Persistent postoperative opioid use in Europe
A systematic review
Taalke Sitter and Patrice Forget

BACKGROUND In the United States, postoperative opioid prescriptions have been implicated in the so-called ‘opioid epidemic’. In Europe, the extent of overprescribing or misuse of opioids is not known.

OBJECTIVES To describe the proportion of persistent postoperative opioid use in adults (>18 years) in European countries.

DESIGN Systematic review of the published data.

DATA SOURCES We searched the electronic literature databases MEDLINE (Ovid), Embase (Ovid), PubMed/MEDLINE and Scopus.

ELIGIBILITY CRITERIA Studies describing opioid use in adult patients (>18 years) at least 3 months after surgery.

RESULTS One thousand three hundred and seven studies were found, and 12 studies were included in this review. The rate of opioid use after 3 to 6 months was extracted from the studies and categorised by the type of surgery. Nine studies investigated opioid use after total hip or total knee arthroplasties (THA and TKA) and reported opioid user rates between 7.9 and 41% after 3 months. In all the included studies, a proportion between 2 and 41% of patients were opioid users 3 months after surgery. The level of evidence varied from high to very low.

CONCLUSION To describe persistent opioid use in relation to specific countries or types of surgery is not possible. Because of the wide ranges observed, we can neither confirm nor rule out a possible public health problem linked to the persistent use of opioids in Europe.

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Introduction
The persistent use of opioids after surgery has been rising over the last few years and may be associated with tolerance, sedation, dizziness, nausea, vomiting, constipation, physical dependence and respiratory depression. Furthermore, prolonged use of opioids is associated with increasing prevalence of opioid misuse, opioid-caused mortality and opioid-addiction. In the United States, postoperative opioid prescriptions have been implicated in the so-called ‘opioid epidemic’.

In 2019, Kent et al. published a systematic review on the incidence of persistent opioid use after surgery in North America. They defined ‘persistent postoperative opioid use’ for opioid-naïve patients as using ‘opioids for 60 days during postoperative days 90 to 365’ and for patients who used opioids before surgery as ‘any increase in opioid use during postoperative days 90 to 365, relative to opioid use in the 90 days before surgery’. They found reported incidence rates between 0.36 and 85%.

In Europe, after surgery, overprescribing or misuse of opioids may differ from the situation in North America, even if the opioid prescription rates, in general, are rising. Although continent-wide comprehensive data are lacking, consistent evidence is available in the UK. In Scotland, prescriptions of strong opioids more than doubled between 2003 and 2012. In England, between 1998 and 2016, an increase of 127% (after correcting for total oral morphine equivalency) has been observed. However, no assessment has been undertaken as regards the persistent postoperative use of opioids in Europe as a whole.

The aim of this systematic review is to summarise the current published data on persistent postoperative opioid
use by adults (>18 years) in European countries. The primary outcome is the rate of persistent postoperative opioid use, defined as using opioids longer than 3 months.” This is a simplified version of the proposed definition of Kent et al. and the ‘American Society of Enhanced Recovery (ASER) and Perioperative Quality Initiative (POQI) joint consensus’, to maximise the data collection.

**Methods**

**Protocol and registration**

The Review was registered under PROSPERO and has the registration number: CRD42019154292.

**Search**

We searched the electronic literature databases MEDLINE (Ovid), Embase (Ovid), PubMed/MEDLINE and Scopus.

The search string used was adapted from the search string of Kent et al. to the specific aims of our study and to the databases that have been used (see Supplemental Table 1, http://links.lww.com/EJA/A362). We used this method to make the results comparable between studies.

Studies that assess postoperative opioid use after any kind of standard surgery were included. Further inclusion criteria were a minimum follow-up of 3 months, a study population of adults (>18 years) and data specific to European hospitals/health settings. The broadest possible definition of ‘Europe’ was used (the explicit countries can be found in the Search-String). No language restriction was applied. As we were interested in investigating standard prescribing behaviours, studies where opioid use was directly influenced by the study design and cases that were not treated according to the standard of care were excluded, for example, intervention studies where the protocol was not followed. Reviews, Letters, Case Reports and qualitative studies were excluded. We considered only the studies published between January 2009 and 30 September 2019, to reflect as much as possible current practices.

