without inflammatory rheumatic conditions for each patient with inflammatory arthritis in each calendar year. NSAID = non-steroidal anti-inflammatory drug. Chronic = ≥3 prescriptions in that calendar-year; intermittent = 1–2 prescriptions in that calendar-year; none: no prescriptions in that calendar year. Annual prevalence of prescriptions with 95% confidence intervals plotted in each calendar-year.

Fɪɢ. 5 Analgesic prescriptions by age and gender in cases
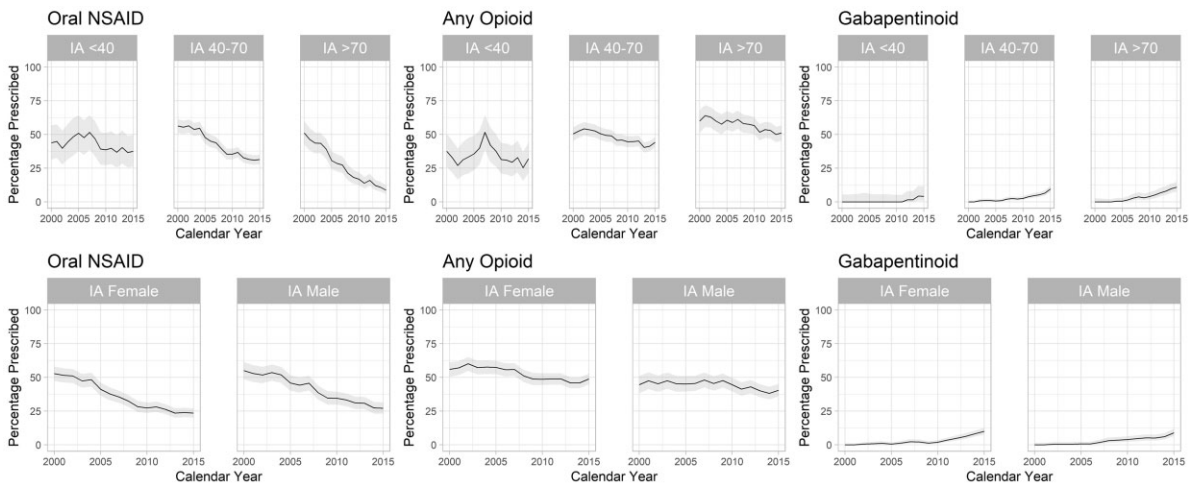
Annual prevalence of prescriptions with 95% CIs plotted in each calendar year, stratified by age and gender. Age cut-offs are in years. 'Inflammatory arthritis' comprises patients with RA, PsA and axial spondyloarthritis.

similar across age groups and the annual prevalence of NSAID prescriptions in 2000 was similar across age categories (Supplementary Fig. S3, available at *Rheumatology* online).

The annual prevalence of opioid prescriptions increased with age in cases (Fig. 5). In 2000, the annual prevalence of opioid prescriptions in those aged <40, 40–70 and >70 years was 37.5% (95% CI: 25.7%, 50.5%), 50.4%

(95% CI: 45.3%, 55.4%) and 59.9% (95% CI: 51.1%, 68.1%), respectively. While the overall annual prevalence of opioid prescriptions fell over time (albeit with an increase observed in those aged <40 between 2000 and 2007, followed by a subsequent reduction) the age differences in prescribing patterns were maintained overall. Similar patterns in opioid prescribing were seen in controls, with the highest prevalence of annual opioid prescriptions seen in those aged >70 (Supplementary Fig. S3, available at *Rheumatology* online).

As with opioids, the annual prevalence of gabapentinoid prescriptions increased with age in cases (Fig. 5), with no patients <40 receiving gabapentinoid prescriptions until the year 2012. In 2015 the annual prevalence of gabapentinoid prescriptions in cases aged <40, 40–70 and >70 years was 4.2% (95% CI: 0.9%, 11.7%), 9.5% (95% CI: 7.4%, 11.9%) and 10.8% (95% CI: 7.7%, 14.7%), respectively. Similar patterns in gabapentinoid prescribing were seen in controls (Supplementary Fig. S3, available at *Rheumatology* online).

Gender
In all years except 2000, the annual prevalence of any analgesic prescription was higher in female than male cases, although the magnitude of difference was small. In all years, the annual prevalence of NSAID prescriptions was slightly lower in females than males (Fig. 5). The opposite was seen for opioids. Gabapentinoid prescribing appeared similar in males and females. In controls, in all years except 2011 the annual prevalence of any analgesic, oral NSAID, opioid and gabapentinoid prescriptions was slightly higher in females than males (Supplementary Fig. S3, available at *Rheumatology* online).

