BMJ Open

Health economic impact of moderate-to-severe chronic pain associated with osteoarthritis in England: a retrospective analysis of linked primary and secondary care data

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To cite: Coates G, Clewes P, Lohan C, *et al*. Health economic impact of moderate-to-severe chronic pain associated with osteoarthritis in England: a retrospective analysis of linked primary and secondary care data. *BMJ Open* 2023;**13**:e067545. doi:10.1136/bmjopen-2022-067545

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-067545).

Received 17 August 2022
Accepted 28 June 2023

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ABSTRACT

Objective Despite the prevalence of osteoarthritis (OA) in England, few studies have examined the health economic impact of chronic pain associated with OA. The aim of this study was to compare outcomes in patients with moderate-to-severe chronic pain associated with OA and matched controls without known OA.

Design Retrospective, longitudinal, observational cohort study.

Setting Electronic records extracted from the Clinical Practice Research Datalink GOLD primary care database linked to Hospital Episode Statistics (HES) data set.

Participants Patients (cases; n=5931) ≥18 years and with existing diagnosis of OA and moderate-to-severe pain associated with their OA, and controls matched on age, sex, comorbidity burden, general practitioner (GP) practice and availability of HES data.

Interventions None.

Primary and secondary outcome measures Total healthcare resource use (HCRU) and direct healthcare costs during 0–6, 0–12, 0–24 and 0–36 months of follow-up. Secondary outcomes measures included pharmacological management and time to total joint replacement.

Results Patients with moderate-to-severe chronic pain associated with OA used significantly more healthcare services versus matched controls, reflected by higher HCRU and significantly higher direct costs. During the first 12 months' follow-up, cases had significantly more GP consultations, outpatient attendances, emergency department visits and inpatient stays than matched controls (all p<0.0001). Total mean costs incurred by cases during 0–12 months' follow-up were five times higher in cases versus controls (mean (SD): £4199 (£3966) vs £781 (£2073), respectively). Extensive cycling through pharmacological therapies was observed; among cases, 2040 (34.4%), 1340 (22.6%), 841 (14.2%), 459 (7.7%) and 706 (11.9%) received 1–5, 6–10, 11–15, 16–20 and >20 lines of therapy, respectively.

Conclusions This wide-ranging, longitudinal, observational study of real-world primary and secondary care data demonstrates the impact of moderate-to-severe chronic pain associated with OA in patients compared with matched controls. Further studies are required to fully quantify the health economic burden of moderate-to-severe pain associated with OA.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study was designed to describe the likely health economic impact of moderate-to-severe chronic pain associated with osteoarthritis—information that is currently lacking.
⇒ Analysis of linked primary and secondary care databases in England identified a large study population with long follow-up.
⇒ Patients with moderate-to-severe chronic pain associated with osteoarthritis were compared with age, sex and comorbidity-matched controls without known osteoarthritis.
⇒ We assessed healthcare resource use and costs, incidence of total joint replacement and pharmacological management in cases and controls, to gain a broad insight into the economic impact of moderate-to-severe chronic pain associated with osteoarthritis.
⇒ Over-the-counter medicine was not captured in this analysis, nor were other elements of care provided outside the primary/secondary healthcare settings. These are important elements of care in people with moderate-to-severe chronic pain associated with osteoarthritis, therefore our data are likely to underestimate the full cost of managing osteoarthritis pain.

INTRODUCTION

Osteoarthritis (OA) refers to a clinical syndrome of pain associated with joint structural changes and accompanied by varying degrees of functional limitation and reduced quality of life (QoL).[1 2] Chronic pain caused by OA profoundly impacts people's lives, and

consequently affects healthcare providers, businesses, government and wider society. Symptomatic, clinically diagnosed OA has been estimated to occur in 10.7% of UK adults, with a standardised incidence of 6.8 per 1000 person-years (95% CI 6.7 to 6.9).[3] Between 2000/2001 and 2017/2018, the UK National Health Service (NHS) Hospital Episode Statistics (HES) database recorded 3 143 928 patients with OA presenting for secondary care in England.[4] OA of the knee was the most common form of disease among these patients, affecting 1 772 318 patients, followed by the hip and first carpometacarpal joints (1 222 446 and 88 178 patients, respectively).

Optimal treatment of OA is holistic, and may include pharmacological therapy and non-invasive or invasive interventions, depending on treatment goals and disease severity.[5] Core treatments should be offered to all people with OA including access to appropriate information and education, advice on activity and exercise, and weight loss interventions when appropriate. Pharmacotherapy may include paracetamol and/or topical non-steroidal anti-inflammatory drugs (NSAIDs). If these provide insufficient pain relief, an oral NSAID, cyclo-oxygenase-2 inhibitor or opioid analgesic might be considered. Intra-articular corticosteroid injections can be considered as an adjunct to core treatments for the relief of moderate-to-severe pain in people with OA. Total joint replacement (TJR) is considered for people with substantially impacted QoL whose symptoms are refractory to non-surgical treatments.

The economic burden of OA is considerable. Between 2008 and 2016, 854 866 patients underwent hip or knee replacement surgery in England at a mean 1-year hospitalisation cost of £7827 and £7805, respectively.[6] Revisions and complications were associated with up to a threefold increase in 1-year hospitalisation costs compared with primary joint replacement surgery. When primary and outpatient care costs were considered, the 2-year per-patient costs were £11 987 and £12 578, respectively. After a period of deteriorating OA symptoms, patients might undergo arthroplasty, after which the OA symptoms might be anticipated to improve. The healthcare costs associated with these transitionary periods might be expected to be higher than in people with stable care, although detailed information about how costs may change in the period before and after surgery are incompletely understood.