The titles and abstracts of potentially eligible studies were screened by one author (TS). Screening the titles and abstracts was combined into one step. After the title and abstracts were screened, two authors (TS and PF) checked all the studies identified as potentially eligible regarding inclusion/exclusion criteria, and discrepancies were resolved by consensus. The full text of the selected studies was read completely.

A data collection form was designed and tested to determine those included and then used for the data extraction.

The country of the study, the study design, the operation type, the study size, the follow-up-time and the proportion of opioid users at 3, 6, 9 and 12 months was extracted.

As some studies reported only postdischarge uses, this time was considered as postoperative and this information was recorded in the extraction form. Further details like age limitations, specific definitions of ‘opioid use’ and information about preoperative users, were recorded too.

All included studies were appraised with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. The risk of bias in individual studies was assessed on a study and on an outcome level. The reasons for decreasing the level of evidence were discussed by TS and PF and can be found in the extraction form in the supplemental data (Supplemental Table 2, http://links.lww.com/EJA/A363 and Supplemental Table 3, http://links.lww.com/EJA/A364).

**Outcomes**

The main outcome is the rate of persistent postoperative opioid use, which has been extracted for all surgical procedures at 3 months after surgery. The percentages of persistent opioid use have been derived from the proportions of users. Whenever possible, the risk of becoming a persistent opioid user has been estimated for opioid-naive users, preoperative opioid users and patients undergoing different surgeries. The 95% confidence intervals (CI) were calculated with a simple asymptotic method without continuity correction (‘Wald Method’).

A qualitative data synthesis was done. The rate of opioid use after 3 to 6 months is categorised into groups, depending on the type of surgery. These categories are described and compared in terms of quality and results. Because of the data heterogeneity, a data aggregation was not possible. Additional analyses included the comparison of operation types, and of opioid-naive and preoperative opioid users. As the data shows significant heterogeneity, a meta-analysis was not possible.

The following potential bias has been considered: limitations in the design (i.e. prospective vs. retrospective, a large loss to follow-up), eligibility criteria (less or more restrictive in terms of population or outcomes), unexplained heterogeneity or inconsistency of results, imprecision of results (few participants) and the risk of publication bias (included the selective outcome reporting bias).

**Results**

**Study selection**

A total of 1307 articles were found. After the removal of duplicates, the title and abstracts of 1018 articles were screened. Nine hundred and three articles were excluded, and 115 articles underwent a full-text screen. In some cases, contact with the authors was necessary to obtain further information. A total of 12 articles were finally included into the systematic review (Fig. 1).
For the included studies, a general overview of the size, the publication year, the country of investigation and the type of surgery can be seen in Table 1. Two studies each are from Denmark, the UK and France. The other studies are from Germany, Belgium, Norway, Spain and the Netherlands, and the study by Dengler et al. reports of patients in Germany, Belgium, Sweden and Italy.

The opioid use was either reported by the patients or was extracted as prescription data from national or hospital databases. An overview of the assessment methods can be found in the Supplementary Table 2, http://links.lww.com/EJA/A363.

The Overall Quality of Evidence was assessed with GRADE and can be found in the Supplementary Table 3, http://links.lww.com/EJA/A364. Three studies have an overall high quality of evidence, two studies are considered as having moderate quality, and seven studies were either rated as having a low or very low quality. According to the assessment of study limitations and risk of bias, 5 of 12 studies have no serious study limitations, 4 studies have serious limitations, and 3 studies have very serious limitations (Supplementary Table 3, http://links.lww.com/EJA/A364).

