**Supplemental Content 1. Systematic Review Protocol, Methods and Search Strategy**

The Preferred Reporting Items for Systematic reviews and Meta-analyses Protocols (PRISMA-P) 2015 checklist has been used in the development of this systematic review.

**Eligibility Criteria**

*Types of study to be included*

Studies included were cohort studies reporting estimates of incidence of persistent (or chronic) opioid use as outcomes. We required a full journal publication, or a conference abstract for analysis. No language or year restrictions were applied.

*Participants*

Adults aged 18 years or older who have never taken opioids (opioid naïve) prior to surgery.

*Exclusion Criteria:* (1) Studies of only palliative care populations as these individuals often use opioids for the purpose of end-of-life care rather than post-operative pain.13 (2) Studies only evaluating patients who consume opioids chronically as this study aims to assess the incidence of new, persistent opioid use among the opioid naïve population. (3) Randomized Controlled Trials as these were likely to be highly selected (selection bias) and were unlikely to represent studies that evaluated the true incidence of new, persistent opioid use. (4) Furthermore, editorials, commentaries, narrative reviews, systematic reviews, brief communications, opinion articles, letters and posters were excluded. (5) Studies where we were unable to extract the relevant data. (6) Studies where opioid use was not measured at least 30 days after discharge from surgery.

*Exposure*

The exposure of each included study was a surgical procedure where a patient could have received perioperative opioids, including major, minor or day surgery.

*Outcome*

The definition of persistent post-operative opioid use employed by the study authors.

**Information Sources**

A professional librarian ran the search of electronic databases (Medline, Embase, CINAHL and the Cochrane Library) independently. Additional searches were conducted in Google Scholar. The strategy was tested and revised, taking into account each database prior to finalization. A senior medical librarian ensured the final search strategy was robust and exhaustive. A database record of the search strategy and included results was maintained. When data or publication was unavailable, authors were contacted for further clarification.

**Search Strategy**

*Electronic Search*

We searched MEDLINE (via Ovid), EMBASE (via Ovid), CINAHL and the Cochrane Library without language or year restrictions. We used a combination of medical subject headings (MeSH) or text word terms, which were combined with “OR” and “AND” operators. Each search was tailored to the respective database. We used both subject headings and textword terms for Opioids AND (surgical procedures or postoperative complications) and (cohort studies or prognosis or risk or time factors).MeSH terms were exploded when necessary. We also searched the reference lists of included studies. The full search strategy can be found below.

**Study Selection and Data Management**

Studies retrieved from searched terms were checked and filtered for duplicates. Each title and abstract was screened and reviewed independently and in duplicate by two review authors to determine eligibility, excluding articles that did meet inclusion criteria. Full text articles were obtained for studies that were not eliminated. Two review authors read these articles independently to include relevant studies and, in the event of disagreement, a third expert reviewer was given an opportunity to adjudicate. Records were managed using DistillerSRTM.

**Data Collection Process**

Data was extracted using a standard form by two independent reviewers and in duplicate. This form was first piloted using the first 10 eligible included studies. Responses from both independent reviewers were invigilated by a third expert reviewer during the pilot to ensure interrater consistency. Subsequently only in the event of disagreement between the two reviewers were expert reviewers asked to discuss study findings.

**Data Items, Outcomes and Prioritization**

Information extracted included: population sampled (eg. geographic location, and sociodemographic factors), methods (eg. Study design, sampling technique, and study aim), surgical procedures sampled, the definition of persistent opioid use employed, and the type of opioids measured. Study authors were approached for missing or unclear information.

