Analgesia Prescribing in Patients with Inflammatory Arthritis in England: An Observational Study Using Electronic Healthcare Record Data.

Ian C Scott[1,2], James Bailey[1], Chris White[1,2], Christian D Mallen[1,2], Sara Muller[1].

Affiliations:

1. Primary Care Centre Versus Arthritis, School of Medicine, Keele University, Keele, UK.
2. Haywood Academic Rheumatology Centre, Haywood Hospital, Midlands Partnership NHS Foundation Trust, High Lane, Burslem, Staffordshire, UK.

Corresponding Author:

Ian Scott

Primary Care Centre Versus Arthritis, School of Medicine, David Weatherall Building, University Road, Keele University, Staffordshire, ST5 5BG, UK.

ORCID: 0000-0002-1268-9808

email: i.scott@keele.ac.uk

Objectives

International data suggest inflammatory arthritis (IA) pain management frequently involves opioid prescribing, despite little evidence of efficacy, and potential harms. We evaluated analgesia 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/prescription data in 9 general practices from 2000-2015) evaluated the annual prevalence of analgesia prescriptions in: (a) IA cases (rheumatoid arthritis [RA]/psoriatic arthritis [PsA]/axial spondyloarthritis [SpA]), and (b) up-to five age/sex/practice-matched controls. Analgesia prescriptions were classified into basic/opioids/gabapentinoids/oral non-steroidal anti-inflammatory drugs (NSAIDs), and sub-classified into chronic and intermittent (≥3 and 1-2 prescriptions/calendar-year, respectively).

Results

In 2000, there were 594 cases/2,652 controls, rising to 1,080 cases/4,703 controls in 2015. In all years, most (65.3-78.5%) cases received analgesia, compared with fewer (37.5-41.1%) controls. Opioid prescribing in cases fell between 2000-2015 but remained common with 45.4% (95% confidence interval [CI] 42.4%, 48.4%) and 32.9% (95% CI 29.8%, 36.0%) receiving at least 1 and ≥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, analgesia prescribing was commoner in RA than PsA/axial SpA, and 1.7-2.0 times higher in cases than controls.

Conclusions

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

Key Words

Inflammatory arthritis; pain; analgesia; opioids.

Key Messages

- Analgesia prescribing in NHS-managed patients with IA is common.
- Oral NSAID prescriptions have fallen substantially from 2000-2015 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 - rheumatoid arthritis (RA), psoriatic arthritis (PsA), axial spondyloarthritis (axial SpA) - affect 1-2% of UK adults in the United Kingdom (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). Whilst 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 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 non-steroidal anti-inflammatory drugs (NSAIDs) in axial SpA, systematic reviews evaluating trials of analgesia in IA demonstrate little impact on pain (8,9). Furthermore, analgesia 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/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 analgesia are widely prescribed in IA, with up to 40% of North American patients with RA “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). Little data exist on analgesia prescribing in patients with IA managed in the English NHS. One historical evaluation of NSAID risks amongst patients with IA in the

Norfolk Arthritis Registry reported that 81.7% were ever-NSAID users between 1990-2003 (16). Another study evaluated the proportion of patients with PsA receiving analgesia 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 analgesia prescribing. Its primary aim was to report the annual prevalence of primary care analgesia prescriptions in patients with IA (cases), compared to patients without inflammatory rheumatic conditions (controls). Secondary aims were to (a) report the annual prevalence of long-term analgesia prescriptions and the co-prescribing of gastro-protection to cases receiving NSAID prescriptions (in-line with national guidance (18,19)), and (b) 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/controls registered with practices contributing to the Consultations in Primary Archive (CiPCA) between 2000-2015 were conducted. CiPCA is a database of anonymised medical record data from 9 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 are at least comparable to national general practice databases (23). >98% of the UK population 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 20/04/2017). 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 to 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 synthetic disease-modifying anti-rheumatic drug (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/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 S1-3 (available at *Rheumatology* online). Patients with ≥1 full calendar-year of data on the 1st 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, systemic lupus erythromatosus (SLE), and vasculitis (defined as never-having Read codes for these conditions; Read code lists in Supplementary Tables S4-6, 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.

