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Johan Liseth Hansen*, Markus Heilig, Eija Kalso, Audun Stubhaug, Douglas Knutsson, Patrik Sandin, Patricia Dorling, Craig Beck, Emilie Toresson Grip, Karin Hygge Blakeman and Lars Arendt-Nielsen

Problematic opioid use among osteoarthritis patients with chronic post-operative pain after joint replacement: analyses from the BISCUITS study

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Abstract

Objectives: Opioids are commonly used to manage pain, despite an increased risk of adverse events and complications when used against recommendations. This register study uses data of osteoarthritis (OA) patients with joint replacement surgery to identify and characterize problematic opioid use (POU) prescription patterns.

Methods: The study population included adult patients diagnosed with OA in specialty care undergoing joint replacement surgery in Denmark, Finland, Norway, and Sweden during 1 January 2011 to 31 December 2014. Those with cancer or OA within three years before the first eligible OA diagnosis were excluded. Patients were allocated into six POU cohorts based on dose escalation, frequency, and dosing of prescription opioids post-surgery (definitions were based on guidelines, previous literature, and clinical experience), and matched on age and sex to patients with opioid use, but not in any of the six cohorts. Data on demographics, non-OA pain diagnoses, cardiovascular diseases, psychiatric disorders, and clinical characteristics were used to study patient characteristics and predictors of POU.

Results: 13.7% of patients with OA and a hip/knee joint replacement were classified as problematic users and they had more comorbidities and higher pre-surgery doses of opioids than matches. Patients dispensing high doses of opioids pre-surgery dispensed increased doses post-surgery, a pattern not seen among patients prescribed lower doses pre-surgery. Being dispensed 1–4,500 oral morphine equivalents in the year pre-surgery or having a non-OA pain diagnosis was associated with post-surgery POU (OR: 1.44–1.50, and 1.11–1.20, respectively).

Conclusions: Based on the discovered POU predictors, the study suggests that prescribers should carefully assess pain management strategies for patients with a history of comorbidities and pre-operative, long-term opioid use. Healthcare units should adopt risk assessment tools and ensure that these patients are followed up closely. The data also demonstrate potential areas for further exploration in improving patient outcomes and trajectories.

Keywords: analgesics; cohort study; national registers; observational study; opioid; osteoarthritis; predictors; problematic opioid use.

***Corresponding author: Johan Liseth Hansen**, Quantify Research, Hantverkargatan 8, 112 21 Stockholm, Sweden; and Institute of Health and Society, Faculty of Medicine, University of Oslo, Oslo, Norway, Phone: +46 70 722 6864, E-mail: johan.liseth-hansen@quantifyresearch.com
Markus Heilig, Center for Social and Affective Neuroscience (CSAN), Department of Biomedical and Clinical Sciences (BKV), Linköping University, Linköping, Sweden
Eija Kalso, Department of Anaesthesiology, Intensive Care and Pain Medicine, Helsinki University Hospital and University of Helsinki, Helsinki, Finland
Audun Stubhaug, Department of Pain Management and Research, Oslo University Hospital, Oslo, Norway; and Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway
Douglas Knutsson and Patrik Sandin, Quantify Research, Stockholm, Sweden
Patricia Dorling, Pfizer Inc., New York, NY, USA
Craig Beck, Pfizer Ltd, Surrey, UK
Emilie Toresson Grip, Quantify Research, Stockholm, Sweden; and Department of Medicine, Huddinge, Karolinska Institutet, Stockholm, Sweden
Karin Hygge Blakeman, Pfizer AB, Sollentuna, Sweden
Lars Arendt-Nielsen, Center for Neuroplasticity and Pain (CNAP), SMI, Department of Health Science and Technology, School of Medicine, Aalborg University, Aalborg, Denmark; and Department of Medical Gastroenterology (Mech-Sense), Aalborg University Hospital, Aalborg, Denmark

Introduction

Opioids have long been a common treatment for pain with positive effects on patients' quality of life and pain relief [1, 2]. Although considered safe and effective for acute and cancer pain, the use of opioids is associated with an increased risk of nausea, constipation, and drowsiness in the short term [2, 3], while prolonged use may cause increased tolerance and withdrawal issues [4, 5], risk of injury, abuse and addiction [2, 6, 7]. Problematic opioid use (POU) is commonly defined as long-term or high-dose opioid use for non-cancer pain, based on duration and/or dosing (e.g., 90+ days of consecutive use [8–10], 90–120 morphine milligram equivalents (MME) daily [11–13] or 90+ days of consecutive opioid use with between 90 and 120 MME/day [14–16]).