Results of individual studies

Hip surgery

Five of 12 studies involved either total hip arthroplasty (THA), hip fracture surgery or sacroiliac joint arthrodesis, making hip surgery the most investigated type of surgery in the included studies. The largest study, Simoni et al. analysed hip surgery. This study included 69,456 cases of hip fracture surgery (≥65 years) in Denmark. After 3 to 6 months, 33.8 (95% CI, 33.4 to 34.2)% of these patients were still using opioids. The second biggest study, Blågestad et al., included 39,688 THA patients in Norway. Their results indicated that 3 to 6 months after the surgery 14.7 (95% CI, 14.5 to 15.0)% ‘redeemed 1 or more prescriptions during the period studied’. In a retrospective cohort, Lindestrand et al. analysed the opioid consumption of 413 hip fracture surgery patients in Denmark. Three months after hospital discharge, 36 (95% CI, 31.4 to 40.6)% were taking opioids. Vanaclocha et al. compared 423 adults undergoing different kinds of surgery for sacroiliac joint pain in Spain up to 6 years after their treatment. Twenty-seven patients had an invasive sacroiliac joint fusion (SIJF). Six months after the operation 7.4 (95% CI, −2.5 to 17.3)% of the SIJF patients used opioids. A limitation of these results is the existence of an inclusion bias related to the access to surgery. In a randomised trial, Dengler et al. assessed the long-term outcomes of sacroiliac joint arthrodesis or a conservative management strategy for chronic low back pain attributed to the sacroiliac joint. This study was conducted in Germany, Belgium, Sweden and Italy; 52 patients had a sacroiliac joint arthrodesis. After 3 months, some 41% of these patients were taking opioids. No exact number was provided for the 3 months follow-up and this information was extracted from Figure 4 of the article (Table 1).
Knee surgery
Two studies assessed the long-term opioid consumption after total knee arthroplasty (TKA). Grosu et al.\textsuperscript{18} conducted a prospective cohort study in Belgium. Three months after surgery, 28 (95% CI, 17.9 to 38.1)% of patients (21 of 76) reported a regular intake of opioids. In 2018, Fenten et al.\textsuperscript{14} analysed TKA patients aged 50 to 80 years in the Netherlands. They randomised the patients to be treated with either a femoral nerve catheter (FNB) or with local infiltration (LIA). After 3 months, 7.9 (95% CI, 0 to 16.5)% of the 38 FNB patients and 13.2 (95% CI, 2.7 to 23.7)% of the 40 LIA patients were opioid users.

Knee and hip surgery
Two studies assessed the long-term outcome from THA and TKA simultaneously.\textsuperscript{13,17} In the retrospective cohort study of Curry et al.,\textsuperscript{13} the data from 79 THA and TKA patients in the UK were analysed.\textsuperscript{13} Three months after hospital discharge, 26 patients [33% (95% CI, 22.6 to 43.3)%] received an opioid prescription. Laufenberg-Feldmann et al.\textsuperscript{17} observed the prevalence of pain 6 months after surgery in patients undergoing joint, back or urological surgeries.\textsuperscript{17} The study was conducted in Germany, and 156 THA/TKA patients were included. After 6 months, 8.7 (95% CI, 4.3 to 13.1) of these patients were using opioids.

A total of nine studies that were included for the analysis, dealt with hip or/knee surgery. The included surgery types are THA, TKA, hip fracture surgery and sacroiliac joint arthrodesis. The results show a wide range of incidence rates for persistent opioid consumption: 3 to 6 months after surgery, between 7.4 and 41% of patients are opioid users. Only including studies, which had a moderate or high quality GRADE score showed a range of persistent opioid consumption, 3 to 6 months after surgery, of between 7.4 and 36%.

