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Osteoarthritis and Cartilage

Chronic opioid use before and after exercise therapy and patient education among patients with knee or hip osteoarthritis

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Objective: To investigate changes in opioid use after supervised exercise therapy and patient education among knee or hip osteoarthritis patients with chronic opioid use.
Method: In this cohort study, we linked data from the Good Life with osteoArthritis in Denmark register (GLA:D®; standardised treatment program for osteoarthritis; January 2013 to November 2018) with national health registries. Among 35,549 patients, 1,262 were classified as chronic opioid users based on amount and temporal distribution of dispensed opioids the year before the intervention. We investigated changes in opioid use, measured as mg oral morphine equivalents (OMEQs), from the year before the intervention to the year after using generalized estimating equations.
Results: We found a 10% decrease in mg OMEQs from the year before to the year after the intervention (incidence rate ratio [IRR]: 0.90, 95% confidence interval [CI]: 0.86, 0.94). Additional analyses suggested this decrease to be mainly attributable to regulatory actions targeting opioid prescribing during the study period (IRR among patients participating in the intervention before: 0.98 [95% CI: 0.89, 1.07] vs after: 0.83 [0.74, 0.93] regulatory actions). In a random general population sample of matched chronic opioid users, a similar opioid use pattern was observed over time, further supporting the impact of regulatory actions on the opioid use in the study population.
Conclusion: Among patients with knee or hip osteoarthritis and chronic opioid use, a standardised treatment program did not change opioid use when regulatory changes in opioid prescribing were taken into account.

Introduction

Knee and hip osteoarthritis constitute an important public health challenge, as they affect 400 million individuals globally and is one of the most important causes of years lived with disability[1–3]. Opioids are often used to treat osteoarthritis-related pain[4,5] despite not being recommended in treatment guidelines[6–8]. Of particular concern is the chronic use of opioids among osteoarthritis patients due to the risk of addiction, adverse events, and premature mortality[9–13]. It is therefore important to identify treatments or other interventions that can reduce the use of opioids among patients with osteoarthritis and chronic opioid use.

Exercise therapy can reduce osteoarthritis-related pain and improve physical function[14,15], and is recommended as first-line treatment in combination with patient education for all patients with knee or hip osteoarthritis[6–8]. Furthermore, exercise therapy is

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safe[16,17] and has effect sizes for osteoarthritis-related pain that are similar to or larger than those of opioids, non-steroidal anti-inflammatory drugs (NSAIDs), and paracetamol[18–20]. However, quality of care studies report that exercise therapy is greatly underutilized[21], which means that many osteoarthritis patients are initially offered second-line pharmacological treatments and miss out on appropriate first-line care[22].

The potential of exercise therapy to reduce opioid use among patients with osteoarthritis is currently unknown. Studies indicate that exercise therapy and patient education could play an important role in reducing analgesic use, including opioids, since the proportion of patients with knee or hip osteoarthritis using analgesic has been reported to decrease after these interventions[23,24]. However, some of these results may be explained by regression to the mean or underlying changes in prescription patterns over time. One way to minimise the influence of these factors in cohort studies, is to focus on patients with a chronic opioid use, since any changes in opioid use from before to after an intervention is less likely caused by regression to the mean, while taking temporal prescription trends into account. Using data from a nationwide osteoarthritis patient-register linked with national prescription data, we aimed to investigate changes in opioid use after an intervention that consists of 8 weeks of supervised exercise therapy and patient education among knee or hip osteoarthritis patients with chronic opioid use.

Methods

Data sources

This cohort study used data from the Good Life with osteoArthritis in Denmark (GLA:D®) register[25] linked with routinely collected health data. The GLA:D® register includes patients with clinical signs of knee or hip osteoarthritis who have participated in GLA:D®, a standardised exercise therapy and patient education program delivered in primary care in Denmark. Briefly, the GLA:D® program consists of two group-based sessions of patient education, and 12 supervised neuromuscular exercise sessions (1 h two times a week for 6 weeks) led by a trained physiotherapist over 8–12 weeks. From the GLA:D® register, we used patient- and clinician-reported data collected at baseline and 3 months follow-up[25].

