TITLE

Persistent postoperative opioid use in Europe: A systematic review

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ABSTRACT

Context: In the United States, the postoperative opioid prescriptions have been implicated in the so called “opioid epidemic”. In Europe the extent of overprescribing or misuse of opioids are unsure.

Objectives: To describe the proportion of persistent postoperative opioid use of 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 of adult patients (>18 years) at least 3 months after surgery.

Results: 1307 studies were found, and 12 studies were included in the review. The rate of opioid users after 3 to 6 months was extracted from the studies and categorised into type of the surgery. Nine studies investigated the opioid use after total hip or total knee arthroplasties (THA and TKA) and reported opioid user rates between 7.9% and 41% after three months. In all included studies a proportion between 2.0% and 41.0% of patients were opioid users three months after surgery. The level of evidence varied from high to very low.

Conclusion: To give statements about the persistent opioid use about specific countries or surgery types is not possible. Because of the observed ranges, we can neither confirm nor rule out a possible public health problem linked to the persistent use of opioids in Europe.

Study registration: PROSPERO: CRD42019154292

INTRODUCTION

The persistent use of opioids after surgery has been rising in the last years and can be associated with tolerance, sedation, dizziness, nausea, vomiting, constipation, physical dependence, and respiratory depression.[1] Furthermore, a prolonged use of opioids is associated with increasing numbers of opioid misuse, opioid-caused mortality and a high prevalence of opioid-addiction.[2,3] In the United States (US), the postoperative opioid prescriptions have been implicated in the so called “opioid epidemic”.

Kent et al. (2019) published a systematic review about the incidence rates of persistent opioid use after surgery in North America.[4] 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 use 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”.[4] 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. Even if continentwide comprehensive data are lacking, consistent evidence is available in the UK. In Scotland, the prescriptions of strong opioids more than doubled between 2003 and 2012.[5] In England, between 1998 and 2016, a parallel increase of 127% (after correcting for total oral morphine equivalency) has been observed.[6] However, no global assessment has been done regarding the persistent postoperative use of opioids in Europe.

The aim of this systematic review is to summarize the current published data on the proportion of persistent postoperative opioid use of adults (>18 Years) in European countries in comparison to North America. The primary outcome is the rates of persistent postoperative opioid use, defined as using opioids longer than 3 months.[7] This is a simplified version of the proposed definition of Kent et al (2019) (14) and the “American Society of Enhanced Recovery (ASER) and Perioperative Quality Initiative (POQI) joint consensus”, maximising 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 (2019) to the specific aims of our study and to the databases that have been used (See Appendix).[4] We used this method to make the results comparable between studies.

Studies that assess postoperative opioid use after any kind of standard operation 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. Because 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 30th 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 post-discharge 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.[8] The risk of bias in individual studies was assessed on a study and 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 appendix.

Outcomes

The main outcome is the rate of persistent postoperative opioid users, which has been extracted for every type surgical procedure at 3 months after surgery. The percentages of persistent opioid use have been derived from the proportions of users. When possible, the risk of becoming a persistent opioid user has been estimated for opioid naïve users, preoperative opioid users and patients undergoing different surgeries. The 95% CIs were calculated with a simple asymptotic method without continuity correction ("Wald Method").[9]

A qualitative data synthesis was done. The rate of opioid users 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. Regarding the data heterogeneity, a data aggregation was not possible. Additional analyses included the comparison of operation types and of opioid naïve and preoperative opioid users. Because the used data shows a big heterogeneity, a meta-analysis is 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. 903 articles were excluded, and 115 articles underwent a full-text screen. In some cases, contact to the authors was necessary to have further information. In the end a total of 12 articles were included into the systematic review. (Figure 1).

A general overview of the size, the publication year, the country of investigation and the investigated surgery types of the studies can be found in table 1. Two studies each are from Denmark,[10,19] the UK[12,13] and France.[20,21] The other studies are from Germany,[17] Belgium,[18] Norway,[16] Spain[15] and the Netherlands,[14] and the study of Dengler et al. reports of patients in Germany, Belgium, Sweden and Italy.[11]

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 Appendix.

