Opioid prescriptions after knee replacement: a retrospective study of pathways and prognostic factors in the Swiss healthcare setting

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ABSTRACT

OBJECTIVES The optimal use of opioids after knee replacement (KR) remains to be determined, given the growing evidence that opioids are no more effective than other analgesics and that their adverse effects can impair quality of life. Therefore, the objective is to examine opioid prescriptions after KR.

DESIGN In this retrospective study, we used descriptive statistics and estimated the association of prognostic factors using generalised negative binomial models.

SETTING The study is based on anonymised claims data of patients with mandatory health insurance at Helsana, a leading Swiss health insurance.

PARTICIPANTS Overall, 9122 patients undergoing KR between 2015 and 2018 were identified.

PRIMARY AND SECONDARY OUTCOME MEASURES Based on reimbursed bills, we calculated the dosage (morphine equivalent dose, MED) and the episode length (acute: <90 days; subacute: ≥90 to <120 days or ≥10 claims; chronic: ≥90 days and ≥10 claims or ≥120 days). The incidence rate ratios (IRRs) for postoperative opioids were calculated.

RESULTS Of all patients, 3445 (37.8%) received opioids in the postoperative year. A large majority had acute episodes (3067, 89.0%), 2211 (65.0%) had peak MED levels above 100 mg/day and most patients received opioids in the first 10 postoperative weeks (2881, 31.6%). Increasing age (66–75 and >75 vs 18–65) was associated with decreased IRR (0.776 (95% CI 0.7 to 0.859); 0.723 (95% CI 0.649 to 0.805)), whereas preoperative non-opioid analgesics and opioids were associated with higher IRR (1.271 (95% CI 1.155 to 1.399); 3.977 (95% CI 4.409 to 3.591)).

CONCLUSION The high opioid demand is unexpected given that current recommendations advise using opioids only when other pain therapies are ineffective. To ensure medication safety, it is important to consider alternative treatment options and ensure that benefits outweigh potential risks.

INTRODUCTION

Knee replacement (KR) is a commonly performed surgical procedure in patients with end-stage osteoarthritis or rheumatoid arthritis of the knee to increase mobility, relieve joint pain and improve quality of life.1–3 However, KR is associated with moderate to severe postoperative pain.4,5 According to a systematic literature review by Beswick et al,6 between 10% and 34% of the patients undergoing KR continue to experience moderate to severe persistent postoperative pain 3 months after surgery. Postoperative pain hinders early mobility and range of motion, poses a risk of thromboembolism, and affects rehabilitation, patient satisfaction and overall outcomes.7,8 Therefore, pain management is a key element in the treatment of KR patients. Historically, opioids have been widely used for this purpose.9,10 However, there is an increasing evidence that for non-cancer pain, opioids are not more effective than non-opioid analgesics11–13 and may impair quality of life due to side effects (eg, nausea, dizziness, constipation and addictive potential).14–16 Moreover, long-term opioid use is associated with increased risk of major trauma, addiction and overdose.17 Thus, it is important to carefully consider the use of opioids in the treatment of KR patients, as they can be effective in managing pain but also have the potential for negative side effects and abuse. Therefore, it is important to weigh the potential risks and benefits of using opioids and to use them when deemed necessary.18–20

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study quantitatively assessed opioid prescriptions after knee replacement based on a representative health insurance claims database covering all parts of Switzerland.

⇒ It contributes to the existing literature by focusing on a comprehensive repository of individual, regional and insurance-related variables.

