**Supplementary materials**

Table S.1. References of articles excluded because of language other than English or French

Table S.2. Medline search strategy

Table S.3. Outcome definitions of opioid use across studies

Table S. 4. Quality appraisal of individual studies

Table S.5. Changes to the published protocol

Supplementary Table S.1. References of articles excluded because of language other than English or French

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| --- |
| Steegers & Wilder-Smith. 2009. Late chronic pain after surgery is prevented with good perioperative analgesics. *Netherlands Tijdschrift voor Geneeskunde.* 153(12). 562-6 (Dutch) |
| Piva, Shaladi, Crestani et al. 2007. Management of pain from osteoporotic vertebral fractures with continuous intrathecal administration of morphine. *Recenti Progressi in Medicina*. 98(4): 225-31 (Italian) |
| Pawlik, Werner & Rudin. 2006. Post-operative pain therapy of a chronic pain patient. *Anasthesiologie, Intensivmedizin, Motfallmedizin, Schmerztherapie.* 41(11). 734-5 (German) |
| Mjobo, Werner, & Rudin. 2011. Prediction of postoperative pain gives new possibilities. Tailored pain relief can prevent development of prolonged severe pain. *Lakartidningen.* 108(22-23): 1244-7. (Swedish) |
| Liu. 2015. Safety of paracetamol for perioperative analgesia of total knee arthroplasty. *Chinese Journal of Tissue Engineering Research.* 19(44): 7103-7. (Standard Chinese) |
| Hensel, Frenzel, Spaker et al. 2013. Postoperative pain management after minimally invasive hysterectomy: Thoracic epidural analgesia versus intravenous patient-controlled analgesia. *Anaesthesist.* 62:10. 797-807. (German) |
| Zandi, Vasquez, Buonanno et al. 2003. PHS repair in femoral hernia surgery. *Minerva Chirurgica.* 58: 6. 797-9. (Italian) |

Supplementary Table S.2. Medline search strategy

|  |
| --- |
| Database |
| Database  | Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to March 28 2018 |
| Interface  | OvidSP |
| Research date | 3 April, 2018  |
| Filters  |  |

|  |
| --- |
| Search strategy  |

1 Thoracic Surgery/ (12090)

2 Surgery Department, Hospital/ (4179)

3 Gynecologic Surgical Procedures/ (8985)

4 Ambulatory Surgical Procedures/ (11168)

5 Surgical Procedures, Operative/ (52730)

6 Cardiovascular Surgical Procedures/ (3154)

7 Digestive System Surgical Procedures/ (16982)

8 Elective Surgical Procedures/ (11522)

9 Endocrine Surgical Procedures/ (442)

10 Minor Surgical Procedures/ (1320)

11 Neurosurgical Procedures/ (25613)

12 Obstetric Surgical Procedures/ (661)

13 Ophthalmologic Surgical Procedures/ (11011)

14 Orthopedic Procedures/ (22530)

15 Otorhinolaryngologic Surgical Procedures/ (4510)

16 Perioperative Care/ (11562)

17 Reconstructive Surgical Procedures/ (43232)

18 Thoracic Surgical Procedures/ (5968)

19 Cardiovascular System/su [Surgery] (220)

20 Bariatric Surgery/ (7236)

21 "Wounds and Injuries"/ (71510)

22 Abdominal Injuries/ (13870)

23 Amputation, Traumatic/ (4494)

24 Arm Injuries/ (5582)

25 Back Injuries/ (1490)

26 BURNS/ (41692)

27 Cold Injury/ (20)

28 Contrecoup Injury/ (10)

29 Crush Injuries/ (51)

30 Electric Injuries/ (2761)

31 Fractures, Bone/ (59971)

32 Hand Injuries/ (9689)

33 Hip Injuries/ (1910)

34 Joint Dislocations/ (22812)

35 Leg Injuries/ (8915)

36 Neck Injuries/ (4592)

37 Occupational Injuries/ (2070)

38 Shoulder Injuries/ (1674)

39 Soft Tissue Injuries/ (4732)

40 "Sprains and Strains"/ (4957)

41 Tendon Injuries/ (12326)

42 Thoracic Injuries/ (12051)

43 Peripheral Nerve Injuries/ (5761)

44 Vascular System Injuries/ (2132)

45 War-Related Injuries/ (197)

46 Wounds, Nonpenetrating/ (20066)

47 Wounds, Penetrating/ (11098)

48 POSTOPERATIVE CARE/ or POSTOPERATIVE PERIOD/ or Pain, Postoperative/ (130296)

49 (injur\* or surger\* or surgical or traum\* or arthroplast\* or accident\* or fracture\* or dislocation\* or postsurger\* or postoperative).tw,sh,kw,kf,oa. (2849771)