Osteoarthritis (OA) is a heterogeneous musculoskeletal disease characterized by a varying degree of chronic pain as the most pervasive symptom, for which no curative treatment exists. Treatment is individualized but mainly starts with non-pharmacological interventions (i.e., patient education and physical therapy), to later be combined with pharmacological treatments [7, 17–19] such as paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs) and opioids. Pharmacological treatments, particularly NSAIDs and opioids, are not recommended for long-term management of OA pain [6, 7, 20, 21]; thus achieving efficacious and safe analgesia in OA can be challenging. As an end-stage OA treatment, patients may undergo joint replacement surgery which has been reported to be an effective treatment with replacements lasting approximately 20 years [22]. However, up to 20% of patients may have continued, and even amplified, chronic pain after a joint replacement [23], a proportion of which may continue to use opioids [24–27].

Pre-surgery use of opioids and/or comorbidities (e.g., alcohol and substance use disorders, anxiety, migraine, pain-related diagnoses) have been found to be risk factors for continued post-surgery POU [24–26, 28]. Patients with prolonged pre-surgery opioid use have longer post-surgery hospitalization stays, greater need for post-surgery pain management, and lower functional scores when compared with patients without prolonged opioid use pre-surgery [28, 29]. Furthermore, they have an increased risk of revision surgeries, vertebral fractures, and opioid overdose when compared to opioid-naïve patients [27]. While several studies have evaluated immediate outcomes associated with surgery, few have followed patients over multiple years to identify trends in opioid use. Furthermore, definitions of POU vary between studies, affecting the results and conclusions reached.

In this study, we wanted to study the group of patients receiving OA surgery to serve as a model for a group of individuals moving from a high need for pain medication (before surgery) to a less need for pain medication (after surgery). In patients with pain, it is hard to tell (on a population basis) what adequate use of opioids is to manage their pain since treatment is individualized. The idea for this study was that, after surgery, the continued use of opioids would not primarily be driven by OA pain and would more likely be problematic than pre-surgery. We specifically wanted to investigate the individuals that after surgery still had a problematic use and compare them to the non-problematic users. We started with hypothesizing six different cohorts to describe POU in the post-surgical timeframe and aim (1) was to describe these POU cohorts before and after surgery and compare them to matches without POU in the post-surgery timeframe and (2) assess how much the pre-surgical characteristics in the POU cohorts are associated to post-surgical problematic use, using nationwide register data in Denmark, Finland, Norway, and Sweden.

Methods

This observational study used nationwide register data on adult (≥18 years) patients with OA having undergone joint replacement surgery in Denmark, Finland, Norway, and Sweden. The study period was January 1st, 2008, until December 31st, 2017.

The study was a part of BISCUITS, a Nordic observational study on osteoarthritis and low back pain, a study which has been described in detail elsewhere [30]. In the present study, data from the national patient [31–34] and prescription registers [35–38] available in all four countries were used. Information on diagnoses/comorbidities, demographics and surgical procedures were retrieved from the national patient registers, and all information on prescriptions and medication use were retrieved from the national prescription registers. The data cover all specialty care visits and prescriptions for the entire population of the respective country and were linked on an individual-level.

Study population and cohorts

Patients with an OA diagnosis (ICD-10 diagnosis codes: M16, M17) in specialty care and a hip/knee joint replacement (Nordic Medico-Statistical Committee [NOMESCO] codes: NFB, NGB) during the inclusion period January 1st, 2011, to December 31st, 2014, were included in the study population. The index date was the first joint replacement date following the first recorded OA diagnosis in the inclusion period. Patients with a diagnosis of OA or cancer (ICD-10 diagnosis codes: C00-43, C45-97) three years before the index date were excluded because we wanted to study patients who could be assumed to seek specialist care for OA pain for the first recorded time. Censoring occurred after the index date at death, diagnosis of cancer or end of study period.

We wanted to look at the groups that have POU after surgery and look at treatment patterns before surgery to see if the POU shows a correlation with any pre-surgery characteristics. Six approaches were used to identify POU cohorts among the study population, based on dispensed opioid prescriptions (ATC-code: N02A) between one month (to limit the impact of immediate post-surgery pain prescriptions) to one year after the joint replacement. The approaches were derived from treatment guidelines, previous literature and clinical experience. The six approaches were:

- Frequent users
  - ≥3 dispensings in a 3-month period between one month to one year after surgery [8–10, 39–45].
- High-dose users (≥4,500 oral morphine equivalents [OMEQ])
  - Dispensed ≥4,500 OMEQ in a 3-month period between one month to one year after surgery. This is equivalent to at least 50 OMEQ per day [11, 46–48].
- First dose escalation
  - ≥4 opioid dispensings between one month to one year after surgery and a dose increase (OMEQ) of ≥100% in dose two compared to dose 1 [49, 50].
- Second dose escalation
  - ≥4 opioid dispensings between one month to one year after surgery and a dose increase (OMEQ) of ≥100% in dose three compared to dose 2 [49, 50].
- Occasional users
  - ≥3 dispensings in a 6-month period between one month to one year after surgery [51–59].
- High-dose II users (≥8,100 OMEQ)
  - Dispensed ≥8,100 OMEQ in a 3-month period between one month to one year after surgery. This is equivalent to at least 90 OMEQ per day [11–13, 47, 48].