Analgesia Classification

We used the hierarchical analgesia classification scheme developed by Bedson et al (21). Devised using consensus methods involving 25 GPs, this comprises 5 analgesia groups of increasing potency, and a separate unclassifiable strength group (oral NSAIDs). Group 1 comprises basic analgesia (e.g. paracetamol); groups 2-5 comprise opioids/compound medications containing opioids of increasing strength (weak/moderate/strong/very strong);

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/controls receiving opioid prescriptions were classified as receiving (a) "chronic" prescriptions, if they received ≥3 prescriptions in a calendar-year (assuming 28-day supply per prescription (13), and consistent with existing definitions of long-term opioid therapy (27,28)), or (b) "intermittent" prescriptions, if they received 1-2 prescriptions in each calendar-year. This was repeated for basic analgesia, oral NSAID, and gabapentinoid prescriptions.

Analgesia Prescription Prevalence

The annual prevalence of analgesia prescriptions was calculated. The numerator was the number of people receiving ≥1 analgesia prescription in a calendar-year. The denominator was the number of people contributing data within that calendar-year. Annual prevalence was reported for any analgesia/analgesia subgroups separately. Annual prevalence was further reported by: (a) IA-subtypes, (b) age groups (<40, 40-70, >70 years), and gender. Approximate ages were calculated, subtracting patient birth year from the current calendar-year (to preserve anonymisation, day/month of birth data were unavailable). Annual prevalence of chronic and intermittent analgesia 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 analgesia, 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 (APC, representing the percentage change in prescribing prevalence/year) was estimated for each time-period separated by identified joinpoints. Timepoints were compared to dates of Medical Healthcare Regulatory Authority (MHRA) interventions to deliver safer NSAID prescribing, which started in 2004 (20).

Statistical Programme

Analyses were conducted using R (version 4.1.0) and the National Cancer Institute's joinpoint regression programme (version 4.9.0) (30).

RESULTS

Patients

The number of cases and controls increased yearly from 594 cases/2,652 controls in 2000 to 1,080 cases/4,703 controls in 2015. The increase in cases reflects the fact each calendar-year includes prevalent and incident cases (the latter from the preceding calendar-year) and many cases remained registered for the majority/whole of the study-period (Supplementary Figures

S1-2, available at *Rheumatology* online). The increase in cases is in-line with the expected annual incidence of IA (15-35/100,000) (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% confidence interval [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/gender of cases/controls reflects the fact that across years, matching controls could not be obtained for 7.9 to 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%). Amongst 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).

Annual Analgesia Prescription Prevalence

Any Analgesia

In all years the majority of cases received an analgesia prescription, falling slightly over time (Figure 1; Supplementary Table S8, available at *Rheumatology* online). In 2000, 77.3% (95% CI 73.7%, 80.6%) received an analgesia 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 analgesia prescription than controls, with prescription prevalence 1.7-2.0 times higher. In all years, analgesia prescriptions were commoner in RA than axial SpA/PsA (Figure 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 (Figure 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 (Figure 2).

Opioids

Minor reductions in the annual prevalence of opioid prescriptions were observed over time in cases but not controls (Figure 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 (Figure 2).

Similar trends in the annual prevalence of weak/moderate strength opioid prescriptions were seen in cases and controls (Figure 3), with the prevalence of weak opioid prescriptions rising, peaking in 2006 (29.2% [95% CI 26.0%, 32.6%] in cases), then falling. The prevalence of moderate opioid prescriptions fell substantially between 2000-2007 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 being relatively static. The annual prevalence of strong opioid prescriptions was relatively static in cases between 2000-2005, and 2008-2015, 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/controls.