50 or/1-49 (3004747)

51 exp Analgesics, Opioid/ (103625)

52 exp CODEINE/ (6370)

53 exp MORPHINE/ (36638)

54 CODEINE/ (4306)

55 FENTANYL/ (12637)

56 HYDROCODONE/ (530)

57 HYDROMORPHONE/ (1162)

58 MEPERIDINE/ (5606)

59 OXYCODONE/ (1885)

60 exp NARCOTICS/ (111509)

61 BUPRENORPHINE/ (4482)

62 BUPRENORPHINE, NALOXONE DRUG COMBINATION/ (191)

63 METHADONE/ (11482)

64 OXYCODONE/ (1885)

65 OXYMORPHONE/ (479)

66 PENTAZOCINE/ (2209)

67 TRAMADOL/ (2724)

68 LEVORPHANOL/ (601)

69 57-27-2.rn. (0)

70 (actiq or adolonta or amadol or analgesic\* or anpec or ardinex or asimadolin\* or astramorph or avinza or biodalgic or bpethidine or buprenorphine or carfentanil or codeine or codinovo or contramal or demerol or dicodid or dihydrocodeinone or dihydrohydroxycodeinone or dihydromorphinone or dihydrone or dilaudid or dinarkon or dolantin or dolargan or dolcontral or dolosal or dolsin or dur?gesic or dur?morph or epimorph or eucodal or exalgo or fentanest or fentanyl or fentora or fortral or hycodan or hycon or hydrocodeinonebitartrate or hydrocodone or hydrocodone\* or hydromorphon or hydromorphone or hydroxyacetanilide or hydroxycodeinon or hysingla or isocodeine or isonipecain or jutadol or kadian or l dromoran or laudacon or levodroman or levodromoran or levo-dromoran or levorphan or levorphanol or lexir or lidol or lorcet or lortab or lydol or meperidine hydrochloride or methadone or morfin or morfine or morphia or morphin or morphine or morphinium or morphium or ms contin or n methylmorphine or narcotic or n-methylmorphine or nobligan or norco or numorphan or operidine or opiate or opioid\* or opso or oramorph sr or oripavine or oxecta or oxiconum or oxycodeinon or oxycodone or oxycone or oxycontin or oxymorphone or palladone or pancodine or pentazocine or percocet or pethidine or phentanyl or prontofort or propoxyphene or robidone or roxicet or roxicodone or skenan or sublimaze or takadol or talwin or thebaine or theocodin or theradol or tiral or topalgic or tradol or tradolpuren or tradonal or tralgiol or trama or tramadin or tramadoc or tramadol or tramadolhameln or tramadolor or tramadorsch or tramadura or tramagetic or tramagit or tramake or tramal or tramex or tramundin or trasedal or ultram or vicodin or zamudol or zohydro or zumalgic or zydol or zytram).tw,sh,kw,kf,oa,nm. (243502)

71 or/51-70 (254622)

72 ((chronic\* or persistent or long-term or "long term" or prolonged or continu\*) adj2 (user\* or "use" or usage or pattern or consumption or therap\* or effect or effects)).tw,sh,kw,kf,oa. (194891)

73 PREVALENCE/ (249170)

74 INCIDENCE/ (227562)

75 Risk Assessment/ (224836)

76 Risk Factors/ (715407)

77 ("long term" or prolonged or chronic\*).tw,sh,kw,kf,oa. (1972160)

78 ("risk factors" and ("long term" or prolonged or chronic\*)).tw,sh,kw,kf,oa. (139304)

79 76 and 77 (106679)

80 or/72-75 (834397)

81 78 or 79 or 80 (932349)

82 50 and 71 and 81 (3436)

83 limit 82 to yr="1998 -Current" (2962)

84 animals/ (6175800)

85 humans/ (16966675)

86 84 not (84 and 85) (4405823)

87 83 not 86 (2808)