We linked the GLA:D® register with individual-level data from Danish national health registries using a unique national person identification number (i.e., the Civil Registration number). Information on dispensed prescription analgesics was retrieved from the Danish National Prescription Registry[26]. Data on migrations and deaths were retrieved from the Danish Civil Registration System and the Danish Register of Causes of Death, respectively[27,28]. Finally, diagnostic and procedure codes from secondary health care contacts were retrieved from the Danish National Patient Registry[29].

Ethics approval of GLA:D® was waived by the ethics committee of the North Denmark Region. The GLA:D® register (registration no.: SDU; 10.084) and the current analyses (registration no.: SDU; 10.124) have been registered at The Danish Data Protection Agency. According to the Danish Data Protection Act, patient consent was not required as personal data was processed exclusively for research and statistical purposes.

Study population

We included patients starting the GLA:D® program (index date) between January 14, 2013 (inception) and November 30, 2018. The restriction in time was implemented to avoid any overlap with the COVID-19-related lockdown starting March 2020 in Denmark.

The required period of register-data coverage was 5 years before (day −1825 to −1), and 1 year after the end of the GLA:D® program (day 90–454), allowing a 90-day period for the intervention (day 0–89; Supplementary Fig. S1). We excluded study participants (**1**) lacking register data coverage due to migration or death, (**2**) with a cancer diagnosis within the 5 years prior to their index date, or (**3**) with a substance abuse diagnosis within the year prior to their index date (Supplementary Table S1).

To be able to compare our results with the opioid use in the background population, a random general population sample matched by year of birth, sex, municipality of residence, and being alive at the time of the index date was retrieved from the Danish Health Data Authority. Controls were assigned the same index date as the study participant they were matched to.

Opioid use groups

We used data on opioids dispensed during the year before the index date (day −365 to −1) to classify patients as (1) chronic opioid users, (2) occasional opioid users, or (3) non-opioid users as previously described[30]. Specifically, patients with >180 defined daily doses (DDDs) or >4,500 mg oral morphine equivalents (OMEQs), and ≥1 dispensed opioid prescriptions in at least three out of four quarters of the year preceding the index date were defined as chronic opioid users. Patients with dispensed opioids in the 1-year period prior to the index date who did not fulfil the criteria for chronic opioid use were classified as occasional users, and those with no dispensed opioids were classified as non-users.

Outcomes

The main outcome was dispensed mg OMEQs per year[31]. For each opioid prescription dispensed during the year before the index date and the year after the intervention, respectively, we calculated mg OMEQs by multiplying mg/DDD[32] with an equianalgesic ratio[30,31,33,34] and the number of DDDs of the dispensing. Subsequently, we calculated the sum of all dispensed opioid prescriptions during the two time periods for each study participant. We included ATC-codes N02A*, R05DA04, and N02BA75 (Supplementary Table S2). Parenteral, sublingual, nasal, and rectal routes of administration, and oral solutions, oral drops, and depot granules for oral suspensions were excluded (Supplementary Table S3).

We also investigated changes in opioid use group classification and changes in classes of analgesics used from the year before to the year after the intervention. Opioid use group classification during the year after the intervention was based on prescription data from day 90–454. Changes in classes of analgesics used by chronic opioid users from before to after the intervention were investigated for paracetamol, NSAIDs, and opioids (or any combination of these) dispensed during the year before the index date and the year after the intervention (≥1 dispensed prescription; Supplementary Table S2).

Statistical analysis

Participant characteristics were described using means with standard deviations (SD) and frequencies with percentages.