⇒ Claims data did not provide information about demand-related (patients’ clinical situation, beliefs and experiences) and supply-related (physicians’ incentives and beliefs) factors.
Switzerland had the highest rates of hip and knee arthroplasty in comparison to other Organization for Economic Cooperation and Development (OECD) nations in 2017. There was an increase in KR procedures over the last 10 years, which can be partly explained by the progressive ageing of the population, advances in medical technology and population expectations. Other studies focusing on opioid prescriptions reported that Switzerland was the world’s seventh-largest consumer of opioids per capita. An increase of opioid prescriptions over the past two decades was reported, especially for musculoskeletal pain. However, opioid prescribing practices in the context of KR have not yet been studied. It is known from international studies that opioid use is directly related to orthopaedic surgery, with clear international differences in postoperative opioid prescriptions. Especially in Switzerland, with such proliferating rate of KR in combination with generally high opioid use, more transparency on opioid prescriptions specifically tailored to KR patients is needed. Consequently, the focus of our work was (1) to assess the change in opioid use around KR surgery over time, (2) to examine characteristics of postoperative opioid prescriptions such as drug potencies and timing of prescriptions, and (3) to estimate associations between postulated prognostic factors and receipt of postoperative opioid prescriptions.

**METHODS**

**Study design and population**

We conducted a retrospective analysis using administrative claims data of adult persons who were hospitalised for KR surgery and were enrolled in mandatory health insurance at Helsana Group, a leading health insurance in Switzerland. The Helsana database covers 15% of the entire population (~1.2 million Swiss residents) across all geographical regions. The mandatory benefit basket in Switzerland is administered at the federal level and insurance companies are not allowed to engage in risk selection. Thus, previous studies have shown that this database is assumed to be approximately representative for the general Swiss population as the results indicated merely marginal differences between crude and adjusted results. In Switzerland, basic health insurance is compulsory for all residents.

**Measures**

Opioid claims were obtained from the health insurance database and catalogued using WHO pharmacological Anatomical Therapeutic Chemical (ATC) codes. Opioid formulations with a morphine conversion factor of ≤0.3 were defined as weak opioids: N02AA59 (codeine and combinations), N02A×02 (tramadol) and N02A×06 (tapentadol). Opioids whose morphine conversion factor exceeded this threshold were classified as ‘strong’ (online supplemental appendix table A1). Conversion factors were determined by information provided by the Swiss Agency for Therapeutic Products (Swissmedic).

Opioids prescribed as part of a drug substitution programme have been reimbursed by health plans since 1999. We used reimbursement codes to identify cases (Tarmed Position 00.0155, positions specifically assigned to substitution programmes in pharmacies or substitution centres for buprenorphine, methadone, heroin and morphine). Whenever a substitute code was found, all the patients were exempted. We excluded all patients from the analysis who were identified as having at least one substitution prescription. We calculated a total amount of substance from each opioid reimbursement, referred to as the morphine equivalent dose (MED), by considering the different potencies of opioid prescriptions as follows:

\[
\text{Dose per unit (mg) \times units per package} \times \text{nr. of packages} \times \text{conversion factor for morphine equivalents}
\]

In this study, the duration of opioid episodes (in days) was calculated by using the difference between the claim date of the initial dispensation and the run-out date of the last prescription dispensed plus one. To calculate the run-out date of the last opioid in the case of multiple prescriptions and the episode duration in the case of a single prescription, we used the defined daily dose provided by the WHO ATC based on the assumed average maintenance dose per day for a drug used for its main indication in adults. Opioid episodes were categorised based on episode characteristics in acute (<90 days), subacute (≥90 to <120 days or <10 claims) and chronic (≥90 days and ≥10 claims or ≥120 days of opioid supply).

In this study, patients who received at least one opioid prescription in the first year after KR are referred to as OU (opioid users), otherwise as NOU (non-OU).

Daily MEDs were calculated by dividing the total MED dose by the duration of opioid episodes. For patches, we assumed that opioids are delivered over a period specified by the manufacturer. Fentanyl patches, for example, deliver the administered (and bioavailable) hourly dose over 72 hours. Thus, we calculated this MED as follows:

\[
\frac{\text{med} \times \text{nr. of patches per package} \times \text{nr. of packages}}{1000} \text{ (fentanyl conversion factor)}
\]

Consequently, the total MED in milligrams for a pack of 10 fentanyl patches, each delivering 12 μg per hour, is 864 mg (12 μg/hour × 72 hour × 10 = 86400 μg/1000 = 864 mg). For buprenorphine transdermal patches, delivery of opioids is expected to last for 96 hours.