**Search Strategy**

**MEDLINE:**

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| --- | --- | --- | --- |
| **#** | **Searches** | **Results** | **Comment** |
| 1 | analgesics, opioid/ or alfentanil/ or alphaprodine/ or buprenorphine/ or buprenorphine, naloxone drug combination/ or butorphanol/ or codeine/ or dextromoramide/ or dextropropoxyphene/ or dihydromorphine/ or diphenoxylate/ or "enkephalin, ala(2)-mephe(4)-gly(5)-"/ or "enkephalin, d-penicillamine (2,5)-"/ or ethylketocyclazocine/ or ethylmorphine/ or etorphine/ or fentanyl/ or heroin/ or hydrocodone/ or hydromorphone/ or levorphanol/ or meperidine/ or meptazinol/ or methadone/ or methadyl acetate/ or morphine/ or nalbuphine/ or opiate alkaloids/ or opium/ or oxycodone/ or oxymorphone/ or pentazocine/ or phenazocine/ or phenoperidine/ or pirinitramide/ or promedol/ or sufentanil/ or tilidine/ or tramadol/ [\*\*\*Check for additional opioids\*\*\*\*]  | 103262  |  |
| 2 | (opioid\* or codeine\* or fentanyl or heroin\* or morphine\* or hydromorphone\* or opiate\* or sufentanil or tilidine or tramadol).mp.  | 155193  |  |
| 3 | opioid-related disorders/ or heroin dependence/ or morphine dependence/ or opium dependence/  | 22306  |  |
| 4 | or/1-3  | 167611  | opioid terms |
| 5 | naive.ti,ab,kf.  | 62046  |  |
| 6 | (persistent or prolonged or chronic or new or "post-operative" or longitudinal or "long-term" or cessation or reduction).ti,ab,kf.  | 4237815  |  |
| 7 | drug misuse/ or prescription drug misuse/ or prescription drug overuse/  | 1347  |  |
| 8 | or/5-7  | 4281026  | naive or usage terms |
| 9 | exp Surgical Procedures, Operative/  | 2829081  |  |
| 10 | exp Postoperative Complications/  | 487773  |  |
| 11 | ("post-op\*" or "post op\*" or "post-surg\*" or "post surg\*").ti,ab,kf.  | 62259  |  |
| 12 | or/9-11  | 2993840  | operative procedure terms |
| 13 | cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/  | 1208741  |  |
| 14 | case-control studies/ or retrospective studies/ or cross-sectional studies/  | 1128113  |  |
| 15 | observational study.pt. or observational study as topic/  | 46498  |  |
| 16 | registries/  | 72486  |  |
| 17 | seer program/ [\*\*\*\*US Cancer registry\*\*\*\*]  | 5910  |  |
| 18 | prognosis/ or disease-free survival/ or medical futility/ or pregnancy outcome/ or treatment outcome/ or treatment failure/  | 1309528  |  |
| 19 | disease progression/  | 135583  |  |
| 20 | morbidity/ or incidence/ or prevalence/ or comorbidity/  | 541201  |  |
| 21 | mortality/ or cause of death/ or fatal outcome/ or hospital mortality/ or infant mortality/ or maternal mortality/ or survival rate/  | 335174  |  |
| 22 | survival analysis/ or disease-free survival/ or kaplan-meier estimate/ or proportional hazards models/  | 248792  |  |
| 23 | early diagnosis/ or early diagnosis of cancer/  | 39178  |  |
| 24 | treatment outcome/ or "early termination of clinical trials"/ or treatment failure/ or watchful waiting/  | 854564  |  |
| 25 | natural histor???.tw.  | 39241  |  |
| 26 | predictive value of tests/  | 178523  |  |
| 27 | time/ or time factors/  | 1123685  |  |
| 28 | logistic models/ or proportional hazards models/  | 181329  |  |
| 29 | "analysis of variance"/ or multivariate analysis/ or exp probability/  | 1430627  |  |
| 30 | risk/ or logistic models/ or protective factors/ or risk assessment/ or adverse outcome pathways/ or "healthcare failure mode and effect analysis"/ or risk factors/  | 1041946  |  |
| 31 | or/13-30  | 5025217  | Time factor or study design terms |
| 32 | 4 and 8 and 12 and 31  | 3489  | Final results |
| 33 | limit 32 to humans  | 3281  | Human limit |