The OMEQ calculation and cut-off were calculated using the same method as in Norwegian clinical guidelines for the use of opioids for long-lasting non-cancer pain [60] and previous literature [48, 61].
A comparison group to patients in the POU cohorts was created, consisting of patients in the study population with post-surgery opioid use that was not defined as problematic use. The comparison group was matched one-to-one with replacement on birth year and sex to control for the most basic characteristics when assessing patient characteristics. Matching was conducted separately for each country. Unmatched patients were excluded from the matched populations. The comparison group was chosen to focus the difference of patterns of opioid use in those using opioids.

However, the two post-surgical groups (non-opioid users and non-POU opioid users) were combined in sensitivity analyses, to assess the whole scope.

Study outcomes and variables

Information to describe patient characteristics at surgery was extracted on index for age and sex, and during the three-year pre-surgery period for opioid use and the presence of comorbidities treated in specialty care (diagnoses of a non-OA chronic pain related diagnosis, cardiovascular disease [CVD], psychiatric disorder, alcohol and substance abuse, OA in multiple joints). These characteristics were chosen based on previous literature [24–26, 28]. We do acknowledge that the level at which the ICD-10 codes for different diseases is not consistent (i.e., higher and stricter reporting of CVD codes than chronic pain related codes) and these patient characteristics should not be used in a comparative, just descriptive fashion. The percentile distribution of OMEQ three years pre- and post-surgery was studied in Finland, Norway, and Sweden, but not in Denmark due to local data privacy rules.

POU, defined as being part of any POU cohort, was used as a binary outcome in logistic regression analyses. Predictors of POU post-surgery were chosen based on the outcomes presented for patient characteristics, and included age and sex at time of surgery, and dispensed OMEQ, opioid prescriptions each year in the three-year pre-surgery period, non-opioid pain medications, alcohol and substance use, psychiatric disorder, chronic pain-related and CVD diagnoses, all measured pre-surgery. An extended model included revision surgery up to three years post-surgery as a proxy for continued pain after the first replacement surgery.

For detailed information, including ICD-10 and ATC codes, on each outcome and covariate, see Tables S1 and S2 in the appendix.

Statistical analysis

The study includes both unmatched (all patients in the study population) and matched populations (POU patients and their matches).

In descriptive analyses, results for both the unmatched and matched populations are presented. Descriptive and matched analyses included patient characteristics and the percentile distribution of OMEQ. Continuous variables are presented with means and standard deviations (SD), while binary variables are presented with frequencies and percentages. In the matched analyses, percentage point differences and 95% confidence intervals (CI) are presented.

A univariate logistic regression model with multiple predictors was used to study the association between the predictors and the binary outcome POU. The data set in this analysis included all patients with at least one opioid prescription post-surgery (an unmatched population). Regression results are reported as odds ratios (OR) and 95% CI.

Data management and statistical analyses were conducted in Rstudio [62]. Country-level data were analysed separately as pooling of individual-level data was not part of data acquisition approvals and ethical approvals, however the results were aggregated when applicable.

Results

Patient numbers

Among 588,540 patients identified with OA during the inclusion period, 170,185 (29%) had a hip/knee joint replacement. Of these patients, 13.7% had POU according to the various definitions (10–20% across the different countries), with proportions varying depending on definitions used (e.g., 1.3% were high-dose II users, requiring ≥8,100 OMEQ) (Figure 1).