Supplementary Table S.3. Outcome definitions of opioid use across studies

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Study | Did the study include only those with peri-operative opioid prescription | Did the outcome definition consider opioid prescription status at 0-3 months in their definition | Criteria of continuity or minimum number of days/number of prescriptions was used | Criteria for minimum dosage was used | Definition |
| Surgical populations |
| Anthony24 | No | Yes | Yes | No  | “postoperative opioid use for one year post-operatively was assessed using the rates of monthly repeat prescriptions” |
| Bedard25 | No | Yes | Yes | No  | “postoperative opioid use for one year post-operatively was assessed using the rates of monthly repeat prescriptions” |
| Bedard26 | No | Yes | Yes | No  | “postoperative opioid use for one year post-operatively was assessed using the rates of monthly repeat prescriptions” |
| Bedard27 | No | Yes | Yes | No  | “postoperative opioid use for one year post-operatively was assessed using the rates of monthly repeat prescriptions” |
| Brummett28 | Yes | No | No | No | … included only patients who filled an opioid prescription either in the month prior to surgery or within 2 weeks after discharge… The outcome of new persistent opioid use was defined as at least 1 opioid prescription fulfillment between 90 and 180 days after the procedure.” |
| Clarke29 | No | Yes | No | No | “.. Prolonged opioid use after hospital discharge was defined as one or more prescriptions for opioids within 1 to 90 days after surgery along with one or more prescriptions for opioids within 91 to 180 days after surgery”.  |
| Soneji47  | No | Yes | Yes | No | “time to opioid cessation for any individual receiving an opioid prescription within 90 days after surgery, with the date of cessation defined by the absence of any opioid prescription within the preceding 90 days.” |
| Connolly30  | No | No | Yes | No | “Long-term opioid use after lumbar fusion, was defined as ≥ 365 days of opioid prescriptions dispensed in the 2 years following surgery, which was measured using pharmacy claims data”. |
| Deyo18  | No | Yes | Yes | No | “Long-term postoperative use was at least 4 opioids fills in the 7 months after index hospitalization, with at least 3 of those more than 30 days after hospitalization” |
| Hadlandsmyth32 | No | Yes | Yes | No | “Prolonged opioid use at 1 year after TKA was defined as Veterans who had continuously received opioids during the 12 months after TKA …, based on the cabinet supply approach”. |
| Hansen33 | No | No | Yes | No | “… We excluded the first 90-day period post-TKA… Chronic opioid use was defined as having at least 90 days of continuous use or at least 120 days of noncontinuous use within the 274 days of potential utilization.” |
| Inacio35 | No | Yes | Yes | No | “Chronic opioid use was defined as having any number of opioid prescriptions or dosing for at least 90 days continuously, or opioid prescriptions for 120 non-consecutive days.” |
| Johnson36 | No | Yes | No | No | “Prolonged opioid use was defined as the proportion of patients who filled a prescription 90 to 180 days after the surgical event among those who initially obtained a perioperative prescription (between 30 days before surgery and 2 weeks after surgery)”. |
| Kim38 | No  | No  | Yes | No | “The index data was defined as the fourteenth day following the hospital discharge date from the index admission… Persistent use was defined as having any use of opioid prescriptions in each of the 12 months continuously based on a group-based trajectory modeling”.  |