Further patient characteristics were used as covariates. They included sex, age group (18–65, 66–75 and >75) and language region (German, French, Italian). The number of Pharmaceutical Cost Groups (PCG; 0–1, 2 and >2) was used to determine the patient’s overall comorbidity. PCGs are a recognised proxy for the presence of chronic diseases using data on medications bills that were reimbursed. Because we included information on cancer and pain relief medication separately in our model and to curb collinearity, we neglected cancer and pain disorders in the count of comorbidities without excluding these patients from the study population. Furthermore, the type of insurance coverage was considered: presence...
of high deductible (ie, CHF1500, CHF2000 or CHF2500 as compared with the standard deductible of CHF300 or CHF500), and managed care model. In addition, binary variables were introduced that reflect whether a patient had used conservative therapies in the year preceding KR. Here, we distinguished between types of conservative therapy (physiotherapy, acupuncture), assistive walking devices (knee bandages, walking aids and foot orthotics) and non-opioid drug therapy to treat pain (PCG ‘Pain’). Assistive walking devices were identified by using specific reimbursement codes from the list of medical devices (Mittel- und Gegenständeliste).34 PCG ‘Pain’ is an established proxy for presence of painful condition and is premised on at least three prescriptions of analgesics per year. To assess preoperative opioid use, we observed opioid prescriptions in the 4 weeks before KR.33

Statistical analysis
We identified 9122 KR patients with 2199, 2381, 2327 and 2215 patients spread across 2015, 2016, 2017 and 2018, respectively. Descriptive statistics were used to characterise the study population, divided into postoperative OU and NOU and to analyse postoperative opioid prescriptions during the 1-year observation period. The 50 postoperative weeks were first divided into 10-week intervals to assess crude opioid prescribing patterns. Subsequently, the first 10 postoperative weeks were divided into 1-week intervals to obtain a more granular picture of postoperative prescribing patterns. To test for differences in the total number of patients receiving opioids between time intervals Cochran tests were used in a first step. Differences between two successive time periods were assessed using post-hoc McNemar tests. Variations in opioid prescriptions between patients with and without preoperative opioid prescriptions were determined using the two-sample χ² test in each interval.

In our regression model, we used the number of opioid prescriptions as dependent variable. As independent variables, we included both sociodemographic (gender, age, language region, comorbidity status) and insurance variables (managed care, high deductible) because we were interested in determining the patient populations with increased opioid needs. At the same time, several studies indicate that conservative physical therapy prior to KR results in lower post-KR opioid needs.35–36 Therefore, we included utilisation of services in physical therapy, acupuncture and medication (non-opioids) for pain management 1 year before the KR intervention. Because a large strand of literature demonstrated the correlation between preoperative and postoperative opioids,9 37–46 we also included the presence of preoperative (12 months preceding KR) opioid prescriptions as an explanatory variable.

To estimate associations between postulated predictors, we selected a negative binomial generalised linear model over a Poisson model based on two criteria: the Akaike information criterion and the least root-mean-square error criterion. Negative binomial model had smaller deviations between the predictions and the actual values as it showed the lowest criterion values. The results of our models are illustrated by the incidence rate ratio (IRRs).

Regarding the specification of the model, a slight correlation was found between older age and presence of supplementary hospital insurance. Thus, 19.5% of patients aged 18–65 years had supplementary hospital insurance, whereas in the oldest age group this proportion amounted to 37.2%. However, we decided not to include an interaction term in the regression model and included both variables separately due to higher model accuracy.

Patient and public involvement
None.

RESULTS
We excluded 317 (3.2%) patients who underwent a second KR within 24 months to take into account potential interference of medical services. Furthermore, we excluded 521 (5.2%) patients without full coverage during the observation period or patients living abroad. Consequently, the final study population included 9122 patients. Table 1 outlines the patient characteristics of the study population, stratified by NOU (62.2%) and OU (37.8%) during the 1-year follow-up period. The mean age was 71 (±9.54) years in female and 70 (±9.38) years in male patients. A substantial portion of the study population (30%) did not receive any conservative care before KR.