Arthroplasty, however, is only one component of healthcare costs for OA. Evidence-based guidelines can be difficult to implement in full, and actual healthcare costs might diverge from those that would be predicted from optimal care. Clarifying the specific contributions to the overall health economic impact of moderate-to-severe chronic OA pain, and those aspects of healthcare that contribute most to costs, will help determine the size and nature of the problem, and help identify where future effort might be focused most productively to best improve the health and well-being of patients.

The present study was undertaken to compare the nature and size of healthcare burden from managing patients seeking care for moderate-to-severe chronic pain associated with OA in England, compared with matched controls from the general population. This formed part of a larger study of the burden of moderate-to-severe chronic pain associated with OA or chronic lower back pain. Specific objectives relating to patients with OA alone were to characterise healthcare resource use (HCRU) and to describe patterns in pharmacological treatment of pain in this cohort.

METHODS

Study design and patients

We conducted a retrospective, longitudinal, observational cohort study of patients presenting to primary care with an episode associated with moderate-to-severe chronic OA pain, and matched non-OA controls using linked Clinical Practice Research Datalink (CPRD) and HES data. The study design is shown in online supplemental eFigure 1.

Patients aged ≥18 years and with an existing diagnosis of OA (Read or International Statistical Classification of Diseases 10th revision (ICD-10) code) were indexed between December 2009 and November 2017 on a moderate-to-severe pain event occurring within a period of chronic pain. The patient's first/earliest date of such a moderate or severe pain event documented within the CPRD determined the index date. Eligible patients had data deemed of acceptable research quality linkable to HES, and had ≥12 months' data available before and following indexing. Patients were not excluded on the basis of any observed comorbidities.

Patients with a TJR were identified using Office of Population Censuses and Surveys (codes O06–O08, O18, O21–O23, O32, W37–W45 or W93–W98).

Moderate-to-severe pain events were defined as any of the following: referral to/attendance with a pain specialist; surgical or non-surgical invasive procedure relating to the treatment of OA, including TJR, osteotomy, arthroscopy, fusion surgery and intra-articular injection; ≥2 NSAID agents and/or ≥2 opioid prescriptions (could be the same opioid) within a 3-month period; or pain-related emergency department (ED) visit with general practitioner (GP) follow-up within 14 days.

A chronic pain episode was defined as a series of pain-related GP consultations relating to pain symptoms associated with OA and/or a pain-related specialist consultation (rheumatology, orthopaedics or pain management) in secondary care, where gaps between visits were ≤12 months.

Inclusion criteria and medical codes were reviewed for clinical relevance and appropriateness by RK, AJD and DW.

Each patient within the study cohort (cases) was index matched (1:1) to a general population control within CPRD who did not have any past or current OA diagnosis in their medical record. Cases and controls were matched on year of birth (±1 year), sex, lifetime Charlson

Comorbidity Index (CCI) score, GP practice and HES linkage eligibility. The CCI is a score calculated on the presence of a number of prespecified chronic conditions; lifetime CCI score is the score calculated across the patient's entire medical record. Each matched control patient was assigned a pseudo-index date equal to the index date of their matched case patient.

Data sources

The CPRD GOLD primary care database is a longitudinal, anonymised research database of computerised medical records held by GPs across the UK. Over 650 primary care practices, covering 11 million people, participate in the CPRD, with clinical records for over 12 million individuals; an estimated 5.5 million people are actively registered. Data are broadly representative of the UK population.[7] Available data include demographics, medical history (including diagnoses and health contacts), clinical investigation results and prescriptions. Diagnostic data are recorded using Read Codes, a coded thesaurus of clinical terms that has been in use since 1985. These provide a standard vocabulary for clinicians to record patient findings and procedures in health and social care systems across primary and secondary care.

Approximately 75% of English practices contributing to CPRD are linked to the HES data set, which provides information on all inpatient and outpatient contacts occurring at NHS hospitals in England, including ED visits, with diagnoses recorded using ICD-10 codes. Surgical and other procedures were recorded in the HES using the Office of Population Census and Surveys Classification of Interventions and Procedures V.4.

Study objectives and outcomes

The primary study objective was to describe HCRU and direct healthcare costs associated with the target patient population during 0–6, 0–12, 0–24 and 0–36 months of follow-up from an index episode. Patients were included in each landmark analysis if they had sufficient follow-up data (eg, patients needed at least 36 months' data to be included in the 0–36 months analysis). The secondary study objectives were to: describe the demographics and clinical characteristics of patients with moderate-to-severe chronic pain associated with OA; describe patterns of treatment, specifically analgesic medicines used in the management of moderate-to-severe chronic pain (primary care only), in patients with OA; characterise the economic burden of disease over time; and estimate the time to TJR.