### Table 1 Results of individual studies

| Study            | Country                  | Surgery                                                                 | Study details: n, follow-up, analgesia | Opioid users (time since surgery: %) | Overall quality of evidence |
|------------------|--------------------------|------------------------------------------------------------------------|----------------------------------------|--------------------------------------|----------------------------|
| Simoni et al.\textsuperscript{10} | Denmark                  | Hip fracture surgery                                                   | All patients: 69456                    | 3 to 6 months: 33.8% 6 to 9 months: 29.7% 9 to 12 months: 28.2% Opioid-naı̈ve: 50839 Preoperative Opioid users: 18617 |
| Dengler et al.\textsuperscript{11} | Germany, Belgium, Sweden, Italy | Sacroilac joint arthrodesis                                             | 52                                      | 3 months: 41% 6 months: 41% 12 months: 39% |
| Chumbley et al.\textsuperscript{12} | UK                       | Thoracotomy                                                            | 3 months: 34 6 months: 32 12 months: 28 | 3 months: 11.76% 6 months: 3.13% 12 months: 3.57% |
| Curry et al.\textsuperscript{13}     | UK                       | TKA/THA                                                                | 94                                      | 3 months: 33% |
| Fenten et al.\textsuperscript{14}    | Netherlands              | TKA                                                                    | 3 months: FNB: 38 LIA: 40 12 months: FNB 37 LIA 36 | 3 months: FNB 7.9% LIA 13.2% |
| Vanaclocha et al.\textsuperscript{15} | Spain                    | Sacroilac joint fusion or denervation                                  | 27                                      | 6 months: 7.4% |
| Blägestad et al.\textsuperscript{16} | Norway                   | THA                                                                    | 39688                                   | 3 to 6 months: 14.7% 6 to 9 months: 14.4% 9 to 12 months: 14.1% |
| Laufenberg-Feldmann et al.\textsuperscript{17} | Germany                  | Joint (THA, TKA) Back (nuleotomy, spondylothesis) cystectomy, prostatectomy, nephrectomy | Joint: 156 Back: 184 Urology: 151       | 6 months: Joint 8.7% Back 13.6% Urology 2% |
| Grosu et al.\textsuperscript{18}     | Belgium                  | TKA                                                                    | 3 months: 76 6 months: 74 12 months: 68 | 3 months: 28% 6 months: 14% 12 months: 8% |
| Lindestrand et al.\textsuperscript{19} | Denmark                  | Hip fracture surgery                                                   | 413                                     | 3 months: 36% 6 months: 30% Opioid-naı̈ve: 6 months: 2.9% |
| Dualé et al.\textsuperscript{20}     | France                   | Thoracotomy                                                            | Opioid-naı̈ve: 35                      | Opioid-naı̈ve: 4 months: 0% |
| Fuzier et al.\textsuperscript{21}    | France                   | Orthopaedic surgery                                                   | 1292                                    | 3 months: 12.15% |

TKA, total knee arthroplasty; THA, total hip arthroplasty; FNB, femoral nerve catheter; LIA, local infiltration.
Other operation types

Two studies observed the long-term outcomes of patients undergoing a thoracotomy. The first study analysed 70 thoracotomy patients in the UK who were not using strong opioids preoperatively. These patients were randomised to receive either intravenous ketamine or saline placebo for 96 h, starting 10 min before surgery. The 34 patients randomised to the ‘saline placebo’ group were relevant for our analysis. Four patients (11.7% CI, 0.9 to 22.6%) were opioid users 3 months after surgery. The second study, a randomised, double-blind, placebo-controlled trial, analysed opioid-naïve patients undergoing thoracotomy. Only the data from placebo group was considered in our analysis, as the intervention group was additionally treated with ketamine, which was not part of the standard of care. After 4 months, a follow-up of 35 placebo group patients was reported. At this time, no patient reported opioid consumption.

In addition to joint-surgery patients, Laufenberg-Feldmann et al. analysed data from 184 back-surgery patients (nucleotomy/spondylodesis) and 151 urological surgery patients (cystectomy, prostatectomy, nephrectomy). After 6 months, 13.6% (95% CI, 8.6 to 18.6%) of back patients and 2.0% (95% CI, 0 to 4.2%) of urological surgery patients used opioids.

Fuzier et al. analysed data from 1292 patients undergoing trauma or orthopaedic surgery. Assuming that patients did not combine different types of opioids, a total of 12.15% (95% CI, 10.7 to 14.3%) of the observed patients were opioid users 3 months after surgery.

Opioid-naïve patients vs. opioid preusers

Simoni et al. recently undertook a direct comparison of opioid use between preoperative opioid users and opioid-naïve patients. In their analysis, 3 to 6 months after hip fracture surgery, 21.8% (95% CI, 21.4 to 22.2%) of 50 839 opioid-naïve patients used opioids. In the smaller sample of 18617 preoperative opioid users, 68 (95% CI, 67.2 to 68.7%) were using opioids 3 to 6 months after surgery. Two studies provided information on the postoperative opioid use of opioid-naïve patients. In hip fracture surgery, 2.9% (95% CI, 1.04 to 4.8%) of opioid-naïve patients used opioids after 6 months. After thoracotomy, of the 35 investigated opioid-naïve patients, none used opioids after 4 months.

Evolution 3 to 12 months after surgery

Comparing the reported user rates at 3 and 12 months after surgery, shows a decrease in every area. In five of seven scenarios (six studies), that gave information about opioid use during the follow-up year, the absolute reduction of opioid users was generally smaller than 10 percentage points. Only two studies reported a greater reduction of opioid use between the 3rd and 12th month after surgery – Grosu et al. 20% and the LIA of Fenten et al. 10.6%.