Gabapentinoids

Between 2000-2006 the annual prevalence of gabapentinoid prescriptions was very low (<1% of cases/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 Analgesia

Chronic basic analgesia 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 (Figure 4/Supplementary Table S9, available at *Rheumatology* online). Intermittent basic analgesia 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 (Figure 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 (Figure 4). Whilst 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 (Figure 4). Chronic and intermittent opioid prescribing prevalence was relatively static over the 15 years in controls.

Gabapentinoids

Chronic gabapentinoid prescriptions were commoner than intermittent prescriptions and both increased over time in cases and controls (Figure 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 Analgesia Prescriptions by Age and Gender

Age

The annual prevalence of analgesia prescriptions increased with age in cases (Supplementary Table S8, available at *Rheumatology* online). In those aged <40 years, the annual prevalence of any analgesia 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 (Figure 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; whilst the annual prevalence of NSAID prescriptions fell in all age categories over 15 years, this was similar across age groups and the annual prevalence of NSAID prescriptions in 2000 was similar across age categories (Supplementary Figure S3, available at *Rheumatology* online).

The annual prevalence of opioid prescriptions increased with age in cases (Figure 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. Whilst 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 Figure S3, available at *Rheumatology* online).

As with opioids, the annual prevalence of gabapentinoid prescriptions increased with age in cases (Figure 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 Figure S3, available at *Rheumatology* online).

Gender

In all years except 2000, the annual prevalence of any analgesia 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 (Figure 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 analgesia, oral NSAID, opioid, and gabapentinoid prescriptions were slightly higher in females than males (Supplementary Figure 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 (Figure 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 Figure S4, available at *Rheumatology* online). The first at 2004 represented the start of a marked, sustained decline in annual NSAID prescription prevalence (APC changing from -2.26 in 2000 to 2004 to -8.09 in 2004 to 2009). The second at 2009 represented a reduction in the rate of decline in NSAID prescribing (APC -4.27 from 2009 to 2015). The 2004 timepoint 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 analgesia prescribing in people with IA. It has three key findings. First, it demonstrates analgesia prescribing is common in IA, with two-thirds to three-quarters of patients receiving an analgesia prescription in each calendar-year. Second, it shows that many analgesia 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 spondylititis managed in non-UK settings (12–15). In North America in the average rheumatologist's practice 40% of patients with RA were reguarly prescribed opioids (13), and >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 analgesia in IA is limited. Whilst 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 ≥one 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 amongst 65.5% of 3,140 patients with RA receiving analgesia, ibuprofen/diclofenac were amongst 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 whilst 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 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 analgesia, make our finding of substantial analgesia prescribing in IA concerning. Systematic literature reviews examining the efficacy of analgesia at managing IA pain consistently demonstrate that, excepting oral NSAIDs in axial SpA (37), analgesia infrequently give clinically-meaningful

pain improvements (8,9,18,38). For example, a Cochrane review reported that amongst 11 heterogeneous studies of short-duration/high-risk of bias, whilst 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 to placebo is inconsistent with regards to pain-relief, and whilst 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 analgesia (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; amongst 1,225 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 analgesia types, in contrast to existing studies focusing on a single analgesia class. Second, it spanned a long time-period. Third, it compared analgesia 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 analgesia prescribing in cases than controls. Fourth, data on prescribing beyond 2015 are unavailable in CiPCA. However, whilst prescribing practice may have changed in the last five years, our study timeframe 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 analgesia use, which may be substantial.

In conclusion, our study demonstrates that whilst the annual prevalence of overall analgesia prescriptions has fallen slightly over 15 years, analgesia 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 analgesia prescribing in this patient population. The crucial first step towards developing such interventions is to understand what drives clinician analgesia prescribing and patient analgesia use in IA.