For the main analysis, we used generalized estimating equations (GEEs)[35,36] to assess the change in mg OMEQs from 1 year before (day −365 to −1) to 1 year after (day 90–454) the intervention. Specifically, the model estimated the ratio between the mean mg oral morphine equivalents (OMEQ) during the year after the intervention and the year before the index date given the covariates of the model. The ratio, expressed as an incidence rate ratio (IRR), hence reflects the relative change in mg OMEQ from before to after the intervention. The unadjusted and adjusted IRRs were estimated using GEE models with a log-link and Poisson variance function, an "exchangeable" working correlation structure, and robust standard errors. To adjust for the over-dispersed outcome, we estimated the dispersion parameter φ. In the adjusted model, we included the following covariates from the GLA:D® register: age (years, continuous), sex (women/men), level of education (self-reported, from primary school to long-cycle higher education), body mass index (BMI, kg/m^2, continuous), average pain intensity last month (visual analogue scale [VAS], 0 [no pain] to 100 mm [worst pain imaginable], continuous), knee/hip surgery at any time before the intervention (self-reported, yes/no), number of comorbidities (self-reported, 0–12 comorbidities, continuous), smoking status (yes/no), and physical activity level (UCLA Activity Score, continuous) (Supplementary Table S4). Cases with missing data in any of the covariates included in the adjusted model were excluded from the adjusted analyses. Differences in the mean and median mg OMEQ between the two time periods was assessed using a paired *t*-test and Wilcoxon sign rank test, respectively.

Overall, opioid prescribing decreased in Denmark from January 1, 2017, and onwards following media attention on opioid use and addiction, and regulatory actions targeted opioid prescribing[37]. To investigate if this influenced our results, we stratified our main analysis based on the temporal placement of study participants' study period relative to January 1, 2017 (i.e., before, crossing, or after; Supplementary Fig. S2). In addition, we compared the opioid use over time among chronic opioid users in the GLA:D® registry with chronic opioid users from the random general population sample (classified using the same chronic opioid use definition).

Several sensitivity analyses were performed. We (**1**) tested the robustness of the main results by applying a more conservative definition of chronic opioid use (same definition as above but with requirements of dispensed prescriptions in four consecutive quarters in the year preceding the index date) and assessed if the main results were influenced by (**2**) compliance to the intervention (good compliance: participating in ≥10 exercise sessions and two sessions of patient education), (**3**) patients undergoing knee or hip arthroplasty the year after the intervention, (**4**) clinically relevant pain relief after the intervention (≥15 mm improvement in VAS-score from baseline to 3 months follow-up), and (**5**) cancer diagnoses received during the study period. See Supplementary files (Sensitivity analyses) for details.

Changes in opioid use group classification in the study population, and changes in classes of analgesics used among chronic opioid users from before to after the intervention were described with alluvial diagrams and frequencies and percentages.

We used the statistical software RStudio (version 1.3.1093) running R for all analyses[38]. GEE models were fitted using the geepack package[39].

Results

The final study population included 35,549 patients, of which 1,262 (4%) were classified as chronic opioid users, 5,662 (16%) as occasional opioid users, and 28,625 (80%) as non-users the year before the intervention (Fig. 1). The study population was on average 65 years old, 72% were women, and the mean BMI was 28.4 kg/m^2. Chronic opioid users reported a higher frequency and intensity of pain, a lower level of physical activity, and a higher number of comorbidities than occasional and non-opioid users (Table I). Among chronic opioid users, the average pain intensity decreased to 48.3 mm at 3-months follow up (difference in means: 11.3, 95% confidence interval: −13.1, −9.6 mm VAS-score).

The annual opioid use decreased about 10% after the intervention among chronic opioid users (Table II and Fig. 2). In the analysis stratified by the placement of study participants' study period relative to January 1, 2017 (media attention and regulatory actions targeted opioid prescribing), we found a larger decrease in opioid use if the study period was placed after January 1, 2017, compared to before (Table III). Also, the decrease depended on which part of the study period that was placed after January 1, 2017 (i.e., pre- or post-intervention period) and to what degree (Supplementary Fig. S3 and Supplementary Table S5). Additionally, the opioid use pattern during the year before and after the intervention was similar among chronic opioid users in the study population and chronic users from the random general population sample (Fig. 2).

Sensitivity analyses indicated that patients with a good compliance had a smaller decrease in opioid use from before to after the intervention compared to those with a poor compliance, and that patients undergoing knee or hip arthroplasty during the follow-up period did not decrease their opioid use. The results of the remaining sensitivity analyses did not differ from the main analysis (Supplementary Tables S6–S10).