Over each observation year, almost one out of five patients had at least one opioid prescription in the 4 weeks before KR (19.9% in 2015; 19.5% in 2016; 18.3% in 2017; 19.2% in 2018; p=0.597) and slightly more than one-third had at least one opioid prescription in the postoperative year (35.5% in 2015; 38.1% in 2016; 39.5% in 2017; 37.5% in 2018; p=0.028). Female patients accounted for a slightly larger proportion in OU compared with NOU (64% vs 67%, p=0.004). Patients receiving at least one prescription were slightly older (70 years vs 72 years, p≤0.001). Physiotherapy, pain medication in the year before and opioid use in the 4 weeks before KR were more frequently found in OU compared with NOU.

Focusing on postoperative opioids, more than half of OU received more than one postoperative opioid prescription over the entire observation period, with the median of one postoperative prescription in each year. The most frequently prescribed opioid was tramadol, followed by the combination of the strong opioid oxycodone with naloxone (online supplemental appendix table A2). Of all OU, a large majority had acute episodes (89.0%), followed by chronic (8.8%) and subacute (2.1%) episodes, with these proportions being relatively stable over the observation period.
The proportion of patients with very high levels of morphine dose was consistently high, with nearly two-thirds of patients having peak MED levels above 100 mg/day in all observation years. Although no clear-cut pattern of change could be observed over the years, the highest mean MED value was reported in 2016 (204.1 mg/day in 2015, 206.6 mg/day in 2016, 206.4 mg/day in 2017, 206.0 mg/day in 2018, p=0.81).

The same holds true for the highest proportion of chronic episode duration.

Considering the timing of prescriptions for all patients included in the study, the highest proportion (more than 31%) received an opioid prescription in the first 10 weeks after KR, with this proportion decreasing to less than 9% (p<0.001) in postoperative weeks 11–20 (figure 1, online supplemental appendix table A3). Subsequently, this proportion decreased by 1.2% in weeks 21–30 and plateaued at this level thereafter. A similar pattern was observed when distinguishing between strong and weak opioids: The largest proportion of patients received opioids in the first 10 weeks (strong opioids: 15.9%; weak opioids: 18.0%), thereafter it decreased sharply in weeks 11–20 (strong opioids: 4.6%; weak opioids: 4.4%) and then experienced another slight decrease before levelling off from week 31. Examining the first 10 weeks in more detail, we see a substantial reduction in the proportion of patients with opioid prescriptions in the transition from