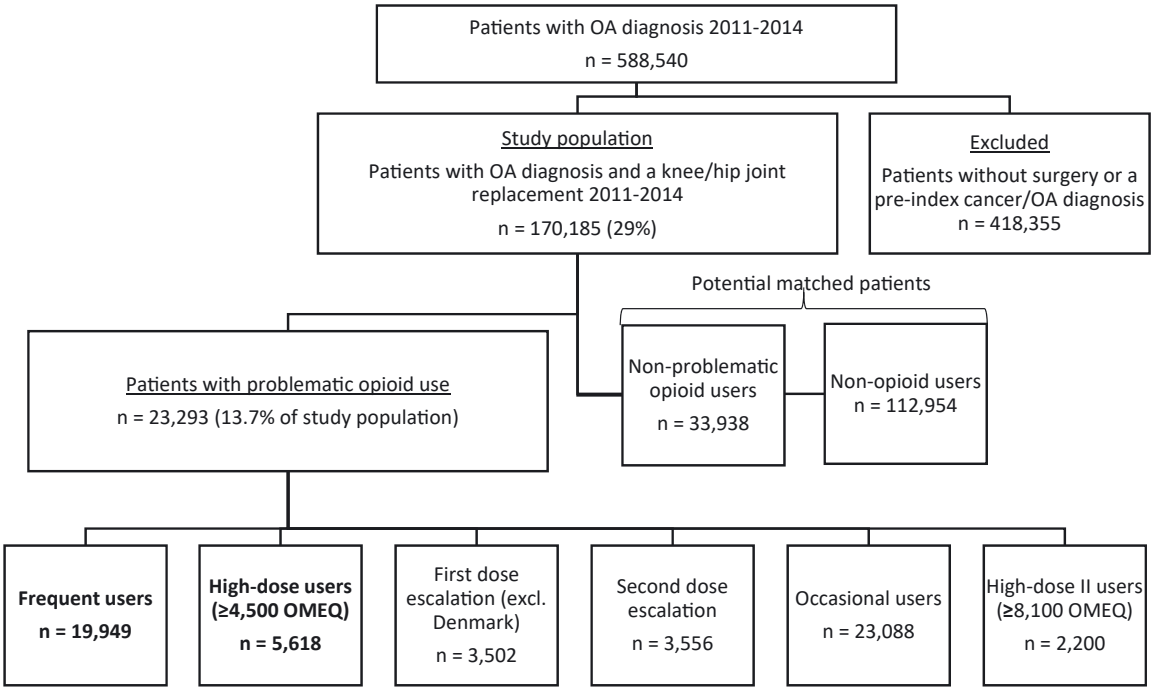

Figure 1: Flow chart of the study population. OA, osteoarthritis; OMEQ, oral morphine equivalents.

Patient characteristics

Frequent users and high-dose users were of similar age at time of surgery (mean age was 67.7 and 66.6 years, respectively) and more likely to be female (34.5 and 34.2% males, respectively) than non-problematic opioid users (mean age was 68.4 years and 40% were males), prior to matching. Pre- and post-matching comorbidities and opioid use three years prior to surgery as well as revision within three years were similar for matched patients and all non-problematic opioid users (Table 1).

After matching the cohorts on age and sex, frequent opioid users presented more comorbidities than matches (differences: 12 percentage points [pp], three pp, 3.6 pp, 1.7 pp and 4.7 pp for chronic pain-related diagnoses, CVD, psychiatric disorder, alcohol and substance use disorder, and OA in multiple joints, respectively).

Similar to frequent users, a larger proportion of high-dose users had CVD, psychiatric disorders, substance use disorders and OA in multiple joints than their matches (differences: 3.9 pp, 6.5 pp, 3.1 pp and 8.5 pp, respectively). High-dose users had more chronic pain-related diagnoses than frequent users (58.3% [95% CI: 56.6–60%] vs. 47.5% [95% CI: 46.5–48.5%]), which was reflected in the difference compared to matches (22 pp).

Both frequent and high-dose users used opioids more prior to surgery compared to the matched cohort. The proportion of patients having used opioids each year for the three years before surgery was 28.1 and 56 pp higher for frequent and high-dose users when compared to their matches, respectively; corresponding differences for using multiple types of opioids pre-surgery were 20.9 and 39.4 pp (Table 1b). Pre-surgery opioid use was more common among high-dose users than frequent users (66.1% [CI: 65.5–67.6%] and 39.1% [CI: 38–40.2%] of high-dose and frequent users had been prescribed opioids each year prior to surgery, respectively).

Patient characteristics for the remaining four POU cohorts are presented in the online appendix (Table S3). Both the unmatched and matched analyses for the POU cohorts are similar to those described above.

When the POU cohorts were compared to the second comparison cohort including both 112,954 non-opioid users and 33,938 non-problematic opioid users, the differences between POU cohorts and matches in patient characteristics (Tables S4 and S5) were generally greater. This derived from the fact that patients not using opioids were less likely to suffer from comorbidities and use opioids three years pre-surgery and have a revision within three years of surgery than non-problematic opioid users.

Distribution of opioids pre- and post-joint surgery

Distributions of OMEQ were calculated on an annual basis from three years before surgery (year –3) to three years after

Table 1: Patient characteristics.

(a) Pre-matching			
	Frequent users, n=19,949	**High-dose users, n=5,618**	**Non-problematic opioid users, n=33,398**
Age, mean, SD	67.7 (10.7)	66.5 (11.2)	68.4 (10)
Males, n, %	6,882 (34.5%)	1,926 (34.3%)	13,567 (40.0%)
Comorbidities 3 years pre-surgery, n, %			
Chronic pain-related	9,489 (47.6%)	3,282 (58.4%)	12,017 (35.4%)
Cardiovascular disease	2,217 (11.1%)	687 (12.2%)	2,983 (8.8%)
Psychiatric disorder	1,470 (7.4%)	560 (10.0%)	1,226 (3.6%)
Alcohol and substance use disorder	628 (3.1%)	274 (4.9%)	447 (1.3%)
OA in multiple joints	5,579 (28.0%)	1,723 (30.7%)	7,930 (23.4%)
Opioid use in 3 years pre-surgery, n, %			
Opioids each year	7,806 (39.1%)	3,713 (66.1%)	3,637 (10.7%)
Opioids any time	16,020 (80.3%)	5,284 (94.1%)	19,606 (57.8%)
Multiple types of opioids	7,604 (38.1%)	3,160 (56.2%)	5,736 (16.9%)
Revision 3 years post-surgery, n, %	1,732 (8.7%)	598 (10.6%)	1,717 (5.1%)