About 74% ($n = 936$) of chronic opioid users remained chronic opioid users after the intervention, while 18% ($n = 232$) and 7% ($n = 94$) were classified as occasional and non-opioid users, respectively, the year after the intervention (Supplementary Fig. S4 and Table S11). Among patients categorized as occasional and non-opioid users prior to the intervention, 6% ($n = 356$) and 0.5% ($n = 157$), respectively, became chronic opioid users. This resulted in a net increase from 1,262 to 1,449 chronic opioid users the year after the intervention. Furthermore, 98% ($n = 1{,}158$) of chronic opioid users continued to use opioids either alone or in combination with paracetamol and/or NSAIDs (Supplementary Fig. S5 and Table S12).

Discussion

We found a 10% decrease in opioid use from before to after a supervised exercise therapy and patient education program among primary care patients with knee or hip osteoarthritis and chronic opioid use. Additional analyses suggested that this decrease was mainly attributable to regulatory actions targeted opioid prescribing in Denmark during the study period.

To our knowledge, no previous studies have investigated whether exercise therapy and patient education can play a role in reducing opioid use among patients with knee or hip osteoarthritis

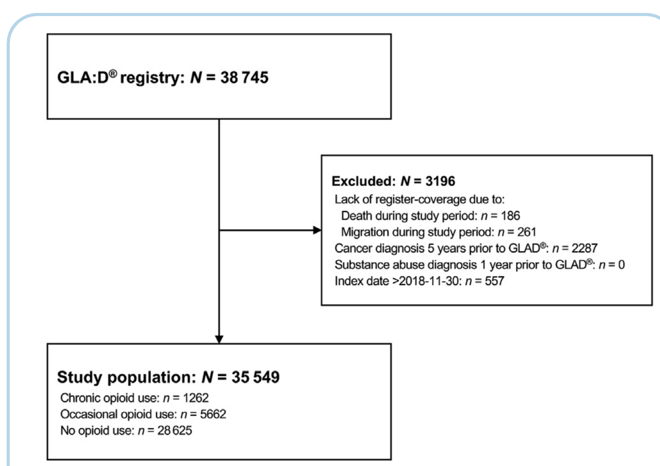

Fig. 1 Osteoarthritis and Cartilage

Formation of study population. The sum across reasons for exclusion exceeds 3,196 since some study participants fulfilled more than one exclusion criterion. GLA:D® is Good Life with osteoArthritis in Denmark.

Characteristic	All participants $N = 35{,}549$ n (%)/Mean (SD)	Opioid use groups 1 year before the intervention n (%)/Mean (SD)		
		Non opioid users $n = 28{,}625$	Occasional opioid users $n = 5{,}662$	Chronic opioid users $n = 1{,}262$
Age at start of intervention	65.4 (9.9)	65.2 (9.8)	66.2 (10.1)	65.9 (9.6)
Sex				
Women	25,544 (72)	20,320 (71)	4,245 (75)	979 (78)
Men	10,005 (28)	8,305 (29)	1,417 (25)	283 (22)
Self-reported level of education				
Primary and lower secondary school	5,544 (18)	4,225 (17)	1,040 (21)	279 (26)
General and vocational upper secondary education	3,476 (11)	2,831 (11)	520 (11)	125 (12)
Short-cycle higher education (<3 yrs beyond secondary school)	6,187 (20)	4,929 (20)	1,044 (21)	214 (20)
Medium-cycle higher education (3–4 yrs beyond secondary school)	12,287 (40)	10,120 (40)	1791 (37)	376 (35)
Long cycle higher education or higher (≥5 yrs beyond secondary school)	3,456 (11)	2,926 (12)	464 (9.5)	66 (6.2)
Smoking status				
Current smoker	2,844 (9)	2,155 (9)	529 (11)	160 (15)
Non-smoker	27,749 (91)	22,599 (91)	4,273 (89)	877 (85)
BMI	28.4 (5.3)	28.1 (5.2)	29.2 (5.6)	30.3 (6.0)
Most affected joint				
Knee	26,462 (74)	21,292 (74)	4,212 (74)	958 (76)
Hip	9,075 (26)	7,325 (26)	1,447 (26)	303 (24)
Average pain intensity last month (VAS)	47.6 (22.0)	45.9 (21.6)	53.6 (22.3)	60.6 (21.5)
Frequency of knee/hip pain				
Never	433 (1)	375 (2)	48 (1)	10 (1)
Monthly	1,258 (4)	1,103 (4)	141 (3)	14 (1)
Weekly	4,057 (13)	3,538 (14)	458 (9)	61 (6)
Daily	19,803 (64)	16,227 (65)	3,027 (62)	549 (52)
Always	5,338 (17)	3,735 (15)	1,179 (24)	424 (40)
Physical activity level (UCLA Activity Score)				
Low (Level 1–4)	9,955 (32)	7,330 (29)	2059 (42)	566 (53)
Moderate (Level 5–6)	10,544 (34)	8,755 (35)	1,498 (31)	291 (27)
High (Level 7–10)	10,494 (34)	8,974 (36)	1,316 (27)	204 (19)
Number of self-reported co-morbidities				
0	11,216 (38)	9,686 (41)	1,362 (30)	168 (17)
1-2	15,606 (53)	12,414 (52)	2,608 (57)	584 (59)
≥3	2,509 (9)	1,659 (7)	612 (13)	238 (24)
Surgery of knee/hip before the intervention				
Yes	4,831 (14)	3,771 (13)	863 (15)	197 (16)
No	30,718 (86)	24,854 (87)	4,799 (85)	1,065 (84)
Compliance to the intervention				
Poor	6,605 (31)	5,407 (31)	981 (31)	217 (33)
Good	14,444 (69)	11,775 (69)	2,225 (69)	444 (67)