**Table 1** Sociodemographic characteristics of the study population, stratified on opioid user status after knee replacement (KR)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total</th>
<th>Non-opioid user</th>
<th>Opioid user</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee replacement, n (%)</td>
<td>9122</td>
<td>5677 (62.2%)</td>
<td>3445 (37.8%)</td>
<td></td>
</tr>
<tr>
<td>Sociodemographic variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td>5944</td>
<td>3636 (64.0%)</td>
<td>2308 (67.0%)</td>
<td>0.004*</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>18–65</td>
<td>2654</td>
<td>1531 (27.0%)</td>
<td>1123 (32.6%)</td>
<td></td>
</tr>
<tr>
<td>66–75</td>
<td>3528</td>
<td>2258 (39.8%)</td>
<td>1270 (36.9%)</td>
<td></td>
</tr>
<tr>
<td>&gt;75</td>
<td>2940</td>
<td>1888 (33.3%)</td>
<td>1052 (30.5%)</td>
<td></td>
</tr>
<tr>
<td>Language region</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>German</td>
<td>7182</td>
<td>4595 (60.9%)</td>
<td>2587 (75.1%)</td>
<td></td>
</tr>
<tr>
<td>French</td>
<td>1262</td>
<td>606 (10.7%)</td>
<td>656 (19.0%)</td>
<td></td>
</tr>
<tr>
<td>Italian</td>
<td>678</td>
<td>476 (6.4%)</td>
<td>202 (5.9%)</td>
<td></td>
</tr>
<tr>
<td>No of comorbidities (neglecting cancer and pain)</td>
<td>&lt;0.001†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>2218</td>
<td>1560 (27.9%)</td>
<td>658 (19.5%)</td>
<td></td>
</tr>
<tr>
<td>2–3</td>
<td>3593</td>
<td>2366 (42.3%)</td>
<td>1227 (36.3%)</td>
<td></td>
</tr>
<tr>
<td>&gt;3</td>
<td>3168</td>
<td>1673 (29.9%)</td>
<td>1495 (44.2%)</td>
<td></td>
</tr>
<tr>
<td>PCG cancer</td>
<td>254</td>
<td>144 (2.5%)</td>
<td>110 (3.2%)</td>
<td>0.066²</td>
</tr>
<tr>
<td>Insurance variables, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High deductible (&gt;CHF500)</td>
<td>790</td>
<td>545 (9.6%)</td>
<td>245 (7.1%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Managed care</td>
<td>4776</td>
<td>2963 (52.2%)</td>
<td>1813 (52.6%)</td>
<td>0.697*</td>
</tr>
<tr>
<td>Conservative therapy, 12 months before KR, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physiotherapy</td>
<td>5071</td>
<td>2960 (52.1%)</td>
<td>2111 (61.3%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Acupuncture</td>
<td>134</td>
<td>75 (1.3%)</td>
<td>59 (1.7%)</td>
<td>0.151*</td>
</tr>
<tr>
<td>Assistive walking devices</td>
<td>763</td>
<td>461 (8.1%)</td>
<td>302 (8.8%)</td>
<td>0.292*</td>
</tr>
<tr>
<td>Drug related</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain medications (non-opioids)</td>
<td>2669</td>
<td>1393 (24.5%)</td>
<td>1276 (37.0%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Opioid use, 4 weeks before KR</td>
<td>1755</td>
<td>676 (11.9%)</td>
<td>1079 (31.3%)</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

P-values below the significance level of 5 % are printed in bold
*Fisher’s exact test.
†χ² test.
PCG, Pharmaceutical Cost Group.

(table 2). The proportion of patients with very high levels of morphine dose was consistently high, with nearly two-thirds of patients having peak MED levels above 100 mg/day in all observation years. Although no clear-cut pattern of change could be observed over the years, the highest mean MED value was reported in 2016 (204.1 mg/day in 2015, 206.6 mg/day in 2016, 206.4 mg/day in 2017, 206.0 mg/day in 2018, p=0.81). The same holds true for the highest proportion of chronic episode duration.
the first to the second postoperative week (all opioids: 18.6%–6.4%; strong: 7.8%–3.0%; weak: 11.5%–3.0%). Another finding of our prescribing pattern analysis is that the likelihood of receiving opioids was higher in patients with preoperative opioids than in patients without preoperative opioid records across all intervals, regardless of opioid strength (figure 2A,B, online supplemental appendix table A4).

Regarding prognostic factors of postoperative opioid use, female sex was associated with a 10.4% higher IRR (1.104 (95% CI 1.155 to 1.399), p=0.030) compared with male sex. Furthermore, higher age was associated with a decrease in opioid rates. Thus, among patients aged between 66 and 75 years and among patients older than 75 years the IRR was 22.4% (0.774 (95% CI 0.7 to 0.859), p<0.001) and 27.7% (0.723 (95% CI 0.649 to 0.805), p<0.001) lower, respectively, compared with the lowest age group (18–64 years) (figure 3, online supplemental appendix table A5). Residence in a French-speaking region, 2–3 and >3 concomitant diseases were associated with increased IRR (1.441 (95% CI 1.283 to 1.62), p<0.001; 1.18 (95% CI 1.052 to 1.324), p<0.001; 1.877 (95% CI 1.658 to 2.124), p<0.001), whereas residence in the Italian-speaking region was associated with decreased IRR (0.587 (95% CI 0.495 to 0.697), p<0.001). Preoperative physiotherapy and non-opioid pain medications were associated with an increase in IRR (1.1261 (95% CI 1.157 to 1.375), p<0.001). Overall, patients with preoperative