The Overall Quality of Evidence was assessed with GRADE and can be found in the Appendix. Three studies have an overall high quality of evidence,[10,16,17] two studies are considered as having moderate quality[14,19] and 7 studies were either rated as having a low[18,20,21] or very low quality.[11-13,15] According to the assessment of study limitations and risk of bias, 5 of 12 studies have no serious study limitations,[10,16,17,19,21] 4 studies have serious limitations[11,14,18,20] and 3 studies[12,13,15] have very serious limitations (Appendix).

Results of individual studies (Table 1)

Hip surgery

Five of 12 studies involved either total hip arthroplasty (THA), hip fracture surgeries or sacroiliac joint arthrodesis. Hip surgeries are therefore the most investigated type of surgery in the included studies. Simoni et al (2019), the study with the biggest study size, analysed hip surgeries as well.[10] They included 69,456 hip fracture surgery patients (≥ 65 years) in Denmark. After 3 to 6 months 33.8% (CI 95%: 33.4 - 34.2) of these patients were using opioids. The second biggest study is from Blågestad et al. (2016), who followed 39,688 THA patients in Norway.[16] Their results showed that 3 to 6 months after the surgery 14.7% (CI 95%: 14.5 – 15.0) “redeemed 1 or more prescriptions during the period studied”. Lindestrand et al. (2015) analysed in a retrospective cohort the opioid consumption of 413 hip fracture surgery patients in Denmark.[19] Three months after hospital discharge 36 % (CI 95%: 31.4 - 40.6) were taking opioids. Vanaclocha et al. (2018) compared 423 adults undergoing different kind of sacroiliac joint pain surgery in Spain up to 6 years after their treatment.[15] Twenty-seven patients had an invasive sacroiliac joint fusion (SIJF). Six months after the operation, 7.4% (CI 95%: -2.5 - 17.3) (2 patients) of the SIJF patients used opioids. A limitation of these results is the existence of an inclusion bias related to the access to surgery. Dengler et al (2019) assessed the long-term outcomes of sacroiliac joint arthrodesis or a conservative management for

chronic low back pain attributed to the sacroiliac joint in a randomised trial.[11] This study was conducted in Germany, Belgium, Sweden and Italy and a total of 52 patients had a sacroiliac joint arthrodesis. After 3 months about 41% of these patients took opioids. Because no exact number was available for 3 months follow-up, this information was extracted from figure 4 in the paper.

Knee surgery

Two studies assessed the long-term opioid consumption after total knee arthroplasty (TKA). Grosu et al (2016) conducted a prospective cohort study in Belgium analysing TKA patient.[18] Three months after surgery 21 of 76 patients (28 % (CI 95%: 17.9 - 38.1)) reported a regular intake of opioids. In 2018, Fenten et al. analysed TKA patients aged 50 to 80 in the Netherlands.[14] They randomised the patients to be either treated with a femoral nerve catheter (FNB) or with local infiltration (LIA). After 3 months 7.9 % (CI 95%: 0 - 16.5) of 38 FNB patients and 13.2 % (CI 95%: 2.7 - 23.7) of 40 LIA patients were opioid users.

Knee and hip surgery

Curry et al. (2019) and Laufenberg-Feldmann et al. (2016) assessed the long-term outcome from THA and TKA simultaneously.[13,17] In the retrospective cohort study of Curry et al. (2019) the data of 79 THA and TKA patients in the UK were analysed.[13] Three months after hospital discharge 26 patients (33% (CI 95%: 22.6 - 43.3)) received an opioid prescription. Laufenberg-Feldmann et al (2016) observed the prevalence of pain of patients undergoing joint-, back- or urological-surgery 6 months after the operation.[17] The study was conducted in Germany and 156 THA/TKA patients were included. After 6 months 8.7% (CI 95%: 4.3 - 13.1) of these patients were using opioids.

A total of 9 studies that were included for the analysis, deal with hip or/and knee surgeries. The included surgery types are THA, TKA, hip fracture surgery and sacroiliac joint arthrodesis. The results show a wide variety of incidence rates of persistent opioid consumption. 3 to 6 months after surgery between 7.4% and 41% of patients are opioid users. Just taking the studies into account, which are having a moderate or high quality, give results between 7.4 % and 36 %.