N/n, number of observations; SD, standard deviation; yrs., years; BMI, body mass index; VAS, visual analogue scale, ranging from 0 to 100 where 0 is 'no pain' and 100 is 'worst pain imaginable'. UCLA Activity Score, the University of California at Los Angeles Activity Rating Scale, self-reported physical activity level during the last month, from very low (level 1) to very high (level 10). Self-reported number of co-morbidities; presence of hypertension, heart disease, stomach ulcer/gastrointestinal disease, lung/respiratory disease, diabetes, kidney- or liver disease, anaemia, cancer, depression, rheumatoid arthritis, neurological disease, and/or other medical disease (0–12). Good compliance was defined as participation in ≥10 exercise sessions and two patient education sessions.

Missing data among all study participants, n (%).
Age, 0 (0).
Sex, 0 (0).
Self-reported level of education, 4,599 (13).
Smoking status, 4,956 (14; part of the missing data is due to late introduction of the question in the baseline questionnaire).
BMI, 127 (<1).
Most affected joint, 12 (<1).
Average pain intensity last month (VAS), 4,599 (13).
Frequency of knee/hip pain, 4,660 (13).
Physical activity level (UCLA Activity Score), 4,556 (13).
Number of self-reported co-morbidities, 6,218 (17; part of the missing data is due to late introduction of the questions in the baseline questionnaire).
Surgery of knee/hip before the intervention, 0 (0).
Compliance to the intervention, 14,501 (41).

Table I

Osteoarthritis and Cartilage

Characteristics of 35,549 patients with knee or hip osteoarthritis participating in a standardised exercise therapy and patient education program, overall and stratified by opioid use group

	Unadjusted $n = 1262$ IRR (95% CI)	Adjusted $n = 981$ IRR (95% CI)
1 year before the intervention	1.0 [Reference]	1.0 [Reference]
1 year after the intervention	0.906 (0.874, 0.939)	0.895 (0.857, 0.934)

	mg OMEQ 1 year before the intervention	mg OMEQ 1 year after the intervention	Difference in mean/median mg OMEQ (95% CI)	P-value
Mean (SD)	13,988 (15,506)	12,671 (15,542)	1,317 (847, 1788)	<0.001
Median (Q1; Q3)	10,000 (6,000; 16,200)	8,929 (3,500; 16,115)	1,100 (786, 1,440)	<0.001

n, number of observations included in model; IRR, incidence rate ratio; CI, confidence interval; SD, standard deviation; Q1, Q3, first and third quartile. Modelled with generalized estimating equations models specified with a Poisson variance function, log-link function, exchangeable working correlation matrix, estimation of robust standard errors, and estimation of the dispersion parameter to adjust for over-dispersed data. The model estimates the ratio between the mean mg OMEQ during the year before index date (day −365 to −1) and the year after the intervention (day 90–454), given the covariates of the model.