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DISCLOSURE STATEMENT

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DATA AVAILABILITY STATEMENT

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

Figure 1. Annual Prevalence of Analgesia Prescriptions in Cases and Controls

"Inflammatory arthritis" comprises patients with rheumatoid arthritis, psoriatic arthritis, 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. NSAID = non-steroidal anti-inflammatory drug. Annual prevalence of analgesia prescriptions with 95% confidence intervals plotted in each calendar-year.

Figure 2. Annual Prevalence of Analgesia Prescriptions by Inflammatory Arthritis Sub-Types

NSAID = non-steroidal anti-inflammatory drug. Annual prevalence of analgesia prescriptions with 95% confidence intervals plotted in each calendar year.

Figure 3. Annual Prevalence of Opioid Prescriptions in Cases and Controls

"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. Opioid strength classified using the approach developed by Bedson et al (21). Annual prevalence of opioid prescriptions with 95% confidence intervals plotted in each calendar-year.

Figure 4. Annual Prevalence of Chronic and Intermittent Analgesia Prescriptions in Inflammatory Arthritis Cases and Controls

"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 per calendar-year; intermittent = 1-2 prescriptions per calendar-year; never = no prescriptions per calendar year. Annual prevalence of prescriptions with 95% confidence intervals plotted in each calendar-year.

Figure 5. Analgesia Prescriptions by Age, and Gender in Cases

"Inflammatory arthritis" comprises patients with rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis. Age cut-offs are in years. NSAID = non-steroidal anti-inflammatory drug. Annual prevalence of prescriptions with 95% confidence intervals plotted in each calendar-year, stratified by age and gender.

Figure 6 Annual Prevalence of Oral NSAID and Gastro-Protection Co-Prescriptions in Inflammatory Arthritis Cases

"Inflammatory arthritis" comprises patients with rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis. NSAID = non-steroidal anti-inflammatory drug. 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 and time in a calendar-year. Same patient = proportion of patients receiving an oral NSAID prescription in a calendar-year, that also receive a prescription for a proton-pump inhibitor and/or H2-receptor antagonist in that calendar-year.

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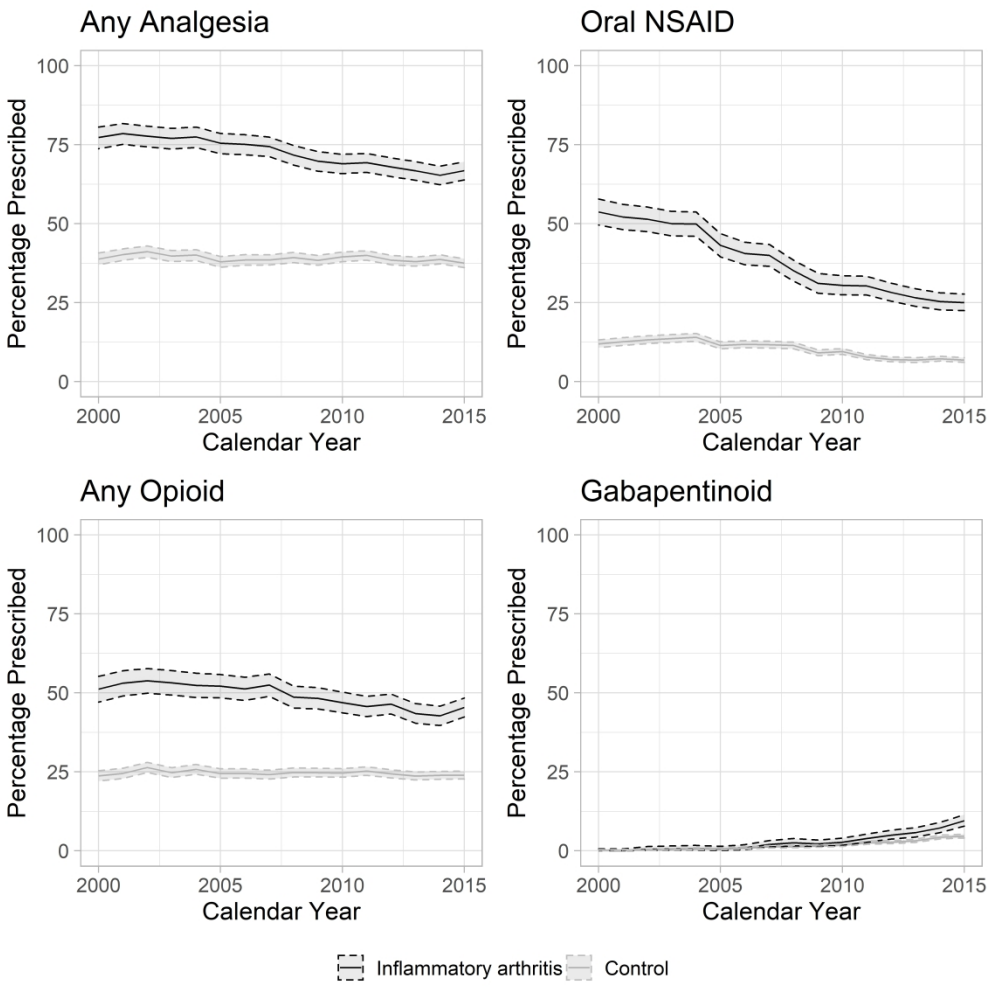