**MEDLINE-in-Process**

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| **#** | **Searches** | **Results** | **Comment** |
| 1 | (alfentanil or alphaprodine or buprenorphine or butorphanol or codeine or dextromoramide or dextropropoxyphene or dihydromorphine or diphenoxylate or enkephalin or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or levorphanol or meperidine or meptazinol or methadone or "methadyl acetate" or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or piritramide or promedol).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]  | 5415  |  |
| 2 | (opioid\* or codeine\* or fentanyl or heroin\* or morphine\* or hydromorphone\* or opiate\* or sufentanil or tilidine or tramadol).mp.  | 11601  |  |
| 3 | or/1-2  | 12865  | opioid terms |
| 4 | naive.ti,ab,kf.  | 7001  |  |
| 5 | (persistent or prolonged or chronic or new or "post-operative" or longitudinal or "long-term" or cessation or reduction).ti,ab,kf.  | 561615  |  |
| 6 | ((drug\* or prescription\*) adj2 (misuse\* or overuse\* or dependen\* or abuse\*)).ti,ab,kf.  | 2912  |  |
| 7 | or/4-6  | 568122  | naive or usage terms |
| 8 | (surgery or surgeries or surgical\* or operative).ti,ab,kf.  | 169745  |  |
| 9 | (postoperative\* or "post-operative\*" or "post operative\*" or "post-op\*" or "post op\*" or "post-surg\*" or "post surg\*").ti,ab,kf.  | 52714  |  |
| 10 | or/8-9  | 182368  | operative procedure terms |
| 11 | ((cohort or longitudinal or "follow-up" or prospective) adj2 (study or studies)).ti,ab,kf.  | 50142  |  |
| 12 | (("case-control\*" or "case control\*" or retrospective\* or "cross-sectional" or "cross sectional") adj2 (study or studies)).ti,ab,kf.  | 60086  |  |
| 13 | observational study/ or (observation\* adj2 (study or studies)).ti,ab,kw.  | 14447  |  |
| 14 | (register\* or registr\*).ti,ab,kf.  | 37012  |  |
| 15 | (seer adj2 program\*).ti,ab,kf. [\*\*\*\*US Cancer registry\*\*\*\*]  | 98  |  |
| 16 | (prognos\* or "disease-free surviv\*" or ((medical or treatment) adj2 (outcome\* or fail\* or futilit\*))).ti,ab,kf.  | 66058  |  |
| 17 | (disease\* adj2 progress\*).ti,ab,kf.  | 11229  |  |
| 18 | (morbidit\* or comorbid\* or incidence\* or prevalence\*).ti,ab,kf.  | 155758  |  |
| 19 | (mortalit\* or (cause\* adj2 death\*) or "fatal outcome\*" or "hospital mortalit\*" or "infant mortalit\*" or "maternal mortalit\*" or ((survival or survivor\*) adj2 rate\*)).ti,ab,kf.  | 83864  |  |
| 20 | ((survival adj2 analys\*) or "disease-free" or "kaplan-meier estimate" or "proportional hazards model\*").ti,ab,kf.  | 10692  |  |
| 21 | "early diagnosis".ti,ab,kf.  | 8582  |  |
| 22 | (treatment adj2 (outcome\* or failure\*)).ti,ab,kf.  | 10767  |  |
| 23 | natural histor???.tw.  | 3714  |  |
| 24 | (predictive adj2 value).ti,ab,kf.  | 7306  |  |
| 25 | time.ti,ab,kf.  | 337931  |  |
| 26 | (logistic adj2 model\*).ti,ab,kf.  | 6423  |  |
| 27 | ("analysis of variance" or (multivariate adj2 analys\*) or probabilit\*).ti,ab,kf.  | 48667  |  |
| 28 | risk\*.ti,ab,kf.  | 195366  |  |
| 29 | or/11-28  | 744412  | Time factor or study design terms |
| 30 | 3 and 7 and 10 and 29 | 788  | Final results |