Key outcomes were as follows: HCRU and direct healthcare costs, healthcare-provided pharmacological management and time to TJR. HCRU and direct healthcare costs included hospitalisations, outpatient appointments, ED attendances, GP appointments and medicine use; total direct healthcare costs comprised the sum of all direct healthcare costs. Other outpatient services, such as physiotherapy, were limited to those provided in the secondary care setting. HCRU was observed during 0–6, 0–12, 0–24 and 0–36 months of follow-up after the index date. Pharmacological management included non-opioid analgesics (paracetamol, systemic NSAIDs, topical NSAIDs, other non-opioid analgesics), opioid analgesics (compound analgesics with weak opioid, weak opioids, strong opioids), adjuvant medicines (antidepressant, anti-epileptic, anxiolytic/hypnotic agents) (online supplemental eTable 1). Pharmacological treatments assessed in this study were driven by the scope of National Institute for Health and Care Excellence Guidelines CG177,[2] with the exception of adjuvant medicines, which are recommended by British National Formulary recommendations.[8] Changes in prescribed treatment (at class level) were considered a new line of therapy. A 45-day permissible gap was implemented, that is, a gap of ≤45 days between the end date of a prescription (determined via number of days' supply) and the start date of a subsequent prescription (of the same class) was considered continuous use. Opioid overuse was defined as an oral morphine-equivalent dose of >120 mg/day.[9] Time to TJR following, and including, indexing was assessed overall (ie, any joint) and by the specific joint replaced (hip, knee or other joint). Direct healthcare costs were derived using appropriate unit cost data. GP consultations were costed using Unit Costs of Health and Social Care document, compiled and provided by the Personal Social Services Research Unit.[10] All medicines prescribed in primary care in the study time frame were identified. Each identified product was matched to its listing in the NHS Drug Tariff.[11] Healthcare Resource Groups (HRGs) were derived for each inpatient admission and outpatient attendance. These are standard groupings of clinically similar treatments/events that use common levels of healthcare resource and are derived for secondary care provision using the Local Payment Grouper. The national tariff workbook, compiled and provided by NHS Improvement and NHS England, is used to attach costs to each HRG.[12]

Study ethics

The study was conducted in accordance with legal and regulatory requirements, and followed generally accepted research practices described in the Guidelines for Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology,[13] and Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research.[14–16]

Institutional Review Board approval was not required; no study participants were put at risk during the study and confidentiality was maintained by use of data from de-identified electronic medical records provided by the CPRD. No informed consent was required as no identifiable patient data were collected.

Statistical analysis

This study was a retrospective analysis that was primarily descriptive in nature. Base size, frequency and percentages

were reported for nominal variables; base size, mean, median, SD, 25th and 75th percentiles and minimum and maximum values were reported for numerical variables.

Standard statistical tests (eg, Student's t-test, analysis of variance) were used for comparisons. Kaplan-Meier estimates were used to assess time to first TJR.

All statistical tests were two-sided in nature; a significance level of p<0.05 was used for comparison of cases and controls. No corrections were made for multiple comparisons.

Analyses were performed using Stata (V. 16.1; StataCorp LLC, College Station, Texas, USA).

Patient and public involvement

No patient involvement was sought for this study.

RESULTS

Patients

The study cohort comprised 5931 patients identified as having moderate-to-severe pain associated with OA between 1 December 2009 and 30 November 2017, as shown in online supplemental eFigure 2. Over half (n=3436; 57.9%) were aged ≥65 years and 3514 (59.2%) were women. Patients were predominantly white (n=3198 of 3304 cases (96.8%) with a recorded ethnicity). Over one-third of cases (n=2205; 37.2%) underwent TJR following indexing.

Patient characteristics are shown in table 1. Although cases and controls were matched on lifetime CCI score among other factors, compared with controls, cases had a statistically significantly (all p<0.001) higher prevalence before indexing of each of the most common observed physical comorbidities (hypertension, hyperlipidaemia, diabetes and asthma), and each of the most common observed rheumatological comorbidities (rheumatoid arthritis, psoriatic arthritis and fibromyalgia), not all of which are included in the CCI. Cases also had a significantly higher prevalence before indexing of depression and anxiety than controls (both p<0.0001). Mean duration of follow-up was 41.2 months.

Table 1 Demographics and clinical characteristics of cases and matched general population controls

Characteristic	Cases (n=5931)	Controls (n=5931)	TJR subcohort (n=2176)
Age at indexing, years*			
Mean (SD)	66.1 (11.9)	66.0 (11.9)	68.6 (9.9)
≥65 years, n (%)	3436 (57.9)	3436 (57.9)	1481 (68.1)
Sex, n (%)*			
Male	2417 (40.8)	2417 (40.8)	892 (41.0)
Female	3514 (59.2)	3514 (59.2)	1284 (59.0)
Mean BMI, kg/m^2 (SD)	30.3 (5.9)†	–	30.5 (5.5)‡
Comorbidities, n (%)§			
Hypertension	2934 (49.5)***	2387 (40.2)	1167 (53.6)
Hyperlipidaemia	1467 (24.7)***	961 (16.2)	541 (24.9)
Asthma	1003 (16.9)***	806 (13.6)	306 (14.1)
Diabetes	708 (11.9)**	577 (9.7)	254 (11.7)
Other CHD	703 (11.9)***	460 (7.8)	258 (11.9)
Rheumatoid arthritis	226 (3.8)***	73 (1.2)	67 (3.1)
Fibromyalgia	67 (1.1)***	10 (0.2)	14 (0.6)
Psoriatic arthritis	39 (0.7)***	8 (0.1)	13 (0.6)
Mental health comorbidities, n (%)			
Depression	1424 (24.0)***	688 (11.6)	420 (19.3)
Anxiety	775 (13.1)***	407 (6.9)	226 (10.4)
Mean CCI, lifetime value (SD)*	1.21 (1.62)	1.21 (1.62)	NA
Length of follow-up, months			
Mean (SD)	41.2 (21.2)	40.9 (21.0)	45.5 (22.4)
Mean time from OA diagnosis to indexing, years (SD)¶	5.0 (4.9)	NA	5.2 (4.8)

*Used to match cases to controls.
**P<0.001, ***p<0.0001 versus controls.
†n=2833 due to missing data.
‡Most common comorbidities recorded before indexing (from a prespecified list; not all possible comorbid conditions were assessed).
§First instance of an OA diagnostic code within the patients' medical record.
¶n=1061 due to missing data.
BMI, body mass index; CCI, Charlson Comorbidity Index; CHD, coronary heart disease; NA, not applicable; OA, osteoarthritis.