Figure 1. Annual prevalence of analgesia prescriptions in cases and controls.
"Inflammatory arthritis" comprises patients with rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis. "Controls" comprise up to five age, sex, and practice-matched patients without inflammatory rheumatic conditions for each patient with inflammatory arthritis in each calendar year. NSAID = non-steroidal anti-inflammatory drug. Annual prevalence of analgesia prescriptions with 95% confidence intervals plotted in each calendar-year.

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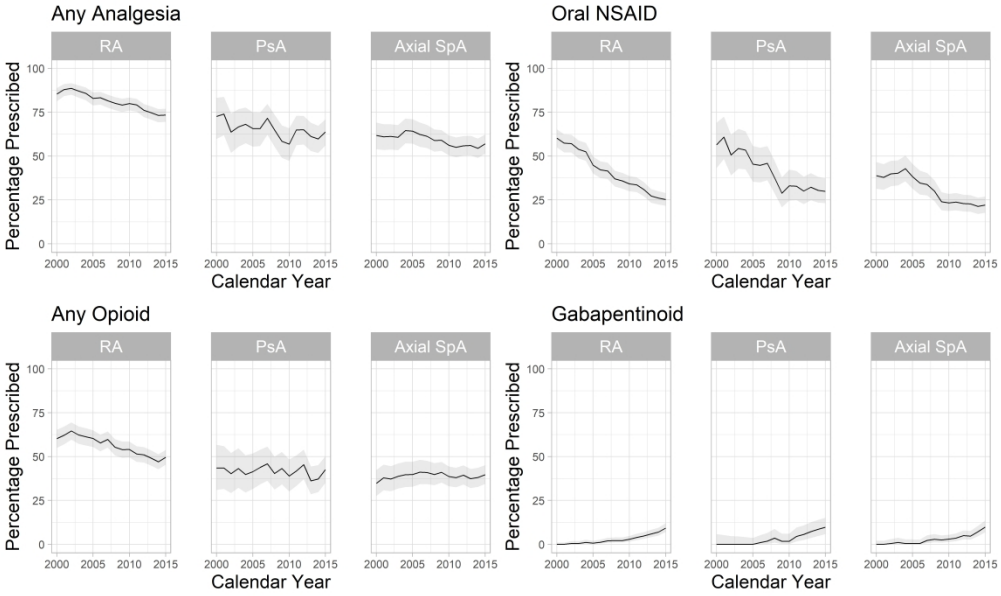

Figure 2. Annual prevalence of analgesia prescriptions by inflammatory arthritis sub-types. NSAID = non-steroidal anti-inflammatory drug. Annual prevalence of analgesia prescriptions with 95% confidence intervals plotted in each calendar year.