(b) Matched analyses						
	Frequent users, n=19,903			**High-dose users, n=5,602**		
	Cases	**Matches**	**Difference, pp (95% CI)**	**Cases**	**Matches**	**Difference, pp (95% CI)**
Comorbidities 3 years pre-surgery, n, %						
Chronic pain-related	9,460 (47.5%)	7,068 (35.5%)	12 (10.5–13.5)	3,267 (58.3%)	2,028 (36.2%)	22.1 (19.4–24.8)
Cardiovascular disease	2,212 (11.1%)	1,614 (8.1%)	3 (1.1–4.9)	687 (12.3%)	466 (8.3%)	4 (0.4–7.5)
Psychiatric disorder	1,461 (7.3%)	740 (3.7%)	3.6 (1.7–5.5)	554 (9.9%)	191 (3.4%)	6.5 (2.9–10.1)
Alcohol and substance use disorder	624 (3.1%)	293 (1.5%)	1.7 (−0.3–3.6)	270 (4.8%)	94 (1.7%)	3.1 (−0.5–6.8)
OA in multiple joints	5,572 (28.0%)	4,644 (23.3%)	4.7 (3–6.4)	1,720 (30.7%)	1,244 (22.2%)	8.5 (5.3–11.7)
Opioid use in 3 years pre-surgery, n, %						
Opioids each year	7,785 (39.1%)	2,192 (11.0%)	28.1 (26.4–29.8)	3,701 (66.1%)	566 (10.1%)	56 (53.1–58.9)
Opioids any time	15,981 (80.3%)	11,516 (57.9%)	22.4 (21.3–23.5)	5,269 (94.1%)	3,228 (57.6%)	36.4 (34.6–38.3)
Multiple types of opioids	7,582 (38.1%)	3,424 (17.2%)	20.9 (19.2–22.6)	3,151 (56.2%)	944 (16.9%)	39.4 (36.5–42.4)
Revision 3 years post-surgery, n, %	1,730 (8.7%)	994 (5.0%)	3.7 (1.8–5.6)	597 (10.7%)	287 (5.1%)	5.5 (2–9.1)

CI, confidence interval; OA, osteoarthritis; pp, percentage point; SD, standard deviation.

surgery (year +2); year 0 denotes the 365 days directly following surgery. The analysis was conducted for the matched populations. Opioid use (dosing in OMEQ) differed greatly in the years pre- and post-surgery across percentiles of opioid use in specific years (Figure 2). The level of opioid use increased in the years leading up to surgery and continued to increase after surgery in the higher percentiles (80th percentile and above). In the lower percentiles (50th percentile and below), opioid use was low before surgery and peaked in the year following surgery, only to decrease in the subsequent years.

In each year and each percentile, opioid use was higher among the high-dose users than the frequent users; however, the groups followed similar patterns. Among the matches, opioid use peaked in the year of surgery for all percentiles and was close to 0 in all other years. Opioid use, in levels, was generally higher in Norway compared to Finland and Sweden among all groups, percentiles and years