Other operation types

Two studies observed the long-term outcomes of patients undergoing a thoracotomy. Chumbley at al. (2019) analysed 70 thoracotomy patients in the UK, that were not using

strong opioids preoperatively.[12] The patients were randomised to receive either intravenous ketamine or saline placebo for 96 hours, starting 10 minutes prior surgery. 34 patients were randomised in the “saline placebo” group and were relevant for us. Four patients (11.76% (CI 95%: 0.9 - 22.6)) were opioid users 3 months after surgery. The second study analysing thoracotomy patients was just including opioid naïve patients in their randomised, double-blind, placebo-controlled clinical trial.[20] Just the placebo group was considered here, because the intervention group was additionally treated with ketamine, not being part of the standard of care. After 4 months a follow-up of 35 placebo group patients was reported. At this time no participant (0%) reported opioid consumption.

Beside joint-surgery patients, Laufenberg-Feldmann et al. (2016) analysed 184 back-surgery patients (nucleotomy / spondylodesis) and 151 urological-surgery patients (cystectomy, prostatectomy, nephrectomy) as well.[17] After 6 months 13.6% (CI 95%: 8.6 - 18.6) of back patients and 2.0% (CI 95%: 0 - 4.2) of urological-surgery patients used opioids.

In the 2015 published study of Fuzier et al. 1292 patients undergoing trauma or orthopaedic surgery were analysed.[21] Assuming that patients did not combine different types of opioids, a total of 12.15% (CI 95%:10.7 - 14.3) of the observed patients were opioid users 3 months after surgery.

Opioid naïve patients vs. pre-users

The direct comparison of opioid use between preoperative opioid users and opioid naïve patients was just made by Simoni et al. (2019).[10] In their analysis 3 to 6 months after hip fracture surgery 21.8 % (CI 95%: 21.4 - 22.2) of 50,839 opioid naïve patients used opioids. In the smaller sample of 18,617 preoperative opioid users, 68% (CI 95%: 67.2 - 68.7) were using opioids 3 to 6 months after operation. Lindestrand et al. (2015) and Dualé et al. (2012) gave information about the postoperative opioid use of opioid naïve patients.[19,20] In the sample of Lindestrand et al. 2.9 % (CI 95%: 1.04 - 4.8) of opioid naïve hip fracture surgery patients used opioids after 6 months.[19] Dualé et al. (2012) just analysed opioid naïve patients after thoracotomy in general.[20] Of the 35 investigated patients, no one used opioids after 4 months (0%).

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 5 of 7 scenarios (6 studies), that give information about use during the

follow up year, the absolute reduction of opioid users was smaller than 10 percentage points (Simoni et al.[10]: -5.6%; Dengler et al. (8): -2 %; Blågestad et al.[16]: -0.6 %; Fenten et al.[14]: FNB -2.5%; Chumbley et al.[12]: -8.19 %). Just Grosu et al.[18] and Fenten et al.[14] (LIA group) reported a higher reduction of user rated from the third to the twelfth month after surgery (Grosu et al.[18]: -20%; Fenten et al.[14]: LIA -10.6%).

Synthesis of results (Table 2)

GRADE was used to evaluate the overall Quality of Evidence of the included studies. Five of 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 surgeries are the most investigated surgeries in terms of long-term opioid use in Europe. Hip surgeries for example show user rates between 7.4 % and 41 % at 3 to 6 months follow up. Excluding studies with a low or very low quality, we see user rate of 14.7% to 36%.

TKA alone and in combination with THA show similar results with user rates between 7.9 and 33%.[13,14,17,18] Excluding low and very low quality studies however leaves us with rates between 7.9 and 13.2 %.

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 in Germany, Belgium, Sweden and Italy at once. It needs to be noticed that both Danish studies analyse hip fracture surgeries, and both have similar user rates after 3 to 6 months (Simoni et al. 2019[10]: 33.8% (CI 95%: 33.4 - 34.2); Lindestrand et al. 2015[19]: 36% (CI 95%: 31.4 - 40.6)).