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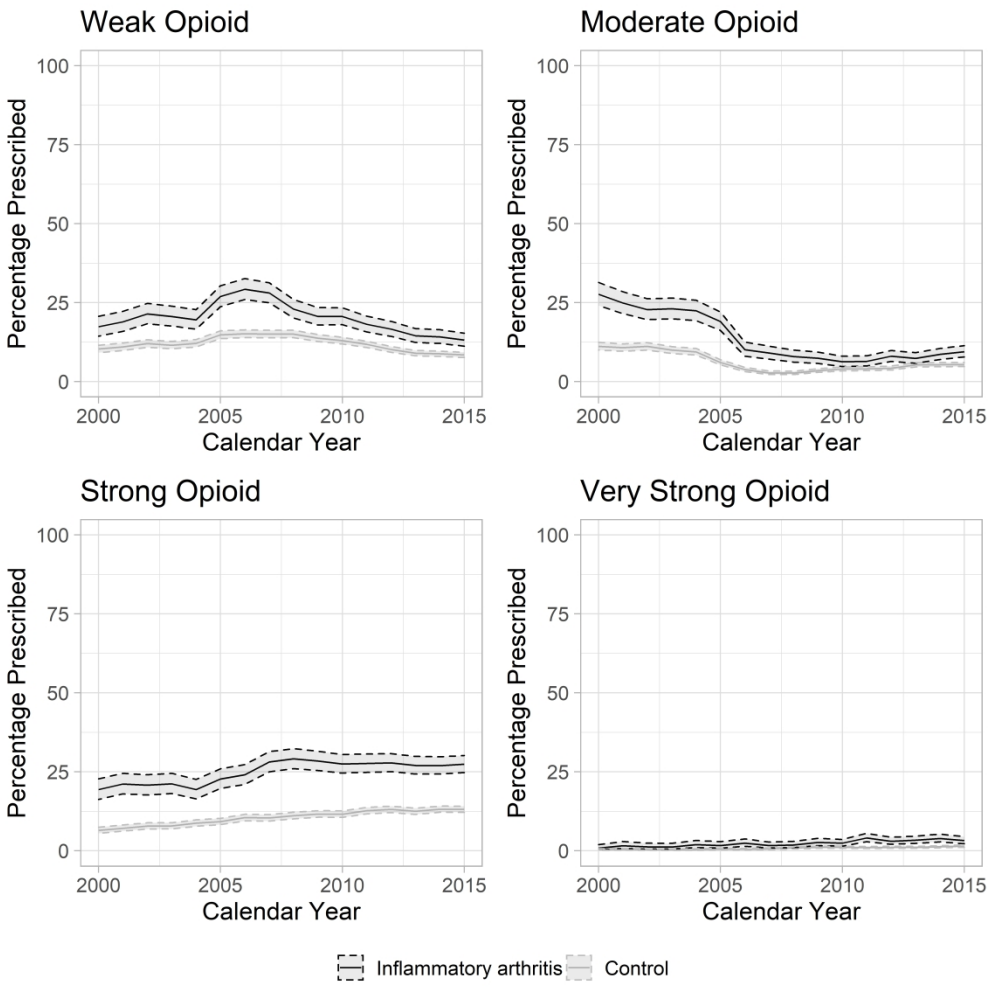

Figure 3. Annual prevalence of opioid prescriptions in cases and controls.
"Inflammatory arthritis" comprises patients with rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis. "Controls" comprises up to five age, sex, and practice-matched patients without inflammatory rheumatic conditions for each patient with inflammatory arthritis in each calendar year. Opioid strength classified using the approach developed by Bedson et al (21). Annual prevalence of opioid prescriptions with 95% confidence intervals plotted in each calendar-year.