**MEDLINE Epub Ahead of print**

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| **#** | **Searches** | **Results** | **Comment** |
| 1 | (alfentanil or alphaprodine or buprenorphine or butorphanol or codeine or dextromoramide or dextropropoxyphene or dihydromorphine or diphenoxylate or enkephalin or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or levorphanol or meperidine or meptazinol or methadone or "methadyl acetate" or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or piritramide or promedol).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]  | 949  |  |
| 2 | (opioid\* or codeine\* or fentanyl or heroin\* or morphine\* or hydromorphone\* or opiate\* or sufentanil or tilidine or tramadol).mp.  | 2294  |  |
| 3 | or/1-2  | 2456  | opioid terms |
| 4 | naive.ti,ab,kf.  | 1527  |  |
| 5 | (persistent or prolonged or chronic or new or "post-operative" or longitudinal or "long-term" or cessation or reduction).ti,ab,kf.  | 95109  |  |
| 6 | ((drug\* or prescription\*) adj2 (misuse\* or overuse\* or dependen\* or abuse\*)).ti,ab,kf.  | 873  |  |
| 7 | or/4-6  | 96720  | naive or usage terms |
| 8 | (surgery or surgeries or surgical\* or operative).ti,ab,kf.  | 27888 |  |
| 9 | (postoperative\* or "post-operative\*" or "post operative\*" or "post-op\*" or "post op\*" or "post-surg\*" or "post surg\*").ti,ab,kf.  | 9191 |  |
| 10 | or/8-9  | 29936 | operative procedure terms |
| 11 | ((cohort or longitudinal or "follow-up" or prospective) adj2 (study or studies)).ti,ab,kf.  | 177 |  |
| 12 | (("case-control\*" or "case control\*" or retrospective\* or "cross-sectional" or "cross sectional") adj2 (study or studies)).ti,ab,kf.  | 11449 |  |
| 13 | observational study/ or (observation\* adj2 (study or studies)).ti,ab,kw.  | 3324 |  |
| 14 | (register\* or registr\*).ti,ab,kf.  | 7551 |  |
| 15 | (seer adj2 program\*).ti,ab,kf. [\*\*\*\*US Cancer registry\*\*\*\*]  | 31  |  |
| 16 | (prognos\* or "disease-free surviv\*" or ((medical or treatment) adj2 (outcome\* or fail\* or futilit\*))).ti,ab,kf.  | 13452 |  |
| 17 | (disease\* adj2 progress\*).ti,ab,kf.  | 2212 |  |
| 18 | (morbidit\* or comorbid\* or incidence\* or prevalence\*).ti,ab,kf.  | 28491 |  |
| 19 | (mortalit\* or (cause\* adj2 death\*) or "fatal outcome\*" or "hospital mortalit\*" or "infant mortalit\*" or "maternal mortalit\*" or ((survival or survivor\*) adj2 rate\*)).ti,ab,kf.  | 16479 |  |
| 20 | ((survival adj2 analys\*) or "disease-free" or "kaplan-meier estimate" or "proportional hazards model\*").ti,ab,kf.  | 2536 |  |
| 21 | "early diagnosis".ti,ab,kf.  | 1146  |  |
| 22 | (treatment adj2 (outcome\* or failure\*)).ti,ab,kf.  | 2233  |  |
| 23 | natural histor???.tw.  | 669  |  |
| 24 | (predictive adj2 value).ti,ab,kf.  | 15591  |  |
| 25 | time.ti,ab,kf.  | 55674 |  |
| 26 | (logistic adj2 model\*).ti,ab,kf.  | 1795  |  |
| 27 | ("analysis of variance" or (multivariate adj2 analys\*) or probabilit\*).ti,ab,kf.  | 10043  |  |
| 28 | risk\*.ti,ab,kf.  | 43912  |  |
| 29 | or/11-28  | 136284 | Time factor or study design terms |
| 30 | 3 and 7 and 10 and 29 | 131 | Final results |