Synthesis of results

GRADE was used to evaluate the overall Quality of Evidence of the included studies. Five of the 12 studies have a moderate or high quality. Due to different surgery types, different countries and different study approaches, there were multiple possible sources of heterogeneity. Orthopaedic surgery was the most investigated in terms of long-term opioid use in Europe. Hip surgery, for example, shows user rates between 7.4 and 41% at 3 to 6 months follow-up. Excluding the studies with a low or very low quality, the opioid user rate was 14.7 to 36% (Table 2).

TKA alone or in combination with THA show similar results with user rates between 7.9 and 33%. However, when the low and very low quality studies were excluded, the range was narrower: 7.9 to 13.2%.

Table 2 Persistent postoperative opioid users per category

| Operation | Author | Operation                      | Opioid users (time since surgery: %) | Overall range at 3 months |
|-----------|--------|--------------------------------|-------------------------------------|---------------------------|
| Hip       | Simoni et al. | Hip fracture surgery | 3 to 6 months: 33.8% (95% CI, 33.4 to 34.2) | 14.7 to 41% |
|           | Lindestrøm et al. | Hip fracture surgery | 3 months: 36% (95% CI, 31.4 to 40.6) |  |
|           | Blågestad et al. | THA | 3 to 6 months: 14.7% (95% CI, 14.5 to 15.0) |  |
|           | Dengler et al. | SI joint arthrodesis | 3 months: 41% (95% CI, 27.6 to 54.4) |  |
| Kase       | Vanaclocha et al. | SI joint fusion or denervation | 6 months: 7.4% (95% CI, 2.5 to 17.3) |  |
| Hip and knee | Fenten et al. | TKA | 3 months: 7.9 to 28% (95% CI, 0.7 to 16.5) | LIA 13.2% (95% CI, 2.7 to 23.7) |
| Other      | Grosu et al. | TKA | 3 months: 28% (95% CI, 17.9 to 38.1) |  |
|           | Curry et al. | TKA; THA | 3 months: 33% (95% CI, 22.6 to 43.3) | 33% |
|           | Laufenberg-Feldmann et al. | THA; TKA | 6 months: 8.7% (95% CI, 4.3 to 13.1) |  |
|           | Laufenberg-Feldmann et al. | Nucleotomy; spondylodesis | 6 months: 13.6% (95% CI, 8.6 to 18.6) | 11.8 to 12.2% |
|           | Fuzier et al. | Trauma or orthopaedic surgery | 3 months: 12.2% (95% CI, 10.7 to 14.3) |  |
|           | Chumbley et al. | Thoracotomy | 3 months: 11.8% (95% CI, 0.9 to 22.6) |  |
|           | Dualé et al. | Thoracotomy (opioid naïve patients) | 4 months: 0% (95% CI, 0 to 0) |  |
|           | Laufenberg-Feldmann et al. | Cystectomy, prostatectomy, nephrectomy | 6 months: 2.0% (95% CI, –0.2 to 4.2) |  |

TKA, total knee arthroplasty; THA, total hip arthroplasty; FNB, femoral nerve catheter; LIA, local infiltration.
Two studies each are from Denmark, the UK and France, one study each is from the Netherlands, Spain, Norway, Germany and Belgium and one study was conducted simultaneously in Germany, Belgium, Sweden and Italy. It should be noticed that both Danish studies analyse hip fracture surgery, and both had similar opioid user rates after 3 to 6 months: Simoni et al. reported 5.5 to 32% persistent postoperative opioid users in the overall sample of arthroplasty surgeries, whereas we found rates of 7.9 to 33%. But, compared with North America, there are only a small number of studies in Europe investigating persistent postoperative opioid use. Kent et al. were able to include 46 studies in their qualitative analysis. On the basis of one study, preoperative opioid use seems to be a risk factor for persistent opioid use. This corresponds with the risk factors identified by Kent et al.

Other risk factors are less clear. In Canada, age has been associated with a decreased proportion of patients that filled a postoperative opioid prescription. However, the initial prescription did not typically differ in older adults. In our analysis, it was difficult to isolate the effect of the age. However, the largest study, with 69,456 patients, and with a high quality of evidence, showed a high rate of persistent use of opioids after hip fracture surgery; more than 15% in opioid-naïve patients, and more than 60% in preoperative opioid users.