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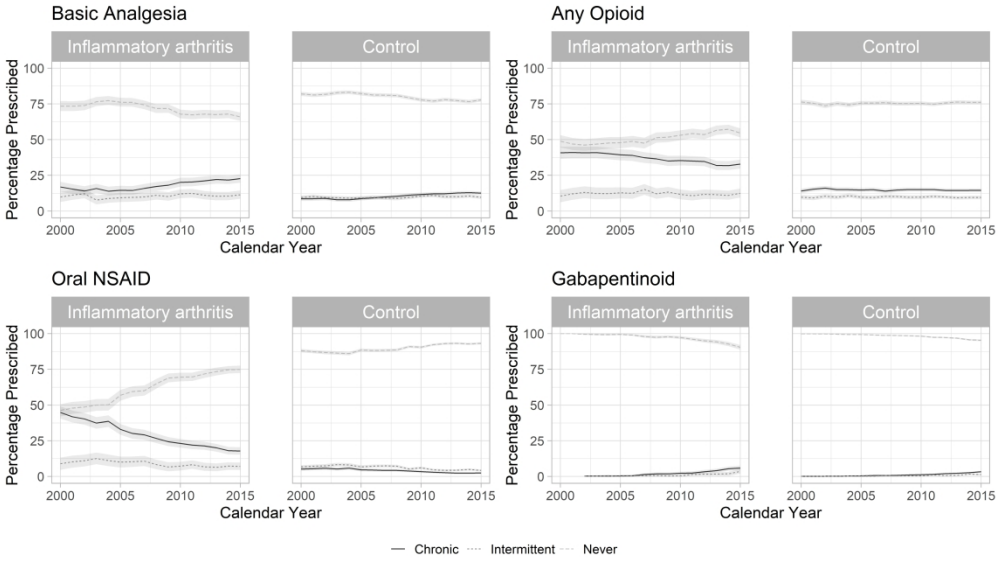

Figure 4. Annual prevalence of chronic and intermittent analgesia prescriptions in inflammatory arthritis cases and controls.
"Inflammatory arthritis" comprises patients with rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis. "Controls" comprises up to five age, sex, and practice-matched patients without inflammatory conditions for each patient with inflammatory arthritis in each calendar year. NSAID = non-steroidal anti-inflammatory drug. Chronic = ≥3 prescriptions per calendar-year; intermittent = 1-2 prescriptions per calendar-year; never = no prescriptions per calendar year. Annual prevalence of prescriptions with 95% confidence intervals plotted in each calendar-year.

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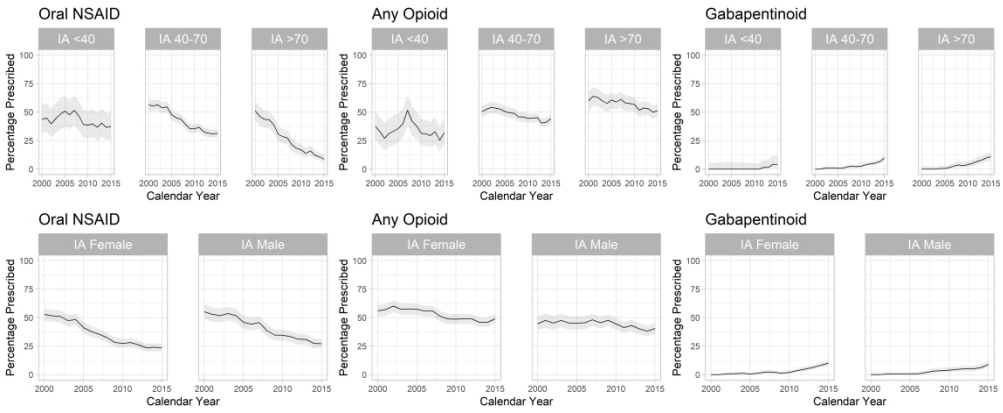

Figure 5. Analgesia prescriptions by age, and gender in cases.
"Inflammatory arthritis" comprises patients with rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis. Age cut-offs are in years. NSAID = non-steroidal anti-inflammatory drug. Annual prevalence of prescriptions with 95% confidence intervals plotted in each calendar-year, stratified by age and gender.