NSAID and gastro-protection co-prescriptions

A substantial increase in co-prescribing NSAIDs with gastro-protection in cases was observed over time (Fig. 6). In 2000, the proportion of oral NSAID prescriptions with which a proton pump inhibitor and/or H2-receptor antagonist prescription was provided on the same date increased from 23.8% (95% CI: 22.1%, 25.5%) in 2000 to 63.4% (95% CI: 61.1%, 65.6%) in 2015. The proportion of cases receiving a prescription for an oral NSAID in whom a proton pump inhibitor and/ or H2-receptor antagonist prescription was also received in the same calendar year increased from 32.9% (95% CI: 27.8%, 38.4%) in 2000 to 79.3% (95% CI: 73.9%, 83.9%) in 2015.

### Relationship between NSAID prescribing and national initiatives

Joinpoint regression identified two joinpoints (Supplementary Fig. S4, available at *Rheumatology* online). The first at 2004 represented the start of a marked, sustained decline in annual NSAID prescription prevalence (annual percentage change changing from −2.26 in 2000–2004 to −8.09 in 2004–2009). The second at 2009 represented a reduction in the rate of decline in NSAID prescribing (annual percentage change −4.27 from 2009

to 2015). The 2004 time point represents the start of a series of regular MHRA announcements around the safety of oral NSAIDs [20, 21].

Discussion

Our study represents the first comprehensive analysis of English NHS analgesic prescribing in people with IA. It has three key findings. First, it demonstrates analgesic prescribing is common in IA, with two-thirds to three-quarters of patients receiving an analgesic prescription in each calendar year. Second, it shows that many analgesic prescriptions are 'long-term', with at least one-third of patients with IA receiving ≥3 opioid prescriptions in each calendar year. Third, although trends towards safer oral NSAID prescribing were observed over 15 years, the annual prevalence of opioid prescriptions remained relatively static, and gabapentinoid prescribing rose. Taken together, our findings indicate that long-term pain remains a major unresolved challenge in IA, and that this patient group is likely to contribute substantially to the current national burden of excessive opioid/gabapentinoid prescribing recently highlighted by Public Health England [32].

Several recent studies have reported high levels of opioid prescribing in patients with RA, and ankylosing spondylitis managed in non-UK settings [12–15]. In North America in the average rheumatologists' practice, 40% of patients with RA were reguarly prescribed opioids [13], and more than three-quarters of patients with ankylosing spondylitis are 'chronic' opioid users [33]. Similar opioid prescribing levels are seen in patients with RA in the Australian biologics registry [15]. Our study indicates opioid prescribing in IA is equally prevalent in the English NHS. In contrast to opioid prescribing, information on the prescribing of other analgesics in IA is limited. While studies on opioid prescribing provide some information on NSAID prescribing, this was a secondary issue reported cross-sectionally. For example, Curtis *et al.* reported that in a single calendar year (2014) 48.9%, 45.2% and 34.1% of regular, intermittent and non-users of opioids with RA also received ≥1 NSAID prescription [13]. Similarly, at Australian biologics registry entry, Black *et al.* reported that 43.6% of patients with RA were NSAID users [15]. A cross-sectional evaluation of German national health insurance data reported that among 65.5% of 3140 patients with RA receiving analgesics, ibuprofen/diclofenac were among the most commonly dispensed items [34], and anti-convulsant prescribing (including gabapentinoids) was infrequent (ranging from 3.6% in those with no/mild pain, to 9.6% in those with severe pain). To our knowledge, our study is the first to evaluate the burden of NSAID and gabapentinoid prescribing in patients with IA in any healthcare setting over time, and provides evidence that while NSAID prescribing has decined, gabapentinoid prescribing has increased. Our finding of a temporal alignment between the commencement of national initiatives for safer NSAID prescribing and a