DISCUSSION

Summary of evidence

In summary the incidence of persistent postoperative opioid use ranges from 2.0% to 44.0%. Compared with Kent et al. (2019) this results have a smaller range, but especially in terms of arthroplasties, they are very similar.[4] Kent et al. reported 5.5% to 32% persistent postoperative opioid users in the overall sample of arthroplasty surgeries, while we found rates of 7.9% to 33%. But compared with North America, there are just 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. Based on one study, preoperative opioid use seems to be a risk factor for persistent opioid use.[10] This corresponds with the identified risk factors of 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.[22] In our study, it is difficult to isolate the effect of the age. However, the Simoni's study, being the largest (69,456 patients) and the with a high level of evidence, showed 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).[10]

The comparison of these studies in terms of their country of origin and in terms of the surgery type is however just 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.[11,12,14,15,18,20,21] Therefore, information like preoperative use or opioid type is mostly missing. The over-representation or orthopaedic surgery is not explained. However, all these questions are essential to understand better the pathophysiology of chronic pain and the patients' risk profile and should be urgently investigated.

Interpretation in the context of postoperative persistent pain

Surgery is a model to study the transition from acute to chronic pain, as it combines a scheduled trauma (the surgical procedure), the opportunity to dissect mechanisms implicated in the resolution of acute pain and its clinical correlate, their dysfunction leading to the transition into chronic states. It permits to investigate the impact of vulnerability factors (patient-related, i.e. the medical history, co-morbidities, genetics; but, also, the 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 sensitization to pain of the central nervous system), and to persistent postoperative opioid use.[23-25]

Limitations

The biggest imitation of this study is the lack of sufficient data. The best approach to capture current postoperative opioid prescriptions, observational studies, was not used

for the methodology in 4 of the 12 included studies. Additionally, 7 of 12 studies did not have the primary aim to investigate opioid prescriptions.[11,12,14,15,18,20,21] The different definitions of opioid consumption might be a limitation as well, because we can not 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 no operation related indications. Finally, we did not capture data at a patient-level, not permitting to integrate the use of non-opioid analgesics that may have changed during the study period, as other unidentified sources of heterogeneity between the studies.

Perspective

To come to a full conclusion in this question, further research is needed. One the one hand, more good quality data about user rates is required, but on the other hand the consequences of long-term opioid use need to be described better as well. Especially for non-arthroplasty-surgeries research is missing.

There are strategies to tackle the so called “opioid epidemic” in the USA that could be easily adapted in European countries as well, if a problem with opioid use manifests. Quinlan et al (2019) proposed interventions like 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”, “Opioid ‘light’ anaesthesia and avoidance of remifentanil”, the “avoidance of more addictive opioids”, a “limit duration of opioid prescription”, to “promote opioid weaning” and the “use of non-pharmacological analgesic strategies” to patients, to “set realistic expectations regarding analgesia” and to “avoid repeat opioid prescriptions”.[26] These could be either used 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 opioid prescription pattern in Europe may be beneficial. Finally, where a problem is confirmed, the opioid overuse as the problem of transition from acute to chronic pain could be elegantly addressed by the development of postoperative transitional pain units, acting after the hospital discharge.[27]

Conclusions

This systematic review of studies about persistent postoperative opioid use in Europe found that there is a reported range of 2.0% to 41.0% of opioid users three months after surgery. To give statements about specific countries or surgery types is not possible.

Therefore, 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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3. Conflicts of interest: PF has been involved as advisory member for Grunenthal and is an Associate Editor of the European Journal of Anaesthesiology. The other author does not have any conflict of interest to declare related to the present work.