Model adjusted for sex, age, level of education, BMI, average pain intensity last month (continuous, Visual Analogue Scale, 0–100), self-reported knee/hip surgery prior to the intervention, number of self-reported comorbidities (0–12), physical activity level (continuous, UCLA, score 0–10), and smoking status. Cases with missing data in any of the covariates included in the adjusted model were excluded from the adjusted analyses. Differences including 95% CI in mean/median mg OMEQs between the year before and after the intervention were estimated using a paired *t*-test and Wilcoxon rank sign test, respectively.

Table II Osteoarthritis and Cartilage

Incidence rate ratios reflecting relative change in annual mg oral morphine equivalents (OMEQ) from before to after supervised exercise therapy and patient education, mean/median mg OMEQ before and after the intervention, and the difference in mean/median among 1,262 chronic opioid users with knee or hip osteoarthritis

and chronic opioid use. Instead, previous studies investigating opioid deprescribing interventions for patients with chronic non-cancer pain have focused on opioid dose reduction protocols, opioid replacement with buprenorphine, non-pharmacological therapies (e.g., mindfulness, cognitive behavioural therapy, and acupuncture), and education-based interventions targeted clinicians[40–43]. However, none of these are sufficiently supported by evidence and the most effective methods are therefore unknown[40–43]. In this study, we used data from a large primary care database reflecting ‘real world’ patients with knee or hip osteoarthritis, linked with high quality national prescription data covering all dispensed prescription analgesics in Denmark. The limited evidence of effect of the intervention on opioid prescribing in this study should be considered in the context that the GLA:D® program was not specifically designed to be a deprescribing intervention. Nevertheless, integrating non-pharmacological treatments in opioid dose reduction protocols has been suggested to be important when a patient is motivated to reduce his or her opioid dose[42], and exercise therapy and patient education may therefore still play a role in multimodal opioid deprescribing interventions.

Based on our analyses, the observed decrease in opioid use among chronic opioid users was most likely attributable to regulatory actions on opioid prescribing in Denmark. This is further supported by the similar opioid use pattern observed among the matched chronic opioid users from a random general population sample (Fig. 2). The regulatory actions included guidelines and courses targeting Danish physicians, mandatory reporting of suspected adverse events related to tramadol use, and changes in classification of tramadol and certain other opioids to the same prescription restrictions and monitoring as opioids with a known abuse potential. These actions led to a general decline in opioid prescribing from early 2017 and onwards as previously reported[37]. In line with some previous studies reporting decreased opioid use, misuse, and changed prescription patterns after regulatory changes[37,44–46], this highlights the potential of systems-based approaches to affect individual-level prescribing behaviour, although reviews summarizing the effectiveness of regulatory changes on opioid use and prescription patterns report mixed findings[47,48].

We conducted several sensitivity analyses, which generally showed similar results as the main analysis. However, we found a larger decrease in opioid use among patients with poor compliance to the intervention compared to those with good compliance. This seemed to be explained by a larger proportion of poor compliers having an index date after the policy change (i.e., inducing a larger decrease in opioid use) compared with good compliers (20% of poor compliers had an index date in 2018 vs 14% of good compliers). We also found that patients undergoing knee or hip arthroplasty during the year after the intervention did not change their opioid use from before to after the intervention. This finding is likely related to post-operative opioid use, since we observed a larger than average opioid dispensing in the 30 days following surgery combined with a shift in the types of opioids dispensed (i.e., larger proportion oxycodone and morphine during the post-intervention period compared to the pre-intervention period; Supplementary Table S13) among those undergoing arthroplasty. Lastly, pre-operative opioid use is associated with higher post-operative opioid consumption[49], which likely also contribute to the lack of reduction in opioid use among patients undergoing arthroplasty.