### Table 2 Opioid prescription characteristics (n, (%)) among opioid users after knee replacement (n=3445)

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
<th>2018</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioid user</td>
<td>3445 (37.8%)</td>
<td>781 (35.5%)</td>
<td>906 (38.1%)</td>
<td>927 (39.5%)</td>
<td>831 (37.5%)</td>
<td>0.028*</td>
</tr>
<tr>
<td>No of prescriptions, mean (SD)</td>
<td>3.82 (6.39)</td>
<td>3.87 (5.56)</td>
<td>3.86 (5.64)</td>
<td>3.41 (5.23)</td>
<td>4.21 (8.65)</td>
<td>0.091</td>
</tr>
<tr>
<td>Episode duration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>3067 (89.0%)</td>
<td>680 (87.1%)</td>
<td>797 (88.0%)</td>
<td>853 (92.0%)</td>
<td>737 (88.7%)</td>
<td>0.005*</td>
</tr>
<tr>
<td>Subacute</td>
<td>74 (2.1%)</td>
<td>24 (3.1%)</td>
<td>19 (2.1%)</td>
<td>10 (1.1%)</td>
<td>21 (2.5%)</td>
<td>0.032*</td>
</tr>
<tr>
<td>Chronic</td>
<td>304 (8.8%)</td>
<td>77 (9.9%)</td>
<td>90 (9.9%)</td>
<td>64 (6.9%)</td>
<td>73 (8.8%)</td>
<td>0.083*</td>
</tr>
<tr>
<td>Highest MED level, mg/day</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.964*</td>
</tr>
<tr>
<td>&lt;20</td>
<td>32 (0.9%)</td>
<td>9 (1.2%)</td>
<td>8 (0.9%)</td>
<td>8 (0.9%)</td>
<td>7 (0.9%)</td>
<td></td>
</tr>
<tr>
<td>20≤×&lt;50</td>
<td>110 (3.2%)</td>
<td>27 (3.5%)</td>
<td>32 (3.6%)</td>
<td>29 (3.1%)</td>
<td>22 (2.7%)</td>
<td></td>
</tr>
<tr>
<td>50≤×&lt;100</td>
<td>1050 (30.9%)</td>
<td>237 (30.7%)</td>
<td>265 (29.5%)</td>
<td>296 (32.1%)</td>
<td>252 (31.1%)</td>
<td></td>
</tr>
<tr>
<td>100≤×</td>
<td>2211 (65.0%)</td>
<td>500 (64.7%)</td>
<td>593 (66.0%)</td>
<td>590 (63.9%)</td>
<td>528 (65.3%)</td>
<td></td>
</tr>
</tbody>
</table>

*p-values below the significance level of 5 % are printed in bold
χ2 test.
MED, morphine equivalent dose.

![Figure 1](image1.png)

**Figure 1** Opioid prescriptions in the first 50 weeks (10 weeks intervals) of patients receiving preoperative opioids. OU, opioid users.

![Figure 2](image2.png)

**Figure 2** Opioid prescriptions in first 50 weeks (10 weeks intervals) of patients receiving (A) and not receiving (B) preoperative opioids, stratified on opioid strength. OU, opioid users.
DISCUSSION

In this study, we analysed opioid prescriptions in the context of KR in Switzerland and revealed three main findings. First, we found a high overall prevalence of opioid prescriptions, but the number of OU did not change significantly over the observation period. Second, opioids were prescribed in relatively high dosages and were most frequently prescribed in the first week after KR. However, the proportion of patients receiving opioids after 10 weeks remained noticeable. Third, increasing age was associated with decreased postoperative opioids, whereas preoperative non-opioid analgesics and opioid prescriptions were associated with more opioid prescriptions following KR. In addition, regional differences in opioid prescriptions were observed.