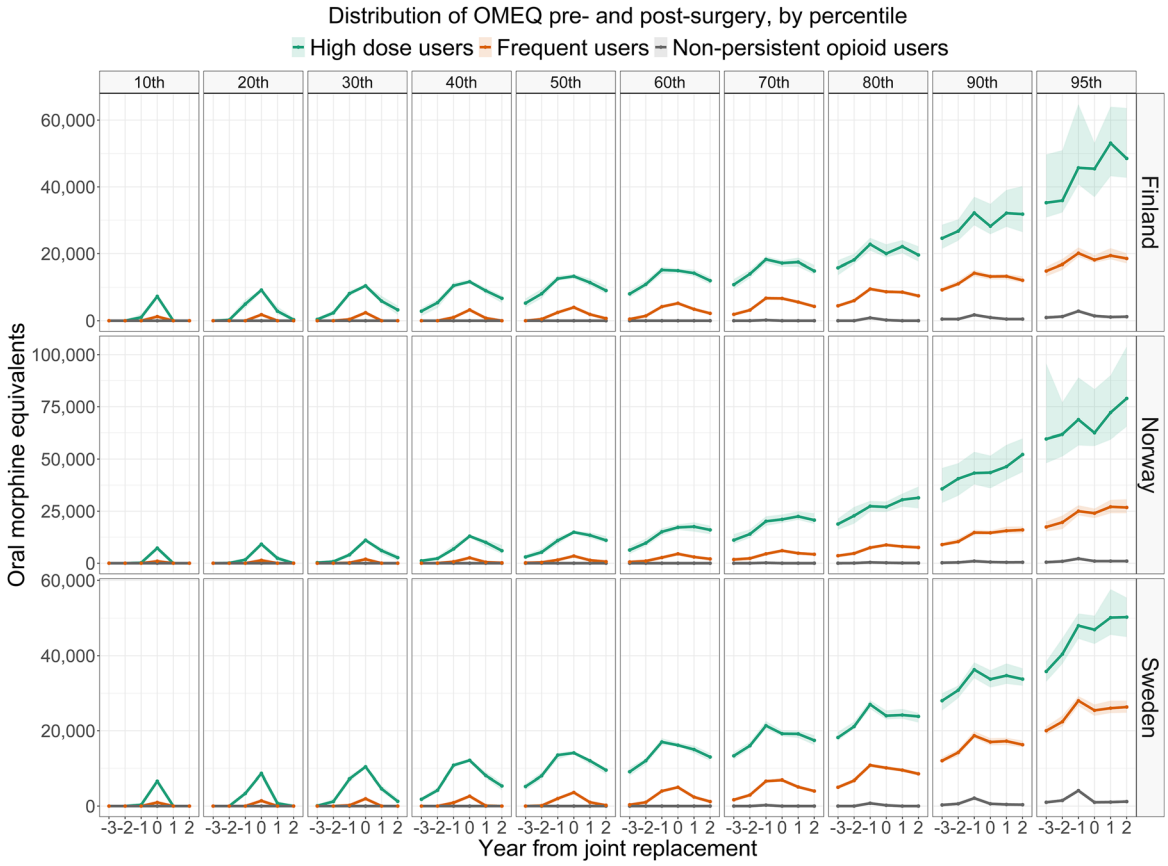

Figure 2: Distribution of OMEQ pre- and post-surgery. Year 0 represents the 365 days following the joint replacement, year −1 the 365 days preceding. Only one matched cohort is shown, for visual clarity, as the two matched cohorts for each case group were nearly identical. The shaded area indicates 95% confidence interval. OMEQ, oral morphine equivalents.

(e.g., in the 95th percentile, Norwegian patients used 59,655-78,972 OMEQ or more annually, corresponding to daily intake of 163-216 OMEQ; the corresponding daily intakes in Finland and Sweden were 96–133 and 98–138, respectively).

Predictors of POU

Predictors of POU were evaluated using a logistic regression analysis with multiple predictors including all patients with an opioid prescription after surgery (Table 2) with being in any of the POU cohorts as the binary outcome. The unmatched populations including all opioid users were used in this analysis.

One year higher age in Sweden, Norway, and Denmark (odds ratio [OR]: 0.99–0.99), but not Finland (OR: 1.00), and being male indicated a lower risk of having POU (all countries; OR: 0.87–0.91). Statistically significant predictors of POU across all countries were having a chronic pain-related diagnosis (OR: 1.10–1.19), having used opioids in the previous year (1–4,500 OMEQ; OR: 1.44–1.56), having a high opioid use in the previous year (>4,500 OMEQ; OR: 4.88–8.01), using opioids each of the three previous years (OR: 2.31–2.81) and a higher number of non-opioid pain medications in the year prior to surgery (OR: 1.09–1.19) (Table 2a). Pre-surgery CVD was statistically significant in Denmark, Finland, and Norway (OR: 1.05–1.14), psychiatric disorder in Finland, Norway, and Sweden (OR: 1.30–1.62) and alcohol and substance use disorder in Finland and Sweden (OR: 1.35–1.60).

The main model was expanded to include whether a patient had a revision surgery within three years after the first joint replacement. This was used as a proxy of continued pain post-surgery and to control for opioid use that was not revision-related. The results were robust to this addition, but the proxy had an independent association with POU (OR: 1.32–1.86) (Table 2b). However, only a small proportion of patients had a revision (8.7 and 10.7% in the frequent users and high-dose users cohorts across the countries, respectively).

The regression models were also conducted by expanding the unmatched population in the analysis to also include non-opioid users (Table S6). In this analysis, the odds

Table 2: Predictors of POU (i.e., belonging to any of the six POU cohorts) in a logistic regression model with multiple predictors.