Although 26% of chronic opioid users became occasional- or non-opioid users, the total number of patients classified as chronic opioid users the year after the intervention increased by 15%. There are several potential explanations for this increase. Development of tolerance and addiction is reported in up to 30% of opioid users[11]. This risk is amplified for patients using tramadol[50], and could have occurred among occasional users in this study since tramadol was the most commonly prescribed opioid in the study population the year before the intervention (Supplementary Table S14). Furthermore, patients with pre-operative opioid use often consume more opioids after surgery and have an increased risk of chronic post-operative opioid use[49]. This was confirmed in our data since a substantial proportion (28%) of “new” chronic opioid users had undergone a knee or hip arthroplasty during the post-intervention period.

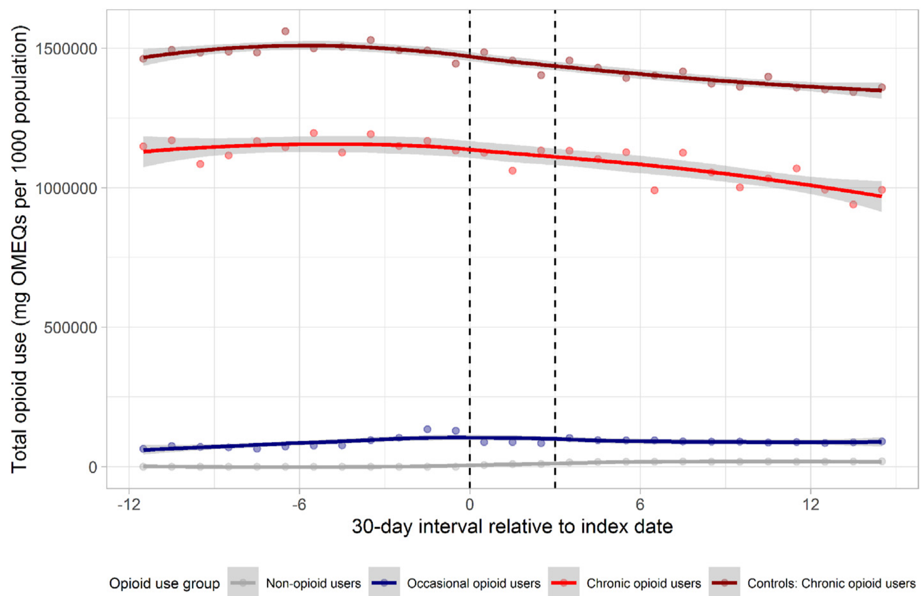

Fig. 2 Osteoarthritis and Cartilage

Total mg oral morphine equivalents (OMEQs) per 1,000 population per 30-day interval relative to the index date, stratified by opioid use group. Curves represent conditional smoothed means generated from local regressions (i.e., locally estimated scatterplot smoothing curves). Shaded areas correspond to 95% confidence intervals. Vertical dashed lines represent intervention period. The number of non-, occasional-, chronic-, and matched chronic opioid users from a random general population sample (controls) were 28,625, 5,662, 1,262, and 27,841, respectively.

No overlap; study period before policy changes	Unadjusted *n* = 270 IRR (95% CI)	Adjusted *n* = 177 IRR (95% CI)
1 year before the intervention 1 year after the intervention	1.0 [Reference] 0.970 (0.903, 1.041)	1.0 [Reference] 0.975 (0.891, 1.069)
Overlap; study period crosses policy changes	Unadjusted n = 731 IRR (95% CI)	Adjusted n = 600 IRR (95% CI)
1 year before the intervention 1 year after the intervention	1.0 [Reference] 0.906 (0.867, 0.947)	1.0 [Reference] 0.895 (0.850, 0.942)
No overlap; study period after policy changes	Unadjusted n = 261 IRR (95% CI)	Adjusted n = 204 IRR (95% CI)
1 year before the intervention 1 year after the intervention	1.0 [Reference] 0.842 (0.764, 0.929)	1.0 [Reference] 0.832 (0.740, 0.934)

n, number of observations included in model; IRR, incidence rate ratio; CI, confidence interval. Modelled with generalized estimating equations models specified with a Poisson variance function, log-link function, exchangeable working correlation matrix, estimation of robust standard errors, and estimation of the dispersion parameter to adjust for over-dispersed data. The model estimates the ratio between the mean mg OMEQ during the year before index date (day −365 to −1) and the year after the intervention (day 90–454), given the covariates of the model.
Model adjusted for sex, age, level of education, BMI, average pain intensity last month (continuous, Visual Analogue Scale, 0–100), number of self-reported comorbidities (0–12), physical activity level (continuous, UCLA, score 0–10), and smoking status. Cases with missing data in any of the covariates included in the adjusted model were excluded from the adjusted analyses.