Healthcare resource use and associated costs

During the first 12 months of follow-up, patients with OA had significantly more GP consultations, outpatient attendances, ED visits and inpatient stays than matched controls (all p<0.0001; table 2). Orthopaedics was the most frequently used pain-related outpatient service among cases in the first 12 months of follow-up (77.8% vs 3.5% of controls; p<0.0001); only 4.3% of cases used pain management outpatient services (vs 0.1% of controls; p<0.0001). The cumulative inpatient length of stay was more than five times longer for cases compared with controls in the first 12 months of follow-up (mean (SD) 3.15 (10.82) vs 0.79 (6.55) days; p<0.0001). Similar findings were observed during 0–6, 0–24 and 0–36 months of follow-up (table 2).

P value<0.0001 for the difference in mean values between cases and controls for each healthcare service, and across all time periods.

Data are for number of attendances unless otherwise indicated.

Time to TJR is shown in figure 1. A rapid shift to TJR surgery after the index event was observed, followed by continued surgical conversion throughout the following 5 years. Specifically, 25% of patients had a TJR at 1 year; 31% at 2 years, 34% at 3 years, 37% at 4 years and 40% at 5 years.

Total mean NHS England healthcare costs incurred during the 0–12 months of follow-up were five times higher in cases compared with controls (mean (SD): £4199 (£3966) vs £781 (£2073); p<0.0001; figure 2). By 36 months, mean (SD) total direct healthcare costs per-patient had risen to £8246 (£6923) among cases and £2329 (£4372) among controls (p<0.0001). Inpatient stay costs accounted for between 69% and 76% of total costs in cases across all time periods. Stays relating to TJR accounted for 48% of the total cost of inpatient stays for cases during the 36 months of follow-up (£2646 (£3751) of £5504 (£5642)).

Pharmacological management of patients with OA

A total of 545 cases (9.2%) were not prescribed any pain medicines during the entire follow-up period (20 343 person-years); 2040 (34.4%), 1340 (22.6%), 841 (14.2%), 459 (7.7%) and 706 (11.9%) cases received 1–5, 6–10, 11–15, 16–20 and >20 lines of therapy, respectively. The mean duration of each line of therapy was approximately 2 months (online supplemental eTable 2).

Prescribing of topical NSAIDs (ranging from 9.9% to 15.2% across treatment lines) and paracetamol only (18.6% to 33.0%) increased substantially from line 1 to 10, whereas the prescribing of systemic NSAIDs (29.2% to 35.3%), weak opioids (10.1% to 12.2%) and strong opioids (18.3% to 23.3%) remained relatively constant (figure 3). Strong opioids were classified as overused in only 77 of 2205 patients (3.5%) prescribed a strong opioid during follow-up; no overuse of weak opioids was observed (data not shown).

Use of antidepressants (7.5% to 20.6%), anti-epileptics (2.7% to 9.2%) and anxiolytics/hypnotics (5.2% to 11.7%) also increased from line 1 to 10 (figure 3).

DISCUSSION

This study of patients with moderate-to-severe chronic pain associated with OA and their matched controls used real-world data from one of the world's largest linked primary care data sets and demonstrates the substantial impact of moderate-to-severe chronic pain associated with OA. This encompasses higher HCRU, extensive cycling through pharmacological therapies, and significantly higher direct costs when compared with controls. Moreover, HCRU and costs were shown to be substantial and incremental before surgery to replace affected joints.

Patients with moderate-to-severe chronic pain associated with OA used significantly more healthcare services compared with matched non-OA controls, thus demonstrating the substantial burden to the healthcare system of OA pain management, in both primary and secondary care settings. Cases had approximately twice as many GP appointments and ED visits as controls, three times as many outpatient appointments and inpatient stays, and a mean length of stay twice as long as that of controls over all follow-up periods. To our knowledge, the impact of moderate-to-severe chronic pain has not been compared with matched controls in this setting; however, Schepman and colleagues reported a higher clinical burden among US patients with moderate-to-severe OA pain compared with mild OA pain among patients participating in the US National Health and Wellness Study.[17] Patients with moderate-to-severe OA pain had significantly more prescribed pain medicines, outpatient and ED visits, plus more hospitalisations than those with mild OA pain, leading the authors to conclude that understanding the burden of OA pain could inform decision-making with the aim of improving pain management.

Higher HCRU in cases resulted in direct costs that were more than double those incurred by matched controls, predominantly driven by costs associated with inpatient care. As all-cause HCRU and associated direct costs were collected in this study, not all healthcare service use by patients could be attributed to moderate-to-severe pain associated with OA; however, the increased HCRU and costs observed in cases versus controls likely indicate the greater comorbidity burden in patients with chronic moderate-to-severe pain associated with OA. Cases and controls were matched on comorbidity profile using the CCI, which accounts for a specific set of comorbidities. However, we found that selected comorbidities (hypertension, hyperlipidaemia, diabetes mellitus, anxiety and depression) were more frequent in cases than controls, and comorbid conditions might contribute to the increased healthcare costs of people with OA. Previous research has highlighted the association between anxiety and depression, specifically, with worsening OA-associated pain, from both the economic and patient

Table 2 Healthcare resource use in patients with moderate-to-severe chronic pain associated with osteoarthritis