| Kim37 | No | Yes | Yes | Yes (> 20mg/d) | “…chronic preoperative opioid users if they were found to have consumed ≥20 mg/d morphine-equivalents for a minimum of 30 consecutive days within 3 months of surgery...these patients were divided into 2 smaller groups: (1) patients who were identified as persistent chronic opioid users at 6 months… and (2) patients who were no longer using opioids at 6 months. … [Results examined] continued chronic opioid habits 6 months following surgery”. |
| Lawrence39 | No | Yes | Yes | No | “using narcotic pain medications chronically… if they took any narcotic pain medication on a daily basis…” |
| Mohanty40 | No | No | No | No | “opioid use at one year after surgery” (self-report) |
| Mosher41  | No | Yes | Yes | No | “Long-term opioid use was defined as an episode of continuous opioid supply for > 90 days and beginning within 30 days of the initial prescription.” |
| Moyer42 | No | Yes | Yes | No | Discontinuation of narcotics.  |
| Mueller43  | No | Yes | No | No | “prescription opioid use during the first 90 postoperative days (PODs) and between POD91 and 365” |
| Politzer44  | No | Yes | Yes | No | “Chronic opioid users were defined as those patients who were prescribed any opioids for over 6 contiguous months postoperatively… Temporary opioid users were defined as patients who were prescribed opioids up to 6 months postoperatively and not after”.  |
| Qureshi45  | No  | No  | No  | No  | “.. having continued narcotic prescriptions > 3 months after lumbar discectomy.” |
| Rios46  | No | Yes | Yes | No | Continued narcotic use after surgery |
| Rozet10  | No | Yes | Yes | No | “opioids were prescribed uninterruptedly longer than 3 months after the surgery” |
| Schoenfeld11  | No | Yes | Yes | No | “consistently filled prescription for ≥ 1 medication within the classes listed [opioid combinations, opioid partial agonists or opioid agonists in categories II or III], beginning within 30 days of hospital discharge and continuing with no more than 30 days elapsing between prescription refills” |
| Sun48 | No | No | Yes | No | “having filled 10 or more prescriptions or more than 120 days’ supply within the first year after surgery, excluding the first 90 postoperative days (ie we measured only postoperative days 91-365)” |
| Westermann50  | No | Yes | Yes | No | “The cumulative incidence of patients receiving opioid prescriptions was analyzed each month after surgery” |
| Yang51  | No | No | No | No | “… being opioid users at follow up”  |
| Zarling52  | No | Yes | Yes |  | “The number of prescriptions filled per 6-week period was recorded for each of the following time intervals: 0-3 months before surgery, 0-6 weeks after surgery, 7-12 weeks after surgery, 3-6 months after surgery and 6-12 months after surgery”. |
| Trauma populations |
| Al Dabbagh (2014)23  | Yes | Yes | Yes | No | “The opioid therapy was considered to be ceased when no new prescription was found during 3 consecutive months of follow-up (after 3 months a new opioid prescription has to be issued)”. |
| Al Dabbagh (2016)3 | Yes | Yes | Yes | No | “During the follow-up the opioid treatment was regarded as ceased when no new prescription had been dispensed for four consecutive months”. |
| Daoust31  | No | No | No | No | “Long-term opioid use was defined filling at least 1 opioid prescription from 305 to 425 days (1 year ± 2 months) after the hospital discharge associated with the target injury… ” |
| Holman34  | No | Yes | Yes  | No | “Postoperatively, we categorized the patients as those who received opiates for less than six weeks, those who received opiates between six and twelve weeks, and those who obtained opiate prescriptions for more than twelve weeks after surgery.” |
| Weiss49  | Yes | Yes | Yes | No | “Cessation of opioid therapy was defined as having no new prescription for at least three consecutive months”. |
| Zwisler53  | No | No | No | No | “Redeemed prescription twice or more six months after the trauma” |