Table III Osteoarthritis and Cartilage

Incidence rate ratios reflecting relative change in annual mg oral morphine equivalents from before to after supervised exercise therapy and patient education among 1,262 chronic opioid users with knee or hip osteoarthritis, stratified by the temporal placement of study participants' study period relative to January 1, 2017 (media attention on opioid use and changes in opioid prescribing policies)

Limitations

The observational nature of this study limits causal inference. Therefore, we focused on chronic opioid users since changes in opioid use among these patients are less likely to be caused by regression-to-the-mean. Paracetamol, NSAIDs, and codeine combination drugs sold over-the-counter, or any analgesics used during hospital admissions, are not included in our analyses. In Denmark, 22% of both the total NSAID and total paracetamol sales are sold over-the-counter[51,52]. Furthermore, over-the-counter analgesics have sales restrictions (e.g., package size) and are not reimbursed, which likely channel most patients with chronic pain towards the use of prescription-based analgesics. Therefore, the potential influence of not including over-the-counter analgesics is likely small. We lack information about the indication for opioid prescribing, and the analgesics may therefore have been prescribed for other non-cancer pain conditions than osteoarthritis, but since all participants participated in the intervention for their knee or hip osteoarthritis, this was likely their main pain complaint. Also, our findings did not change when we adjusted for number of pain sites (variable not included in main analysis due to limited number of observations caused by technical problems with data collection). As in all studies using prescription registry data, we do not know whether the patients consumed the dispensed analgesics. A large proportion of patients in our study were likely motivated to participate in an exercise therapy and patient education program, which may affect the generalizability of the study findings.

Conclusions

Among patients with knee or hip osteoarthritis and chronic opioid use, we found that opioid use decreased with 10% after a supervised exercise therapy and patient education program delivered in primary care. The observed decrease was most likely attributed to regulatory changes in opioid prescribing. The potential role of exercise therapy and patient education as part of multimodal deprescribing interventions in reducing chronic opioid use requires further investigation.

Author contributions

GLA:D® was designed and initiated by STS and EMR. JBT developed the initial study idea for the study. MSJ and JBT developed the analysis plan with critical input from AP, JS, ME, DTG, STS, and EMR. MSJ conducted the analyses. MSJ and JBT performed the initial data interpretation and drafted the first version of the manuscript. AP, JS, ME, DTG, STS, and EMR critically revised the manuscript. All authors have approved the final version of the manuscript. Data was stored at a secured server managed by the Danish Health Data Authority. MSJ had full access to all the data in the study through an institutional authorization and takes responsibility for the integrity of the data and the accuracy of the data analysis.

MSJ (msjohansson@health.sdu.dk) takes responsibility for the integrity of the work, from inception to the final version of the manuscript.

Conflict of interest

EMR is deputy editor of Osteoarthritis and Cartilage, the developer of the Knee injury and Osteoarthritis Outcome Score (KOOS) and several other freely available patient-reported outcome measures. STS is associate editor of the Journal of Orthopaedic & Sports Physical Therapy. STS is currently funded by a program grant from Region Zealand (Exercise First) and two grants from the European Union's Horizon 2020 research and innovation program (European Research Council, MOBILIZE, grant agreement number: 801790; ESCAPE, grant agreement number: 945377), and has received grants from The Lundbeck Foundation, personal fees from Munksgaard, all of which are outside the submitted work. All remaining authors declare that they have no conflicts of interests.

The data underlying this article cannot be shared publicly due to potentially identifiable or sensitive information (General Data Protection Regulation, European Union). Data may be accessed by contacting GLA:D® (https://gladinternational.org/contact/).

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Supplementary data

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