A comparison of these studies related to their country of origin and type of surgery is, however, just not possible under the consideration of the huge variety of factors. In some studies, the authors report opioid use as a secondary outcome or opioid use is assessed as a parameter for pain. Therefore, information, such as preoperative use or opioid type is mostly missing. The over-representation or orthopaedic surgery is not explained. However, answers to all these questions are essential for a better understanding of the pathophysiology of chronic pain and the patients’ risk profile and studies should investigate these aspects urgently.

Interpretation in the context of postoperative persistent pain
Surgery is a model for the study of the transition from acute to chronic pain; it combines a scheduled trauma (the surgical procedure) with the opportunity to dissect mechanisms implicated in the resolution of acute pain and its clinical correlate, and dysfunction in these mechanisms leading to the transition into chronic states. Surgery permits the investigation of the impact of vulnerability factors (e.g. patient-related, such as the medical history, co-morbidities, genetics and also iatrogenic factors). In this context, opioids may have a role: either by under-prescription (leading potentially to poor pain management); or by the use of high doses that may lead to acute or chronic opioid-induced hyperalgesia (playing a potential role in the sensitisation of the central nervous system to pain), and to persistent postoperative opioid use.

Discussion
Summary of evidence
In summary, the incidence of persistent postoperative opioid use ranges from 2 to 44%. Compared with Kent et al., these results have a smaller range but, especially in terms of arthroplasties, they are very similar. Kent et al. reported 5.5 to 32% persistent postoperative opioid users in the overall sample of arthroplasty surgeries, whereas we found rates of 7.9 to 33%. But, compared with North America, there are only a small number of studies in Europe investigating persistent postoperative opioid use. Kent et al. were able to include 46 studies in their qualitative analysis. On the basis of one study, preoperative opioid use seems to be a risk factor for persistent opioid use. This corresponds with the risk factors identified by Kent et al.

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Limitations
The main limitation of this study is the lack of sufficient data. The best approach to capture current postoperative opioid prescriptions, observational studies, was not used as the methodology in 4 of the 12 included studies. Additionally, 7 of the 12 studies did not have as their primary aim the investigation of opioid prescriptions. The different definitions of opioid consumption might also be a limitation as we cannot be sure if prescribed drugs were redeemed and completely used by the patients. This information does not cover the size of the prescribed opioid package as well. Moreover, patients might be using opioids for nonsurgery-related indications. Finally, we did not capture data at a patient-level, thus we were not able to investigate the use of nonopioid analgesics that may have changed during the study period. Other unidentified sources of heterogeneity between the studies may also have changed during the study period.

Perspective
To reach a final conclusion on this question, further research is needed. On the one hand, more good quality data about user rates is required but on the other hand the consequences of long-term opioid use also need to be described better. In particular, for nonarthroplasty-surgeries, research is missing.

There are strategies to tackle the so-called ‘opioid epidemic’ in the USA that could be easily adapted for European countries if a problem with opioid use manifests. Quinlan et al. proposed interventions, such as the ‘identification of patients at risk of developing CPSP’ and of ‘patients developing opioid substance use disorder’; the ‘administration of both paracetamol and NSAIDs where safe’; the use of ‘opioid “light” anaesthesia and avoidance of remifentanil’; the ‘avoidance of more addictive opioids’; ‘limit the duration of opioid prescription’, to ‘promote opioid weaning’; the ‘use of nonpharmacological analgesic strategies’ to ‘avoid repeat opioid prescriptions’; to ‘set realistic expectations regarding analgesia’ for patients. These could be used either to solve or to prevent opioid dependence, misuse of opioids and opioid-related death but should be supported by more evidence. Either way a monitoring of the
opoid prescription pattern in Europe may be beneficial. Finally, if a problem is confirmed, opioid overuse as a problem of the transition from acute to chronic pain could be elegantly addressed by the development of postoperative transitional pain units, acting after the hospital discharge.27

Conclusion
This systematic review of studies regarding persistent postoperative opioid use in Europe noted a range of 2 to 41% of opioid users 3 months after surgery. To give statements about specific countries or surgery types is not possible. We can neither confirm nor refute a possible public health problem linked to the persistent use of opioids in Europe.

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