Healthcare service use	0–6 months		0–12 months		0–24 months*		0–36 months*	
	Cases (n=5391)	Controls (n=5391)	Cases (n=5391)	Controls (n=5391)	Cases (n=4197)	Controls (n=4197)	Cases (n=2813)	Controls (n=2813)
GP consultation								
Mean (SD)	6.86 (5.52)	3.03 (3.80)	12.88 (10.03)	6.09 (6.85)	23.41 (17.90)	12.22 (12.77)	33.72 (24.62)	18.63 (18.79)
Median (IQR)	6 (3–9)	2 (0–4)	11 (6–16)	4 (1–8)	19 (12–30)	9 (4–16)	28 (18–43)	14 (7–25)
Outpatient attendance								
Mean (SD)	4.10 (3.89)	0.83 (2.18)	7.37 (6.94)	1.73 (3.96)	12.25 (11.89)	3.50 (8.09)	16.52 (16.81)	5.19 (10.82)
Median (IQR)	3 (2–6)	0 (0–1)	6 (3–10)	0 (0–2)	9 (5–16)	0 (0–4)	13 (7–22)	1 (0–6)
ED visit								
Mean (SD)	0.22 (0.62)	0.09 (0.37)	0.40 (0.90)	0.20 (0.63)	0.69 (1.40)	0.38 (0.98)	0.96 (1.64)	0.58 (1.39)
Median (IQR)	0 (0–0)	0 (0–0)	0 (0–1)	0 (0–0)	0 (0–1)	0 (0–0)	0 (0–1)	0 (0–1)
Inpatient stay								
Mean (SD)	0.71 (1.26)	0.13 (0.55)	1.16 (1.76)	0.26 (0.93)	1.80 (2.45)	0.53 (1.65)	2.43 (3.30)	0.77 (2.16)
Median (IQR)	1 (0–1)	0 (0–0)	1 (0–2)	0 (0–0)	1 (1–2)	0 (0–0)	2 (1–3)	0 (0–1)
Length of stay, days†								
Mean (SD)	1.91 (7.56)	0.35 (4.17)	3.15 (10.82)	0.79 (6.55)	4.57 (15.86)	1.57 (12.95)	5.84 (18.40)	2.45 (16.66)
Median (IQR)	0 (0–2)	0 (0–0)	0 (0–3)	0 (0–0)	1 (0–5)	0 (0–0)	2 (0–6)	0 (0–0)

*Not all cases/controls had 24 months of follow-up.
†Cumulative across all inpatient stays within each time period.
ED, emergency department; GP, general practitioner.

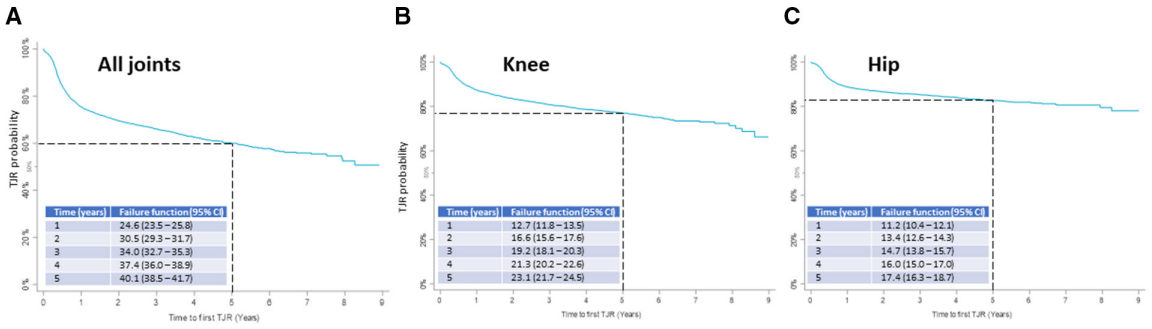

Figure 1 Outcomes in patients with osteoarthritis before TJR of (A) all joints, (B) knees and (C) hips. The 5-year TJR rate for other joints combined was 1.7%; the median survival time (ie, the time point at which 50% of patients are yet to have a TJR) was not achieved for any joints. TJR, total joint replacement.

perspectives.[18–20] This might be due to requirements for treatment of comorbidities in their own right, to minimise the risks of interventions for OA, or to manage the increased pain severity that has been associated with these comorbidities in other studies.[21–24]

Analysis of medicine use suggests that patients with moderate-to-severe chronic pain associated with OA are cycling through available pharmacological therapies to manage their pain. These medicines represent incremental costs, being prescribed on top of pre-existing therapies; additional physician appointments are also likely needed to implement medicine changes, as reflected in the higher number of GP visits among cases. Each line of therapy had a mean duration of approximately 2 months, suggesting suboptimal pain management, intolerable side effects and/or lack of effective alternative treatment options. Some lines of therapy duplicated previous treatments, which might suggest a 'revolving door' through which, in the absence of effective or acceptable alternatives, treatments that had not provided long-term benefit in the past are reinstigated. However, some of these renewed lines of therapy might reflect appropriate use of treatments that were effective during previous pain events, even if benefits proved not to be long-lasting.