4. Presentation: None declared.

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FIGURE LEGEND

Figure 1 : Study flow diagram

TABLES LEGENDS

Table 1: Results of individual studies

Table 2: Persistent postoperative opioid users per category

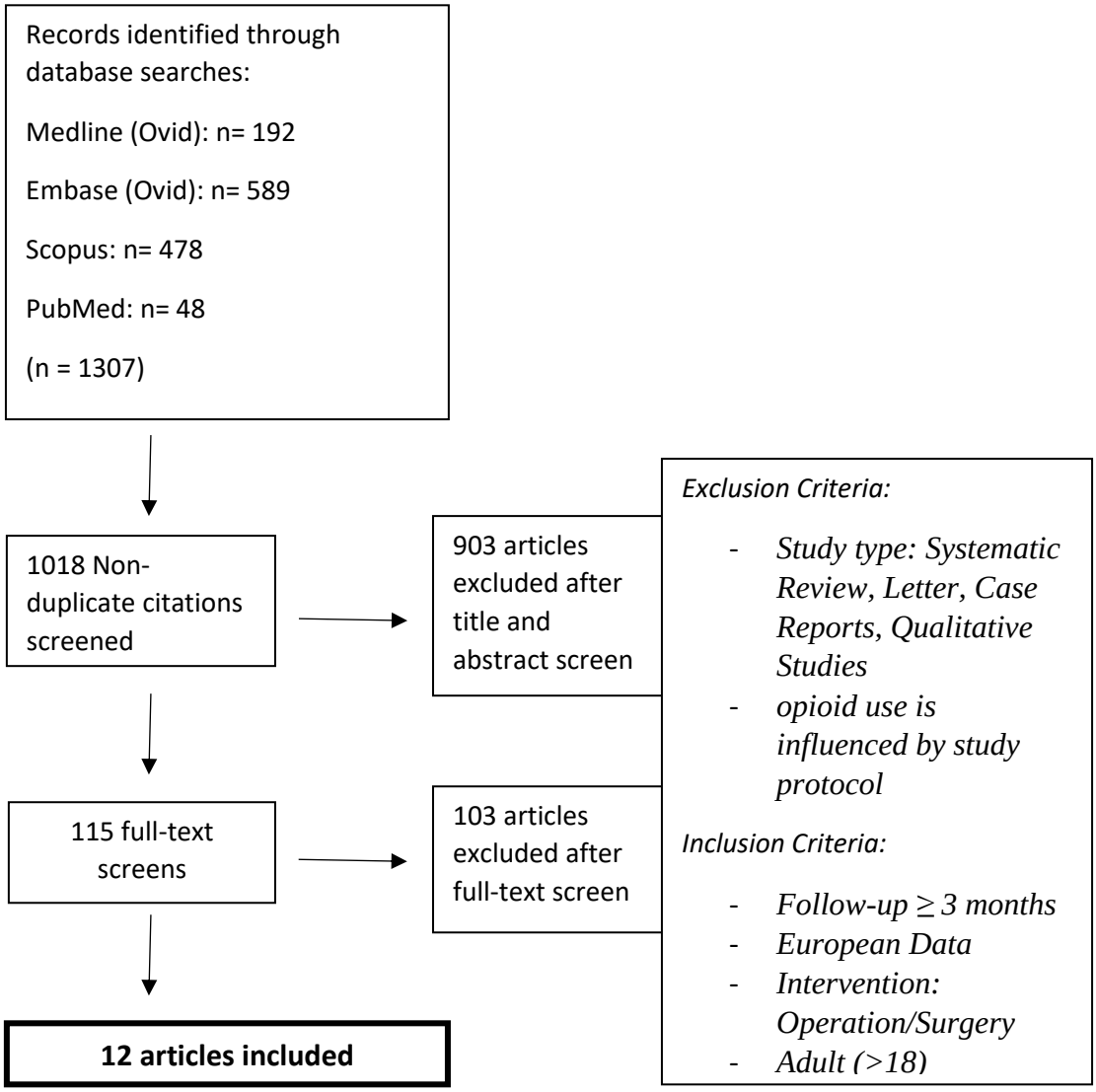
Records identified through database searches:
Medline (Ovid): n= 192
Embase (Ovid): n= 589
Scopus: n= 478
PubMed: n= 48
(n = 1307)
1018 Non-duplicate citations screened
903 articles excluded after title and abstract screen
115 full-text screens
103 articles excluded after full-text screen
12 articles included
Exclusion Criteria:
- Study type: Systematic Review, Letter, Case Reports, Qualitative Studies
- opioid use is influenced by study protocol
Inclusion Criteria:
- Follow-up ≥ 3 months
- European Data
- Intervention: Operation/Surgery
- Adult (>18)