We found lower preoperative opioid prevalence compared with existing literature. For example, DeMik et al and Goplen et al showed that 28% and 31%, respectively, of the sample population were classified as preoperative OU as compared with 19% in our study.7 40 Other US studies reported even a higher percentage amounting up to 40%.9 46 49 In contrast, the proportion of postoperative OU in our study amounting to 38% was higher compared with prior study findings. In a recent systematic review and meta-analysis of 19 studies the proportion made up 21% (95% CI 12% to 29%).46 Although our study reports different opioid rates compared with prior studies, specifications (eg, definition of observation period and OU) may have influenced the reported proportions, in combination with possible different provider-specific and geography-specific prescribing practices.9 51–53

Studies that used comparable definitions of preoperative37 54 and postoperative opioid use35 reported only a marginally lower overall preoperative (by 4% and 15%, respectively) and a slightly higher (by 8%) postoperative rate of opioid use. In comparison to a Swiss study, we found a higher degree of acute opioid use and a lower degree of chronic opioid use.25 The lower chronic use may be based on the presumption that an implantation of a new knee joint provides relief from constant pain. Another explanation might be that patients after KR have contact with a healthcare provider, and thus inappropriate medications are more likely to be detected.56–58 Despite the small proportion of patients with chronic episodes, the total number remains noticeable. Chronic opioid use after KR has also been documented in previous studies.37 39 53 Regarding opioid dosage, another Swiss study found lower maximum daily MED of non-cancer opioid applications compared with our calculated dosages.67 However, acute episodes were observed more frequently in our study. This may explain the higher MED values, as chronic high opioid dosages are discouraged and guidelines recommend decreasing opioid dosage over time.17 60 61 The increased dosage emphasizes the need for careful opioid administration, especially for KR patients. The temporal prescription patterns seem to follow the clinical experience of KR patients. Because KR is a fairly painful procedure, pain therapy is often started immediately after the intervention, after which it can be discontinued depending on the pain profile.62 Thus, a study by Brander et al, for example, reports that significant pain relief did not occur until 1–3 months after surgery.63

As far as prognostic factors of opioid were concerned, patients of female sex reported higher rates of opioid use compared with patients of male sex. This can be explained by the fact that, based on findings from some studies, patients of female sex might have a higher pain profile and thus demonstrate poorer therapeutic outcomes after KR.54–67 The higher pain profile after KR is explained in the literature by a delayed decision to for KR,68 69 less frequent referral from the primary care physician to an orthopaedist.70 71 Our regression model showed that age was a significant predictor of low levels of opioid use, which is consistent with prior studies.15 72–75 This might be due to more frequent side effects in older patients. Another explanation may be a result of recommendations to detect and discontinue potentially inappropriate prescriptions specifically targeting this demographic population.76 79 Use of preoperative analgesics was a predictor of postoperative opioids, with preoperative opioid use being the strongest predictor, and is in line with numerous previous findings.9 37–44 Using analgesics might be associated with a higher prevalence of pain, increased pain sensitivity or opioid tolerance.80–81 In line with previous studies,32–44 we found that high comorbidity status was...
associated with an increase in opioid prescriptions. This could be attributed to the reduced existence of effective treatment alternatives for these patients. Previous studies showed that inadequate communication between hospitals and ambulatory care physicians and different physician-related beliefs and perceptions (prescribing attitudes, habits and preferences) can be a challenge to medication safety, especially for patients with many healthcare claims. In line with a previous Swiss study, we found a higher opioid rate in French-speaking cantons, with a lower rate in Italian-speaking cantons. These regional differences may be the result of a spectrum of variables that differ between cantons such as higher density of medical services in urban regions, different patient characteristics and cultural differences. In our study, patients with physiotherapy and acupuncture showed a slightly increased opioid prevalence. This result might be explained by the observation that these patients tend to have a more advanced underlying disease and are thus more dependent on medication for pain control. Surprisingly, a considerable proportion of patients did not receive conservative care before KR, given the recommendation that a surgical intervention seems justified when conservative treatment does not yield any benefits or when the medical condition of the knee makes such intervention unavoidable. However, this observed proportion may be overestimated because we considered only selected services, while other therapies of a conservative nature (i.e., physical activity, diets, weight loss programmes) were not included in our data.