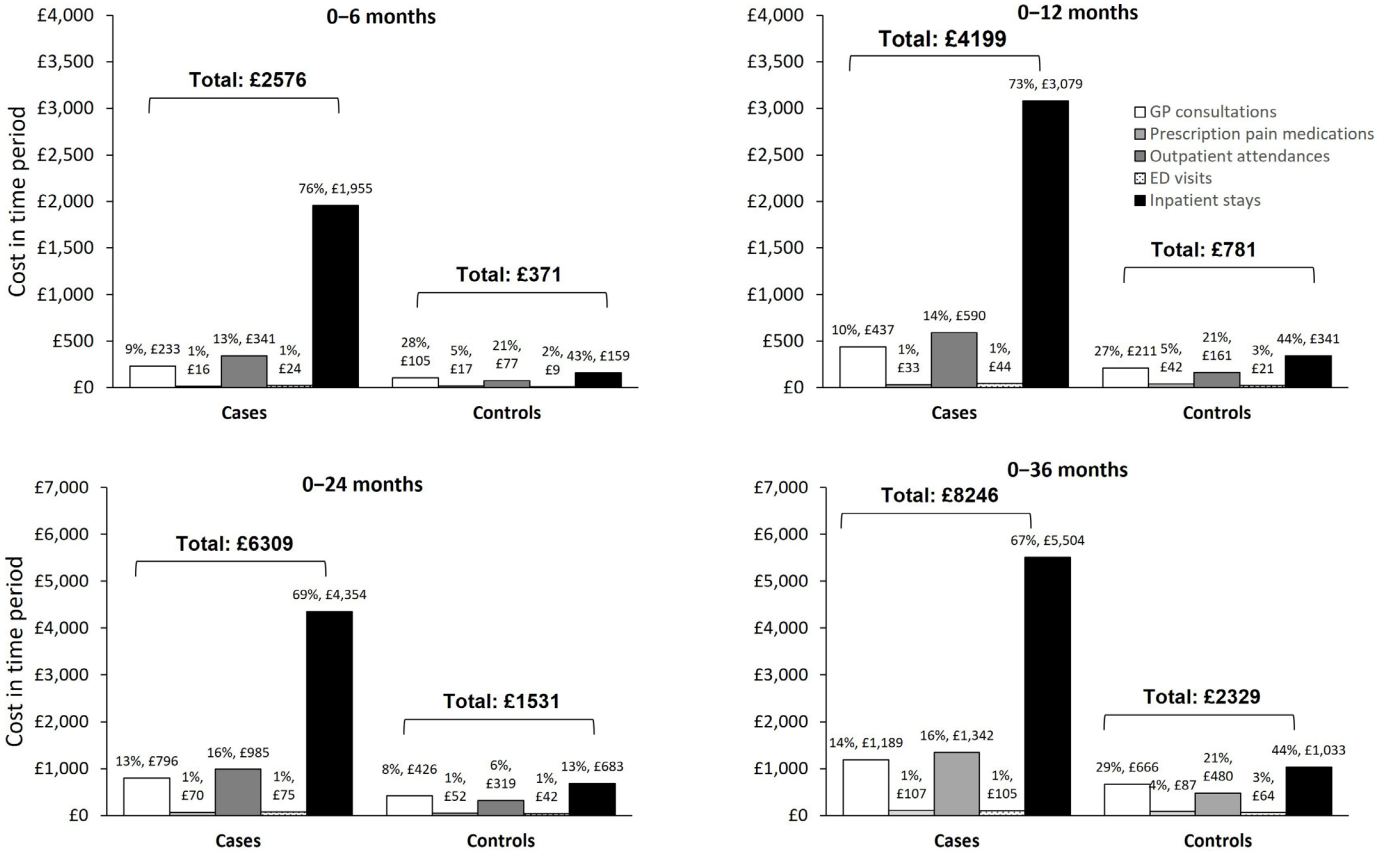

Figure 2 Mean all-cause direct healthcare costs associated with management of patients with moderate-to-severe chronic pain associated with osteoarthritis. Not all cases/controls had 24 or 36 months of follow-up. P value<0.0001 for the difference in mean costs between cases and controls for each healthcare service (with the exception of medicine) and for total costs, across all time periods. ED, emergency department; GP, general practitioner.