Table 3: Results of individual studies

Study	Country	Surgery	Study Size n	opioid us surgery:
Simoni et al. 2019[10]	Denmark	Hip fracture surgery	All patients: 69,456 *Opioid-naive: 50,839* *Preoperative opioid users: 18,617*	3 - 6 mor 6 - 9 mor 9 - 12 mo *opioid-na* 3 - 6 *mor* 6 - 9 *mor* 9 - 12 *mo* *preopera* 3 - 6 *mor* 6 - 9 *mor* 9 - 12 *mo*
Dengler et al. 2019[11]	Germany Belgium Sweden Italy	Sacroiliac joint arthrodesis	52	3 months 6 months 12 month
Chumbley et al. 2019[12]	UK	Thoracotomy	3 months: 34 6 months: 32 12 months: 28	3 months 6 months 12 month
Curry et al. 2019[13]	UK	TKA / THA	94	3 months
Fenten et al. 2018[14]	Netherlands	TKA	3 months: FNB: 38 LIA: 40 12 months: FNB 37 LIA 36	3 months FNB 7. LIA 13. 12 month FNB 5. LIA: 2.6
Vanaclocha et al. 2018[15]	Spain	Sacroiliac joint fusion or denervation	27	6 months
Blågestad et al. 2016[16]	Norway	THA	39,688	3 - 6 mor 6 - 9 mor 9 - 12 mo
Laufenberg - Feldmann et al. 2016[17]	Germany	Joint (THA, TKA) Back (nucleotomy, spondylodesis) Uro (cystectomy, prostatectomy, nephrectomy)	Joint: 156 Back: 184 Uro: 151	6 months Joint 8.7 Back 13 Uro 2.0
Grosu et al. 2016[18]	Belgium	TKA	3 months: 76 6 months: 74 12 months: 68	3 months 6 months 12 month
Lindestrand et al. 2015[19]	Denmark	Hip fracture surgery	413	3 months 6 months *Opioid Na* *6 months*

Dualé et al. 2012[20]	France	Thoracotomy	*Opioid naïve: 35*	*Opioid na 4 months*
Fuzier et al. 2015[21]	France	Orthopaedic surgery	1292	3 months

TKA: Total Knee Arthroplasty; THA: Total Hip Arthroplasty; FNB: femoral nerve catheter; LIA: local infiltration

Table 4: Persistent postoperative opioid users per category

Operation Category	**Author**	**Operation**	**Opioid users (time %)**
Hip	Simoni et al. 2019[10]	Hip fracture surgery	3 - 6 months: 33.8 % 34.2)
	Lindestrand et al. 2015[19]	Hip fracture surgery	3 months: 36% (CI 9
	Blågestad et al. 2016[16]	THA	3 – 6 months: 14.7 % 15.0)
	Dengler et al. 2019[11]	SI joint arthrodesis	3 months: 41% (CI 9
	Vanaclocha et al. 2018[15]	SI joint fusion or denervation	6 months: 7.4 % (CI
Knee	Fenten et al. 2018[14]	TKA	3 months: FNB 7.9 % (CI 95%: LIA 13.2% (CI 95%:
	Grosu et al. 2016[18]	TKA	3 months: 28 % (CI
Hip and Knee	Curry et al. 2019[13]	TKA; THA	3 months: 33 % (CI 9
	Laufenberg - Feldmann et al. 2016[17]	THA; TKA	6 months: 8.7 % (CI
Other	Laufenberg - Feldmann et al. 2016[17]	Nucleotomy; spondylodesis	6 months: 13.6% (CI
	Fuzier et al. 2015[21]	Trauma or orthopaedic surgery	3 months: 12.2 % (C 14.3)
	Chumbley et al. 2019[12]	Thoracotomy	3 months: 11.8 % (C
	Dualé et al. 2012[20]	Thoracotomy (opioid naïve patients)	4 months: 0 % (CI 95
	Laufenberg - Feldmann et al. 2016[17]	Cystectomy, prostatectomy, nephrectomy	6 months: 2.0 % (CI

TKA: Total Knee Arthroplasty; THA: Total Hip Arthroplasty; FNB: femoral nerve catheter; LIA: local infiltration