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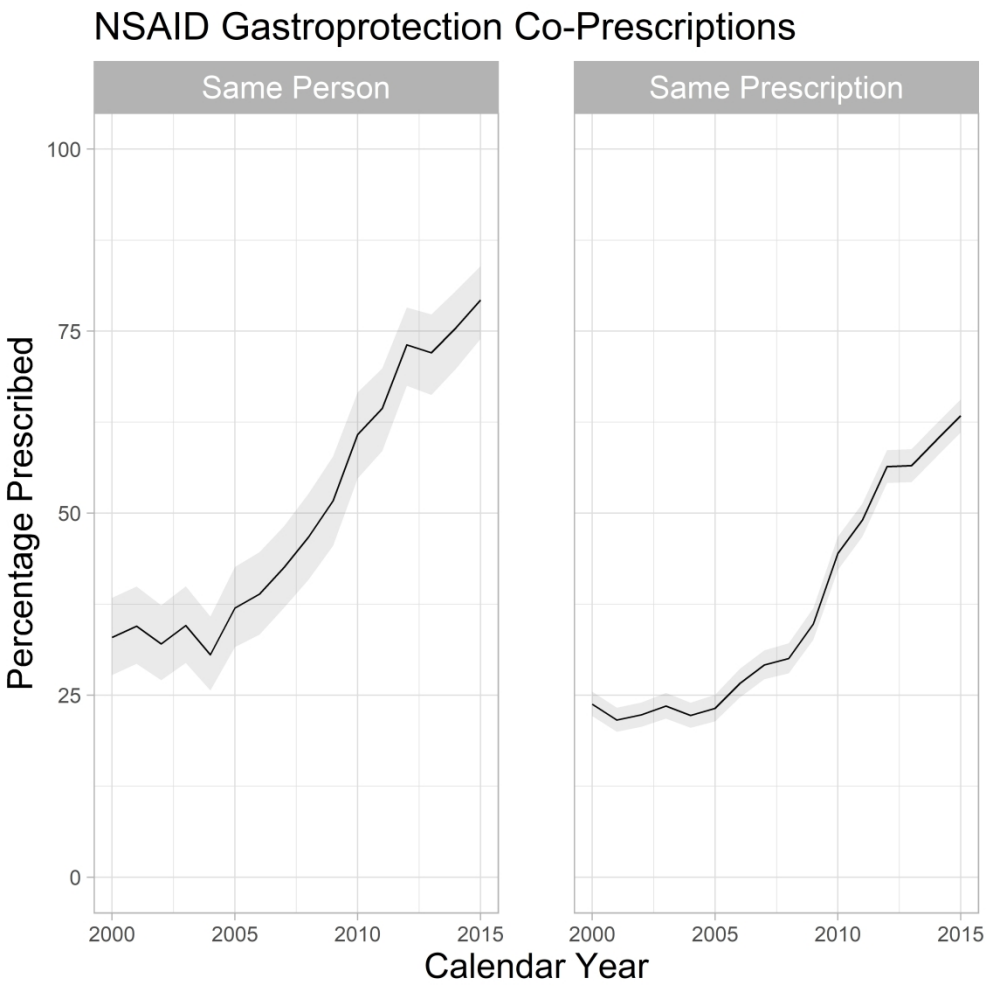

Figure 6. Annual prevalence of oral NSAID and gastro-protection co-prescriptions in inflammatory arthritis cases.
"Inflammatory arthritis" comprises patients with rheumatoid arthritis, psoriatic arthritis, and axial spondyloarhritis. NSAID = non-steroidal anti-inflammatory drug. Same prescription = proportion 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 and time in a calendar-year. Same patient = proportion of patients receiving an oral NSAID prescription in a calendar-year, that also receive a prescription for a proton-pump inhibitor and/or H2-receptor antagonist in that calendar-year.

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