**EMBASE**

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| **#** | **Searches** | **Results** | **Comment** |
| 1 | \*narcotic analgesic agent/ or \*buprenorphine/ or \*buprenorphine plus naloxone/ or \*butorphanol/ or \*codeine/ or \*dextromoramide/ or \*dextropropoxyphene/ or \*dihydromorphine/ or \*ethylmorphine/ or \*etorphine/ or \*hydrocodone/ or \*hydromorphone/ or \*levorphanol/ or \*meptazinol/ or \*methadone/ or \*morphine/ or \*morphine 6 acetate/ or \*morphine 6 glucuronide/ or \*morphine glucuronide/ or \*morphine sulfate/ or \*morphinomimetic agent/ or \*nalbuphine/ or \*opiate/ or \*oxycodone/ or \*oxycodone plus oxycodone terephthalate plus paracetamol/ or \*oxycodone plus paracetamol/ or \*oxycodone terephthalate/ or \*oxymorphone/ or \*pentazocine/ or \*phenazocine/ or \*phenoperidine/ or \*piritramide/ or \*tilidine/ or \*tramadol/ or \*fentanyl derivative/ or \*alfentanil/ or \*fentanyl/ or \*fentanyl citrate/ or \*fentanyl citrate plus metformin plus pioglitazone/ or \*fentanyl isothiocyanate/ or \*sufentanil/ or \*sufentanil citrate/ or \*nalbuphine/ or \*dinalbuphine sebacate/ or \*diphenoxylate/ or \*"enkephalin[2 dextro alanine 4 methylphenylalanine 5 glycine]"/ or \*opiate agonist/ or \*"enkephalin[2,5 dextro penicillamine]"/ or \*ethylketazocine/ or \*diamorphine/ or \*morphine derivative/ or \*pethidine/ or \*meperidine/ or \*acetylmethadol/ or \*piritramide/ or \*trimeperidine/ or \*narcotic dependence/ or \*drug dependence/ or \*heroin dependence/ or \*morphine addiction/ or \*opiate addiction/  | 164206  |  |
| 2 | (opioid\* or codeine\* or fentanyl or heroin\* or morphine\* or hydromorphone\* or opiate\* or sufentanil or tilidine or tramadol or "methadyl acetate" or pirinitramide\* or promedol or meperidine).mp.  | 311547  |  |
| 3 | or/1-3  | 349261  | Opioid terms |
| 4 | naive.ti,ab,kw.  | 110580  |  |
| 5 | (persistent or prolonged or chronic or new or "post-operative" or longitudinal or "long-term" or cessation or reduction).ti,ab,kw.  | 6596458  |  |
| 6 | drug misuse/ or drug abuse/ or drug dependence/  | 98402  |  |
| 7 | substance abuse/  | 49446  |  |
| 8 | or/4-8  | 6768124  | naive or usage terms |
| 9 | exp \*surgery/  | 2213550  |  |
| 10 | \*postoperative complication/  | 62802  |  |
| 11 | ("post-op\*" or "post op\*" or "post-surg\*" or "post surg\*").ti,ab,kw.  | 152885  |  |
| 12 | or/9-11  | 2316560  | operative procedure terms |
| 13 | cohort analysis/ or longitudinal study/ or prospective study/  | 796709  |  |
| 14 | case control study/ or hospital based case control study/ or population based case control study/ or retrospective study/  | 744297  |  |
| 15 | observational study/ or (observational adj2 (study or studies)).ti,ab.  | 187894  |  |
| 16 | Register/ or cancer registry/  | 135139  |  |
| 17 | cancer recurrence/ or cancer regression/ or cancer relapse/ or disease duration/ or disease exacerbation/ or prognosis/ or recurrent disease/ or reinfection/ or relapse/ or remission/ or tumor recurrence/ or tumor regression/ or survival/ or cancer survival/ or disease free survival/ or overall survival/ or survival rate/ or survival time/  | 1903312  |  |
| 18 | prognosis/  | 556473  |  |
| 19 | incidence/ or cancer incidence/ or familial incidence/  | 364764  |  |
| 20 | morbidity/ or comorbidity/ or comorbidity assessment/ or maternal morbidity/ or perinatal morbidity/ or newborn morbidity/  | 516133  |  |
| 21 | mortality/ or cancer mortality/ or childhood mortality/ or embryo mortality/ or fetus mortality/ or infant mortality/ or maternal mortality/ or prenatal mortality/ or surgical mortality/ or perinatal mortality/ or newborn mortality/  | 901778  |  |
| 22 | death/ or "cause of death"/ or dying/ or heart death/ or sudden death/ or child death/ or newborn death/  | 452609  |  |
| 23 | prevalence/  | 576744  |  |
| 24 | treatment outcome/ or disease free interval/ or treatment failure/ or drug treatment failure/  | 866758  |  |
| 25 | (natural adj2 history).ti,ab.  | 60438  |  |
| 26 | risk/ or attributable risk/ or genetic risk/ or high risk patient/ or high risk population/ or low risk patient/ or low risk population/ or population risk/ or recurrence risk/ or risk factor/ or risk management/ or risk reduction/  | 1623997  |  |
| 27 | Odds ratio/ or (odds adj2 ratio:).ti,ab.  | 272456  |  |
| 28 | cardiovascular risk/  | 168738  |  |
| 29 | fall risk/ or fall risk assessment/  | 4147  |  |
| 30 | high risk behavior/  | 22886  |  |
| 31 | high risk infant/ or high risk pregnancy/  | 12154  |  |
| 32 | infection risk/  | 72559  |  |
| 33 | Causality/  | 1121  |  |
| 34 | (precipitat\* adj2 factor\*).ti,ab.  | 6908  |  |
| 35 | Poisson distribution/ or statistical model/ or multivariate analysis/  | 293635  |  |
| 36 | asymptomatic disease/  | 9828  |  |
| 37 | (risk: or cause or causal or causation or relative risk).ti,ab.  | 3662438  |  |
| 38 | time/ or time factor/  | 408941  |  |
| 39 | (logistic\* adj2 model\*).ti,ab,kw.  | 78576  |  |
| 40 | proportional hazards model/  | 82180  |  |
| 41 | "analysis of variance"/  | 138531  |  |
| 42 | exp multivariate analysis/  | 362503  |  |
| 43 | probability/  | 79989  |  |
| 44 | or/13-43  | 8386036  | Time factor or study design terms |
| 45 | 3 and 8 and 12 and 44  | 6922  | Final results |
| 46 | limit 45 to human  | 6366  | Human limit |