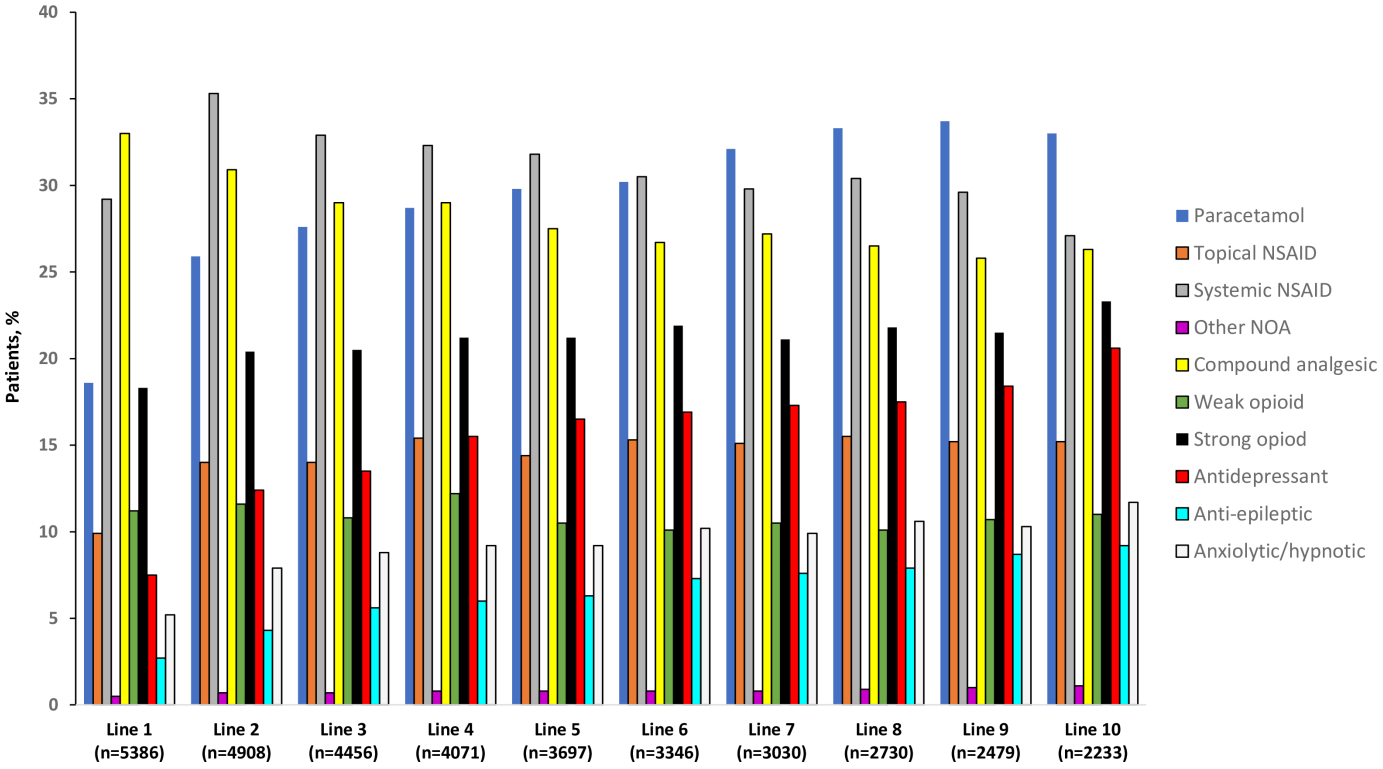

Figure 3 Pharmacological management of patients with moderate-to-severe chronic pain associated with osteoarthritis: most common lines of therapy used. NOA, non-opioid analgesic; NSAID, non-steroidal anti-inflammatory drug.

Several new lines of therapy were instigated during the follow-up period, suggesting that previous lines were not considered successful. We observed an increase over treatment lines in the use of the anti-epileptics gabapentin and pregabalin: 10% of patients were prescribed these agents within the 36-month follow-up, despite limited evidence for their efficacy in OA-related pain and the potential for harm.[25] A trend towards use of gabapentinoids in people with OA has been observed by others; Appleyard and colleagues reported that the likelihood of UK patients with OA being prescribed gabapentinoids increased between 2000 and 2015, although the lack of relevant diagnostic codes made it difficult to ascertain the reason for some prescriptions.[26] It is not clear whether antidepressants and anxiolytics agents were prescribed off label for the treatment of pain in the present study or for the management of anxiety or depression associated with OA, as a higher proportion of cases than controls had depression and anxiety at indexing, in line with other studies.[27] Our data, indicating a high use of multiple lines of pharmacological therapy and joint replacement surgery, support earlier findings that medications alone might not lead to patient satisfaction with their symptom control[17] and suggest a need for more effective pain management approaches in the OA setting.

Some study limitations, including those inherent in studies such as this, warrant consideration. The chronic pain end date may not indicate the date when the chronic pain episode ended; some patients may instead have decided not to use the NHS further and/or self-manage despite minimal improvements (if any) in their chronic pain. We were not able to classify patients by site of OA due to the inconsistency of site-specific diagnostic coding. Furthermore, diagnoses identified using ICD-10 and Read Codes are subject to potential miscoding. The absence of a specific diagnosis code must be interpreted as an absence of the disease, resulting in a high positive predictive value, but a lower sensitivity. In particular, mental health conditions including depression and anxiety are likely to be under-reported, potentially resulting in misclassification bias. CPRD is, however, widely considered a gold standard in healthcare event reporting and missed diagnoses or prescriptions are likely to be rare.[7] The requirement for 12 months of follow-up data following the index date introduces a survivorship bias to the study as patients were only included if they were still alive after this 12-month period.

In the absence of data regarding the use of community-based physiotherapy, access to supported self-management programmes in the community, social care and use of over-the-counter medicine, our insight into pain medicine use and its effectiveness is incomplete. Furthermore, inpatient stay costs were not split by specialty or department, therefore it is not known if non-orthopaedic costs were also higher in cases versus controls, as might be expected given the extra comorbidities in cases that might lead to inpatient treatment. Not all HRGs have a national tariff, as some prices are negotiated locally; therefore, direct healthcare costs are likely to be underestimated as missing costs were not imputed.

The CPRD does not capture data on private patients and procedures, nor are indirect and societal costs captured;

the true cost of managing pain associated with OA is likely underestimated. CPRD captures prescriptions written by GPs but not whether the prescription was dispensed/consumed—a limitation of most such databases. Medicines bought over the counter and those administered in the secondary care setting are not captured in linked CPRD-HES data. This may particularly affect the patient population of interest, as many of the assessed pain medicines are freely available over the counter in the UK, with the exception of strong opioids, and are often advocated by clinicians to be purchased out of pocket rather than on prescription. Nonetheless, the overall HCRU cost findings of this study remain largely unaffected because of the low costs of these products. Finally, it should be noted that observed statistically significant differences may be driven in part by large sample sizes; comparisons should emphasise absolute differences.

Study strengths include the real-world nature of the data and generalisability of the data to the wider population of patients with OA seeking care for chronic pain. The linked CPRD and HES data sets have broad coverage, encompassing 75% of patients in English GP practices. Consequently, our findings are likely to be representative of adults in England.

CONCLUSION

This wide-ranging, longitudinal, observational study of real-world primary and secondary care data provides meaningful and relevant insights into the impact of moderate-to-severe chronic pain associated with OA in patients compared with matched controls. Our findings suggest that available treatments and guidelines may be inadequate for some patients, resulting in them cycling through treatments and having high levels of HCRU and associated costs. A more consistent and evidence-based approach to repeat or new treatment cycles may be beneficial for people with OA, and there is a need to better define when it is appropriate to 'try again' with pharmacological approaches or instigate prompt surgical intervention. Additional studies are needed to better understand the effect of pain severity—including mild pain—on HCRU, costs and medicine use after diagnosis, as well as how outcomes vary once patients have had a TJR. With the increasing size of NHS waiting times for patients awaiting TJR, analysis of whether HCRU costs increase in a linear or exponential manner as patients await surgery would also be useful and timely. Further exploration of the elements of care not covered in this analysis would contribute to a better understanding of the overall cost of pain management in this setting. In the absence of better pain management therapies, our study findings may indicate areas where cost savings could be achieved and where improvements in patient services are needed.