Predictor	Denmark, n=15,032		Finland, n=12,875		Norway, n=9,712		Sweden, n=19,612	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
(a) Main model								
Age	0.99	(0.99–0.99)	1	(1.00–1.01)	0.99	(0.99–1.00)	0.99	(0.99–0.99)
Male (ref: female)	0.87	(0.81–0.94)	0.88	(0.81–0.95)	0.89	(0.80–0.98)	0.91	(0.86–0.98)
OMEQ previous year: 1–4,500 (ref: 0)	1.44	(1.33–1.56)	1.56	(1.41–1.73)	1.54	(1.38–1.72)	1.44	(1.34–1.55)
OMEQ previous year: >4,500 (ref: 0)	5.25	(4.64–5.95)	5.9	(4.85–7.19)	8.01	(6.60–9.77)	4.88	(4.40–5.42)
Used opioids each year 3 years pre-surgery (ref: no)	2.49	(2.22–2.79)	2.31	(1.89–2.82)	2.81	(2.49–3.17)	2.34	(2.13–2.57)
Non-opioid pain medications year prior to surgery (continuous)	1.14	(1.11–1.18)	1.19	(1.16–1.22)	1.11	(1.07–1.15)	1.09	(1.06–1.13)
Psychiatric disorder pre-surgery (ref: no)	1.2	(0.98–1.47)	1.31	(1.08–1.58)	1.62	(1.33–1.97)	1.37	(1.19–1.58)
Alcohol and substance use disorder pre-surgery (ref: no)	1.29	(0.99–1.69)	1.6	(1.17–2.19)	1.41	(0.91–2.19)	1.35	(1.09–1.68)
Pain diagnosis pre-surgery (ref: no)	1.11	(1.03–1.20)	1.13	(1.04–1.23)	1.16	(1.06–1.28)	1.2	(1.13–1.28)
CVD comorbidity pre-surgery (ref: no)	1.11	(1.03–1.20)	1.14	(1.04–1.25)	1.14	(1.03–1.27)	1.05	(0.98–1.13)
(b) Model including revision surgery within three years								
Age	0.99	(0.99–1.00)	1	(1.00–1.01)	0.99	(0.99–1.00)	0.99	(0.99–0.99)
Male (ref: female)	0.87	(0.80–0.93)	0.88	(0.81–0.95)	0.88	(0.79–0.97)	0.9	(0.84–0.96)
OMEQ previous year: 1–4,500 (ref: 0)	1.45	(1.33–1.57)	1.56	(1.41–1.73)	1.54	(1.38–1.72)	1.44	(1.34–1.55)
OMEQ previous year: >4,500 (ref: 0)	5.36	(4.74–6.08)	5.91	(4.86–7.21)	8	(6.58–9.76)	4.92	(4.44–5.47)
Used opioids each year three years pre-surgery (ref: no)	2.49	(2.22–2.79)	2.3	(1.89–2.81)	2.83	(2.51–3.20)	2.34	(2.14–2.57)
Revision surgery within 3 years (ref: no)	1.96	(1.72–2.24)	1.32	(1.13–1.54)	1.81	(1.52–2.16)	1.86	(1.61–2.14)
Non-opioid pain medications year prior to surgery (continuous)	1.14	(1.10–1.18)	1.19	(1.16–1.22)	1.11	(1.07–1.15)	1.09	(1.06–1.12)
Psychiatric disorder pre-surgery (ref: no)	1.19	(0.97–1.46)	1.3	(1.07–1.57)	1.62	(1.33–1.97)	1.37	(1.19–1.58)
Alcohol and substance use disorder pre-surgery (ref: no)	1.26	(0.97–1.65)	1.58	(1.15–2.16)	1.43	(0.92–2.23)	1.32	(1.07–1.65)
Pain diagnosis pre-surgery (ref: no)	1.1	(1.02–1.19)	1.12	(1.03–1.22)	1.15	(1.05–1.27)	1.19	(1.11–1.27)
CVD comorbidity pre-surgery (ref: no)	1.12	(1.03–1.21)	1.14	(1.05–1.25)	1.14	(1.03–1.27)	1.05	(0.98–1.13)

All predictors in the table were added simultaneously in a logistic regression model with multiple predictors. When the confidence intervals do not include 1, the predictor is statistically significant at the 95% level. CI, confidence interval; CVD, cardiovascular disease; OMEQ, oral morphine equivalents; OR, odds-ratio; POU, problematic opioid us.

ratios of all predictors were of similar sign as in Table 2, however, the magnitude and size of the odds ratios were greater for all opioid-related predictors, non-opioid pain medications and comorbidities (with the exception of pre-surgery psychiatric diagnosis in Finland, for which the OR decreased from 1.31 to 1.22), compared to those seen in Table 2.

Discussion

Almost 15% of OA patients after joint replacement are defined as problematic users of opioids in the Nordics. The results indicate heterogeneity among those defined as post-surgical problematic opioid users, with pre-surgery opioid use being more common among high-dose users than frequent users. However, the differences when comparing to the matched non-problematic opioid use cohort were substantial for both cohorts; the largest difference being the proportion of patients using opioids each of the three years prior to surgery and in the proportion with another chronic pain related diagnosis.

Opioid use over time, comorbidities and predictive factors for problematic use

Post-surgery problematic use is predicted by a range of clinical factors such as having a chronic pain-related diagnosis other than OA, cardiovascular disease, psychiatric disorder and long-term pre-surgery opioid use.