Supplementary Table S.4. Quality appraisal of individual studies

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Research question or objective clearly stated? | Study population clearly specified and defined? | Participation rate of eligible persons at least 50%? | Inclusion and exclusion criteria prespecified and applied uniformly to all participants? | Sample size justification, power description, or variance and effect estimates provided? | Were the exposure(s) of interest measured prior to outcome(s) being measured? | Timeframe sufficient to see an association between exposure and outcome if it existed? | Did the study examine different levels of the exposure as related to the outcome? | Were the exposure measures clearly defined, valid, reliable, and implemented consistently across study participants? | Was the exposure(s) assessed more than once over time? | Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants? | Were the outcome assessors blinded to the exposure status of participants? | Was loss to follow-up after baseline 20% or less? | Were key potential confounding variables adjusted for? |
| Zarling (2016) | + | ? | + | + | - | + | + | - | - | + | - | ? | ? | - |
| Yang (2015) | + | - | - | + | - | + | + | - | + | - | + | ? | - | - |
| Westermann (2017) | + | + | + | - | - | + | + | - | + | - | + | ? | ? | + |
| Mueller (2017) | + | + | ? | + | + | + | + | - | + | - | - | ? | ? | + |
| Sun (2016) | + | + | ? | - | - | + | + | - | + | - | + | ? | ? | + |
| Soneji (2016) | + | + | ? | - | - | + | + | - | + | - | + | ? | ? | - |
| Schoenfeld (2017) | + | + | ? | - | - | + | + | - | + | - | + | ? | ? | + |
| Rozet (2014) | + | + | ? | + | + | + | - | - | + | - | - | ? | ? | + |
| Rios (1998) | - | + | ? | - | - | + | + | - | - | - | + | ? | ? | - |
| Qureshi (2018) | + | + | ? | + | - | + | + | - | + | - | + | ? | ? | + |
| Politzer (829) | + | + | ? | - | - | + | + | - | + | - | + | ? | ? | + |
| Moyer (2011) | + | + | ? | + | - | + | + | ? | + | - | + | ? | ? | ? |
| Lawrence (2008) | + | + | ? | + | - | + | + | - | ? | - | - | ? | ? | - |
| Kim (2017) | + | + | ? | - | - | + | + | - | + | - | + | ? | ? | + |
| Kim (2018) | + | + | ? | + | - | + | + | - | + | - | + | ? | ? | + |
| Johnson (2016) | + | + | ? | + | ? | + | + | - | + | - | + | ? | ? | + |
| Inacio (2016) | + | + | ? | - | - | + | + | - | + | - | + | ? | ? | + |
| Holman (2013) | + | + | ? | + | - | + | + | - | + | ? | + | ? | ? | - |
| Hansen (2017) | + | + | ? | - | - | + | + | - | + | - | + | ? | ? | + |
| Hadlandsmyth (2018) | + | + | ? | + | - | + | + | - | + | ? | + | ? | ? | + |
| Deyo (2018) | + | + | ? | + | - | + | + | + | + | ? | + | ? | ? | + |
| Daoust (2017) | + | + | ? | - | - | + | + | - | + | - | - | ? | ? | + |
| Connolly (2017) | + | + | ? | + | - | + | + | - | + | - | + | ? | ? | + |
| Clarke (2014) | + | + | ? | + | - | + | + | - | + | - | + | ? | ? | + |
| Brummett (2017) | + | + | ? | + | - | + | + | - | + | - | + | ? | ? | + |
| Bedard (2017)31  | + | + | ? | - | - | + | + | - | + | - | + | ? | ? | + |
| Bedard (2017)32  | + | + | ? | + | - | + | + | - | + | - | + | ? | ? | + |
| Bedard (2018) | + | + | ? | - | - | + | + | - | + | - | + | ? | ? | + |
| Anthony (2017) | + | - | ? | + | - | + | + | - | + | - | + | ? | ? | - |
| Al Dabbagh (2016) | + | + | ? | + | - | + | + | - | + | - | + | ? | ? | - |
| Al Dabbagh (2014) | + | + | ? | + | - | + | + | - | + | - | + | ? | ? | - |
| Mohanty (2017) | + | - | ? | ? | - | + | + | - | + | - | - | ? | ? | - |
| Weiss (2012) | + | + | ? | + | - | + | + | - | + | - | + | ? | ? | - |
| Zwisler (2015) | + | + | ? | + | - | + | + | - | + | - | + | ? | ? | - |
| Mosher (2018) | + | + | ? | + | - | + | + | + | + | - | + | ? | ? | - |

Supplementary Table S.5. Changes to the published protocol

|  |  |  |
| --- | --- | --- |
| **Protocol Section** | **Change** | **Rational** |
| 3.1 Operationalization of key constructs | Opioid therapy: * Transient opioid prescription was removed
 | Too few studies provided information in transient opioid (between 1.5 and 3 months) so we did not examine this category. The definition of prolonged opioid prescription remains relatively the same.  |
| * Chronic opioid therapy renamed long-term opioid prescribing
 | Given that the vast majority of studies examined opioid prescriptions using medico-administrative databases, we modified the terminology accordingly.  |
| * Pre-event opioid prescription renamed to no/short-term opioid prescription vs. ongoing opioid prescription
 |
| * Acute postoperative opioid consumption status – accepted inferred definition
 |
| * Daily dosing – not examined
 | We accepted some studies using medico-administrative databases that had inferred opioid status in the acute period because their studied population underwent major surgery or severe trauma. We have added this information in Table 1 for increased transparency. |
| * - Included Clarke’s study that had 26% of patients operated for cancer
 | There were very few studies that examined daily dosing of opioids and as such this information was not considered in the manuscript.  |
| 3.2.1 Participants | Unknown opioid status acutely post-event | This decision was made since authors explicitly stated in their article that surgeries were selected due to their low frequency of associated pre-operative pain. |
| * Primary outcome was not reported at the state time points
 | A limited number of articles had unknown opioid status in the acute phase period. However most of them studied patients already on opioids before surgery. The other articles made an explicit statement of inference that opioid prescription at the follow-up time was attributed to the surgery or trauma. |
| 3.2.4 Outcomes  | * Risk and protective factors
 | There was a lack of data on frequency of opioid prescription at 45 days, 90 days, 6 and 12 months. As such results were reported for 2 time periods (3-6 months; > 6 months). Individual results are shown in Figure 2 with the associated follow-up time at which the data was collected.  |
|  | No data was collected on health care providers and health care system risk factors. |
| 3.2.6 Limits | * Included only English or French articles
 | This changed was made due to limited resources and the large number of articles identified in the literature search. |