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Acknowledgements This study is based in part on data from the Clinical Practice Research Datalink obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. The data is provided by patients and collected by the National Health Service (NHS) as part of their care and support. The interpretation and conclusions contained in this study are those of the author/s alone. Hospital Episode Statistics data are copyright 2022, re-used with the permission of The Health & Social Care Information Centre. All rights reserved. The Office of Population Censuses and Surveys Classification of Interventions and Procedures, codes, terms and text is Crown copyright (2016) published by Health and Social Care Information Centre, also known as NHS Digital and licensed under the Open Government Licence available at www.nationalarchives.gov.uk/doc/open-government-licence/open-government-licence.htm.

Contributors HS, GC, PC and CL conceived of the work. HS, GC, PC, CL, RW, TT, RK, AJD and DW contributed to the design of the work. RW and TT acquired the data for the work and contributed to analysis of data; HS, GC, PC, CL, RW, TT, RK, AJD and DW contributed to interpretation of the data, drafting the work and revising it critically for important intellectual content, provide final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy of integrity of any part of the work are appropriately investigated and resolved. RW is the guarantor of the work.

Funding This work was supported by Pfizer UK. Adelphi Real World received funding from Pfizer UK to conduct the study. Medical writing and editorial support was provided by Deirdre Carman PhD (Alispera Communications Ltd) and was funded by Pfizer and Eli Lilly and Company.

Competing interests GC and PC are employees of Pfizer UK, which provided funding for this study. CL was an employee of Pfizer UK at the time of the work and is now employed by Pfizer Australia. HS was an employee of Pfizer UK during the conduct of the work. RW and TT are employees of Adelphi Real World, which received funding to conduct this study. RK declares a personal financial interest in his employment by the University of Nottingham, which receives funding for his salary in part from the Primary Integrated Community Solutions. In the past 36 months, RK declares consultancy through his employment with the University of Nottingham to Pfizer and Mibe. AJD declares a personal financial interest in his employment with York Medical Group (YMG), and over the past 36 months with NHS111 and RCP (London), from whom he receives payment for his work as a part-time salaried general practitioner (GP) with YMG, and over the past 36 months as a GP on the NHS111 COVID-19 Response and the NICE Gout Committee, respectively, and in his ownership and directorship of AD Outcomes. In the past 36 months, AJD declares the following personal financial interests through medical and health economics consultancy work for AD Outcomes for: Emotive (Agency), Grunenthal (UK), Grunenthal (GmbH), Pfizer (UK), Pharmacy Magazine, Spink Health, Tilray (Portugal) and RCGP, as a racecourse doctor for various racecourses (Croft, Doncaster, Market Rasen, Newcastle, Pontefract, Redcar, Southwell and Thirsk) and as a locum GP with out-of-hours, NHS111 and urgent care work for Vocare part of Totally. AJD has a non-personal financial interest in his roles as a Trustee of the Primary Care Rheumatology & Musculoskeletal Medicine (PCRMM) Society (Trustee from 2017 to 2020) and as Trustee of the UK Gout Society (ongoing). The PCRMM Society has received funding from multiple companies for its annual conference including from Pfizer (UK) in 2020. AJD's work as a Trustee of PCRMM Society and UK Gout Society and as GP Clinical Lead for the North of England Low Back Pain Group are voluntary and unpaid. DW declares a personal financial interest in his employment by the University of Nottingham, which receives funding for his salary from the UK Government, Sherwood Forest Hospitals NHS Foundation Trust and UKRI. He is Director UKRI/Versus Arthritis Advanced Pain Discovery Platform (personal pecuniary: paid by University of Nottingham as part of job plan, funded by UKRI), Honorary Consultant Rheumatologist at Sherwood Forest Hospitals NHS Foundation Trust (personal pecuniary; paid by University of Nottingham as part of job plan, funded by Sherwood Forest Hospitals) and Professor of Rheumatology, University of Nottingham (personal pecuniary; paid by University of Nottingham). In the past 36 months DW declares the following non-personal financial interests:

research support to the University of Nottingham from Versus Arthritis and National Institute for Health and care Research; grants from Pfizer, Eli Lilly, and UCB Pharma; consultancy through his employment with the University of Nottingham to Pfizer, Eli Lilly, AbbVie, AKL R&D, Galapagos, Reckitt Benckiser Health, and GlaxoSmithKline, and responsibilities for investigator-led grants outside the work in this presentation held by the University of Nottingham from Pfizer, Lilly and UCB Pharma, and research grants from Versus Arthritis; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events (to University of Nottingham) from Pfizer and AbbVie.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study was approved by the Independent Scientific Advisory Committee of the Medicines and Healthcare Products Regulation Agency; protocol No. 19_158; approval date 31 July 2019.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. The study data analysed in this publication are derived from the Clinical Practice Research Datalink (www.cprd.com) and Hospital Episode Statistics database (https://digital.nhs.uk/ data-and-information/data-tools-and-services/data-services/hospital-episode-statistics). Authors had access to the study data for the purposes of this work only. Data were accessed through an individual data set study licence to address prespecified research questions only. Therefore, the data cannot be broadly disclosed or made publicly available at this time. Access to each database can be requested via the respective websites.

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