The annual distribution of OMEQ by percentile reveals a large difference in prescription patterns of opioids. In the higher percentiles (80th and above), opioid use increased both pre-surgery and post-surgery, a pattern not reflected in the lower percentiles. This was confirmed in the regression analyses, where the two predictors capturing pre-surgery opioid use were both statistically significant predictors of POU, while simultaneously controlling for confounders related to comorbidities. The results remained largely unchanged when adding revision surgery within three years post-surgery as a proxy for continued pain. Furthermore, the results were robust to studying only patients with OA in one joint to control for severity of the disease, as these patients should be pain-free after joint replacement. Additionally, the study is consistent with previous smaller studies exploring predictors of persistent use (e.g. pre-surgery opioid use and pain-related comorbidities [24, 26]), and in addition found a small effect of age and sex.

The predictors of POU investigated in this study are, however, unlikely to capture the full picture of potential predictors of POU; chronic post-surgical pain is likely affected by e.g., psychological factors not captured by ICD-10 diagnoses (e.g., catastrophizing [63]). Additionally, the estimates are not causal, meaning that these patients need to be studied further to better understand the causal pathways why some patients become problematic opioid users.

The differences between POU patients and the second matched cohort, including both non-opioid users and non-problematic opioid patients, were generally larger than when comparing the POU patients to only non-problematic opioid patients (i.e., patients exposed to opioids). This indicates that non-opioid users can be perceived as healthier pre-surgery (e.g., have less comorbidities and are less likely to have used opioids prior to surgery), confirming the results of a previous study studying opioid use among patients undergoing joint replacement in the US [27].

The demographic profile of patients in this study was in accordance to previous studies, reporting ages of patients with POU to vary between approximately 60 [24, 26] to 70 years [25, 27]. Although the proportion of females differed between studies, the proportion of females was higher in the more problematic opioid groups across all studies [24–26].

Previous research has varied in the definitions of POU and the population studied, applying definitions such as continued opioid use at 6 months post-surgery [24], problematic high-dose use post-surgery [25] and patients who filled ≥1 opioid prescription every month during the 1-year postoperative period [26]. This has resulted in different estimates of the proportion of patients with POU after surgery, varying between 7.6 and 15.3% [24–26], roughly in line with the estimates presented in the current study. While our POU groups were not identical to each other in terms of size or characteristics, the POU groups were more similar to each other, than to their matches. The general similarities between the POU cohorts indicate that groups of patients with distinct opioid prescription patterns were identified.

Limitations

Due to data limitations, we were unable to capture non-prescription pain medication, use of non-pain medications, adherence to dispensed medication and disease progression. For prescribed medications, we were also unable to capture the indication of the prescription, causing uncertainty whether medication was indicated for OA-related pain or comorbidities; however, an attempt to control for this was done by adding comorbidities to the regression analyses. While most patients in the Nordics are treated in the public healthcare system and therefore included in our analyses, a small number of patients may have had their surgery in a private hospital; these surgeries could not be accounted for. The aim of converting opioids into OMEQs is to equalize the analgesic effect of different opioids, and not to equalize the addiction/overdose risk between different opioids, which could skew comparisons of POU between opioids. Furthermore, POU is a complex phenomenon, potentially caused by other factors not investigated in this study, such as prescriber behaviour pre- and post-surgery, patients' tolerance to the substance, family and genetics, and/or policy effects. Future studies should focus on these interaction effects.

Strengths

This study used a large cohort identified in the unique Nordic national register systems, known for a high degree of validity, completeness, and quality, in combination with a long follow-up. This provided a possibility to study prescribed opioid use among all patients with OA and a joint replacement in 2011–2014, with no loss to follow-up other than cancer or death. Furthermore, employing multiple definitions of POU enabled us to give a more complete picture of POU patients than previous studies on the same patient population.

Future directions

This study indicates that patients with long-term pre-surgery use of opioids and comorbidities are at risk of becoming problematic opioid users after surgery. This sends a strong

signal to prescribers to carefully assess patients presenting with complexities such as pre-surgery opioid use, non-OA chronic pain, psychiatric disorder and use of other non-opioid pain medications. Cautiousness is also advised when conducting revision surgery as it may render patients with even more pain [23]. This highlights the need for healthcare units performing joint replacement surgery to introduce risk assessment tools to identify high risk patients. Opioid weaning pre-surgery may be an important strategy [64] and should be studied further. Patients should, additionally, be followed up with targeted programs, e.g., in functioning acute pain services and acute pain service outpatient clinics to tackle potential chronic post-surgical pain and POU, not only in the immediate post-operative period, but also in the long term [65]. As patients may still be in pain after surgery and long-term pharmacological treatment is not warranted, there is need for both pharmacological treatments less likely to cause adverse events and non-pharmacological approaches, e.g., cognitive behavioural therapy [66] aimed to reduce the impact of chronic pain.

Conclusions

POU is present in 13.7% of OA patients after joint replacement surgery. These patients are difficult-to-treat as they have a complex history of pre-surgical medication use, comorbidities, and revision surgery. Cautiousness is warranted when treating these vulnerable patients. Patients need special post-surgery follow-up when prescribing opioids to avoid patients developing problematic opioid use and potentially causing long-term harm.

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