Fig. 6 Annual prevalence of Oral NSAID and gastro-protection co-prescriptions in inflammatory arthritis cases
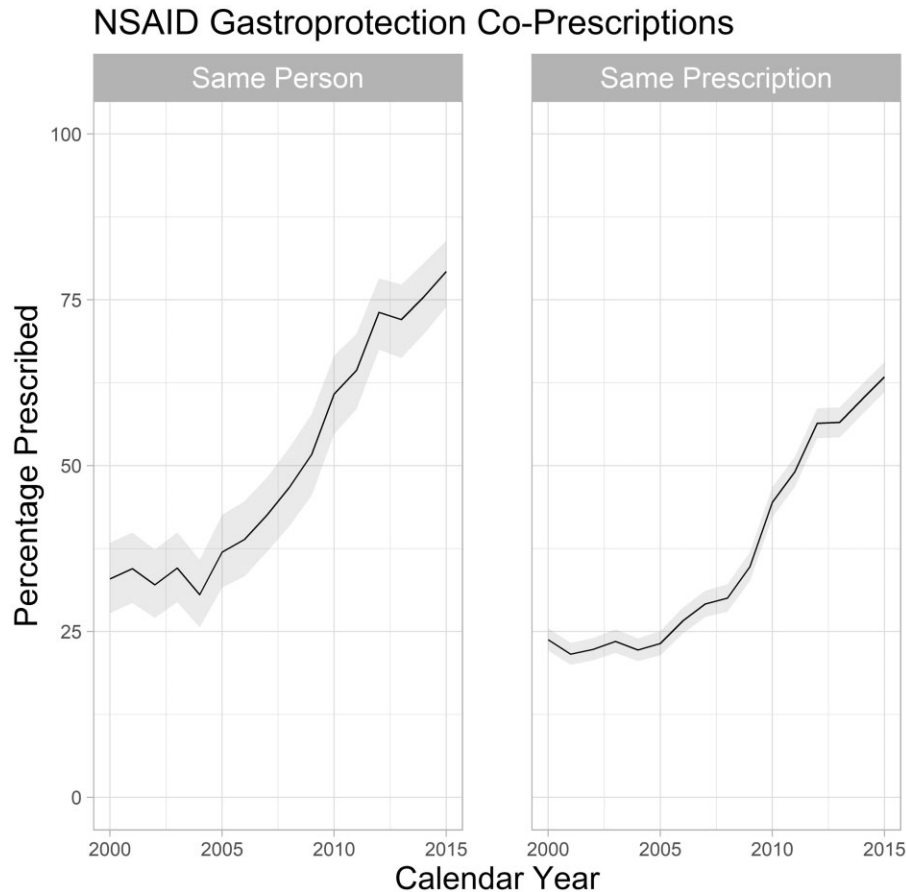
'Inflammatory arthritis' comprises patients with RA, PsA and axial spondyloarthritis. Same prescription: proportion of prescriptions for an oral NSAID that have a prescription for a proton-pump inhibitor and/or H2-receptor antagonist co-prescribed on the same date in a calendar year. Same person: proportion of patients receiving an oral NSAID prescription in a calendar year that also received a prescription for a proton-pump inhibitor and/or H2-receptor antagonist in that calendar year.

sustained acceleration in the decline in NSAID prescribing suggests these national interventions contributed to the change in prescribing practice. The impact of more recent initiatives on reducing opioid/gabapentionoid prescribing [35, 36] may have similar effects on the prescribing of these analgesics with time.

The paucity of evidence for long-term efficacy and known harms of analgesics make our finding of substantial analgesic prescribing in IA concerning. Systematic literature reviews examining the efficacy of analgesics at managing IA pain consistently demonstrate that, excepting oral NSAIDs in axial SpA [37], analgesics infrequently give clinically meaningful pain improvements [8, 9, 18, 38]. For example, a Cochrane review reported that among 11 heterogeneous studies of short-duration/high-risk of bias, while there was weak evidence opioids provided clinically relevant pain improvements, frequent adverse events offset any benefits [8]. Similarly, a systematic review informing current NICE RA guidance concluded the evidence for NSAIDs compared with

placebo is inconsistent with regards to pain relief, and while NSAIDs appear to provide some pain reduction, the magnitude of effect is often not sufficiently large to be clinically important [39]. In contrast, there is substantial evidence all analgesics [28, 40, 41] have potential harms. This is particularly highlighted in an analysis of admission data for adverse drug reactions in two large English hospitals: among 1225 admissions related to an adverse drug reaction, 30% were attributable to NSAIDs (18% aspirin, 12% other NSAIDs) and 6% to opioids [10].

Our study has several strengths. First, it considered many analgesic types, in contrast to existing studies focusing on a single analgesic class. Second, it spanned a long time period. Third, it compared analgesic prescribing across the main IA subtypes. It also has several limitations. First, it evaluated prescribing data from a single English region. Second, it evaluated primary care prescribing data; however, primary care usually takes over the prescribing of any specialist-initiated analgesics. Third, we used Read codes to identify patients

with IA, raising the possibility of misclassification. However, if misclassification were a substantial issue, we would expect it to bias our findings to the null, and we found substantially higher analgesic prescribing in cases than controls. Fourth, data on prescribing beyond 2015 are unavailable in CiPCA. However, while prescribing practice may have changed in the last 6 years, our study time frame spans the widespread implementation of early intensive treatment with combination synthetic and biologic DMARDs, and its findings are therefore of relevance to contemporary practice. Fifth, CiPCA does not contain data on over-the-counter analgesic use, which may be substantial.

In conclusion, our study demonstrates that while the annual prevalence of overall analgesic prescriptions has fallen slightly over 15 years, analgesic prescribing (particularly of long-term opioids) remains commonplace in patients with IA managed in the English NHS. Such practice reflects neither the clinical evidence nor guideline recommendations. There is an urgent need for interventions to deliver safer analgesic prescribing in this patient population. The crucial first step towards developing such interventions is to understand what drives clinician analgesic prescribing and patient analgesic use in IA.

Acknowledgements

Data availability statement

The data underlying this article cannot be shared publicly as (i) they represent pseudoanonymized routine electronic healthcare record data from local GP practices with the potential for the privacy of participating individuals to be affected; and (ii) it is a requirement of the ethical approvals that study data are analysed on Keele University's secure network. All summarized data from the study have been made available as supplementary data files.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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