The greatest strength of this study is the wide range of information on opioid prescriptions and possible influencing factors obtained from a representative dataset of the Swiss population. The major limitation is that claims data did not provide information on relevant predictors of opioid prescriptions, such as demand-related factors (patients’ clinical situation, beliefs and experiences) and supply-related factors (physicians’ incentives and beliefs). However, we attempted to counteract the lack of clinical information by adjusting for potential confounders using comorbidity measures based on reimbursed medications. To avoid overly penalising non-adherence to opioid therapy, we calculated episode length as the difference between the time of first and run-out date of the last prescription, thus, slightly overestimating episode length. Consequently, since the MED is a division of total dose by episode length, the MED tends to be underestimated. This bias is counteracted by an overestimation as we do not know whether all prescribed opioids were taken. Studies indicate that there is often a pool of opioids remaining available for potential abuse, dependence and overdose is a central public health problem and a fundamental element of the opioid crisis. Nevertheless, the data represent an accurate picture of opioid provision, as at least some of the prescribed medications were presumably also taken. Furthermore, opioid prescriptions—particularly those occurring long time after KR—might not be attributable to the index KR surgery but might arise from other injuries and procedures. However, we tried to curb this effect by limiting the postoperative period to year. Another source of bias might be the exclusion of patients with a consecutive KR within 12 months. However, these patients did not differ significantly over the observed characteristics and only accounted for 3.2% of the entire study population. Therefore, the exclusion is not believed to have a great impact on the statistical analysis. In some instances, patients have been categorised as OU and NOU for the benefit of readability. As a result, information on the extent of prescriptions may have been lost. Nonetheless, in various calculations, we included the entire number of prescriptions and dosages to provide a more accurate picture of opioid prescriptions.

Because of the well-established side effects, reduction of chronic opioid use is the goal of various medication therapy improvement efforts. If opioids should continuously be used, then side effects (e.g., dependence potential) of should be monitored. According to Goesling et al, adherence to a previously published new opioid-sparing protocol for KR patients reduces the risk of becoming chronically opioid dependent from 8.2% to 0.28%. However, reduction and discontinuation of opioids must be approached cautiously, as some studies suggest that rapid dose reduction is associated with increased number of emergency department visits, opioid overdose and opioid use disorder. To further improve medication safety during postoperative care, it is important to strengthen patient engagement in a structured and coordinated interprofessional pain management programme. In this regard, an electronic patient record can be of great help to facilitate data exchange between healthcare providers. To enable further improvement in drug safety, studies are needed to provide a more comprehensive understanding of the motivations for opioid prescribing practices in Switzerland.

CONCLUSION

In summary, we found a high prevalence of OU after KR in Switzerland between 2015 and 2018, which remained constant over time. In addition, opioids were prescribed in high doses and the proportion of patients with chronic opioid use was considerable. To avoid severe side effects and to ensure optimal pain management, opioid prescriptions should be reviewed for chronic users. To provide the most optimal pain management, multidisciplinary collaboration and a close follow-up care after KR should be strengthened.

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Ethics approval In compliance with privacy laws and regulations, this study used data that were retrospective, pre-existing, de-identified and anonymised. Because this study used retrospective, de-identified and anonymised data, it was exempt from Swiss Federal Law on Human Research (Humanenversuchsgesetz) and was thus exempted from the local ethics committee approval (ethical committee of the Canton Zurich) and from seeking informed consent of patients.

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