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INCIDENCE ET FACTEURS ASSOCIÉS A LA PRESCRIPTION À LONG TERME D'OPIOÏDES DANS LA POPULATION NON ATTEINTE DE CANCER : REVUE SYSTEMATIQUE ET META-ANALYSE

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AINS : Anti-Inflammatoires Non Stéroïdiens (AINS)
ANSM : Agence Nationale de Sécurité du Médicament et des produits de santé
BWC : Bureau of Workers' Compensation
CC : Case-control
CPRD : Clinical Practice Research Datalink
CORRONA : Consortium of Rheumatology Researchers of North America
CSS : Cross-sectional study
CTBIE : Comprehensive Traumatic Brain Injury Evaluation
DANCOS : Danish National Cohort Study; EMRs: Electronic Medical Records
DCI : Dénomination Commune Internationale
DCNC : Douleur Chronique Non Cancéreuse
DEM : Dose Equivalent Morphine
FDA : Food and Drug Administration
GH : Group Health
HES : Hospital Episode Statistics
IASP: International Association for the Study of Pain
JBI : Joanna Briggs Institute
KPNC : Kaiser Permanente Northern California
KPNW : Kaiser Permanente Northwest
LTPO : Long-Term Prescription Opioid
MS : Information Management System
MEPS : Medical Expenditure Panel Survey
NA : Non-applicable
NHs : National health service
NorPD : Norwegian Prescription Database
OICS : Organe International de Contrôle des Stupéfiants
PC : Prospective cohort
RAMQ : Régie de l'Assurance Maladie du Québec
RC : Retrospective cohort
REMS : Risk Evaluation and Mitigation Strategies
RPDR : Research Patient Data Registry
SFDT: Société Française d'Etude et de Traitement de la Douleur
UC : Uncertain
UK : United-Kingdom
US : United-States
VA : Veterans Affairs
VHA : Veterans Health Administration

1. INTRODUCTION

1.1. GENERALITES SUR LES OPIOIDES

La douleur serait à l'origine de près de deux tiers des consultations médicales en France aujourd'hui (1). L'homme a ainsi toujours cherché à la soulager, notamment via des principes actifs extraits de plantes comme le saule blanc (*Salix alba)* ou le pavot à opium (*Papaver somniferum ;* Figure 1). De ces plantes ont été extraites et synthétisées les principales molécules aujourd'hui utilisées dans la prise en charge de la douleur. Le saule blanc (*Salix alba)* a permis la découverte de l'aspirine et de ses dérivés et le pavot à opium (*Papaver somniferum*) celle de la morphine et des autres antalgiques opioïdes.

a. Qu'est-ce qu'un opioïde ?

Par définition, un opioïde définit « toute substance exogène, naturelle ou synthétique qui se fixe à certains récepteurs opioïdes spécifiques et qui produit un effet semblable à celui de la morphine » (2). La morphine fait référence car il s'agit du premier opioïde à avoir été découvert en 1805.

b. Découverte de la morphine et de ses dérivés

Dans l'antiquité, le pavot à opium (*Papaver somniferum*) est décrit comme « la plante de joie ». Elle est en effet ajoutée à des préparations médicales après incision des capsules de pavot qui laissent s'écouler un latex contenant l'opium (Figure 1). En 1550 av. J.-C., des documents décrivent une préparation à base d'opium utilisée pour les pleurs d'enfants (*Papyrus d'Ebers*). En 400 av. J.-C., Hippocrate (460-377 av. J.-C.) et son école grecque de Cos publient des textes fondateurs dans lesquels on utilise le latex de pavot pour « resserrer le ventre ». Il semblerait que la peur des opioïdes se soient inscrite dans l'inconscient collectif à ce moment-là avec les œuvres de Virgile, lorsqu'Hercule tue le dragon à cents têtes du jardin des Hespérides grâce à un mélange de miel et de pavots (3).

Dans l'ère chrétienne, Galien (129-201), père de la pharmacie, utilise l'opium très largement, à la fois en traitement des douleurs comme les céphalées et des douleurs abdominales et urinaires mais également pour la toux, l'asthme, l'épilepsie ou comme antidote de certains poisons. Une de ses préparations magistrales, la thériaque, à base de vin, miel et de plus de 50 extraits de plantes, compte le pavot comme ingrédient majeur. Cette préparation figura à la pharmacopée française jusqu'en 1908 (3).

Au XVIe siècle, Paracelse (1490-1541) apporte les prémices de la chimie thérapeutique. Il obtient notamment une teinture d'opium safranée en procédant à l'extraction de l'opium dans le l'alcool, le « laudanum » dont la formule sera publiée et standardisée. Au XVIIe siècle, les effets secondaires de l'opium instaurent une méfiance autour de son utilisation. Ettmuller, médecin allemand, accuse l'opium : « il ôte la douleur, mais c'est un tuant et non un guérissant ». L'usage du laudanum restera cependant très répandu en Europe, en vente libre chez les apothicaires (3).

En 1805, Friedrich Sertürner (1783-1841), pharmacien allemand, isole un alcali végétal d'opium qu'il appellera sels de morphine, nom inspiré de Morphée, dieu des songes grecs. Ses travaux publiés démontrent alors l'effet psychotrope et sédatif de la morphine sur quatre volontaires sains dont lui-même. En 1824, Pierre-Jean Robiquet (1780-1840), isole la codéine (3).

Au cours du XXe siècle, la morphine est utilisée et identifiée comme l'antalgique le plus puissant et les découvertes des dérivés morphiniques s'accélèrent, aboutissant à la production de multiples opioïdes semi-synthétique et synthétiques disponibles aujourd'hui (3).

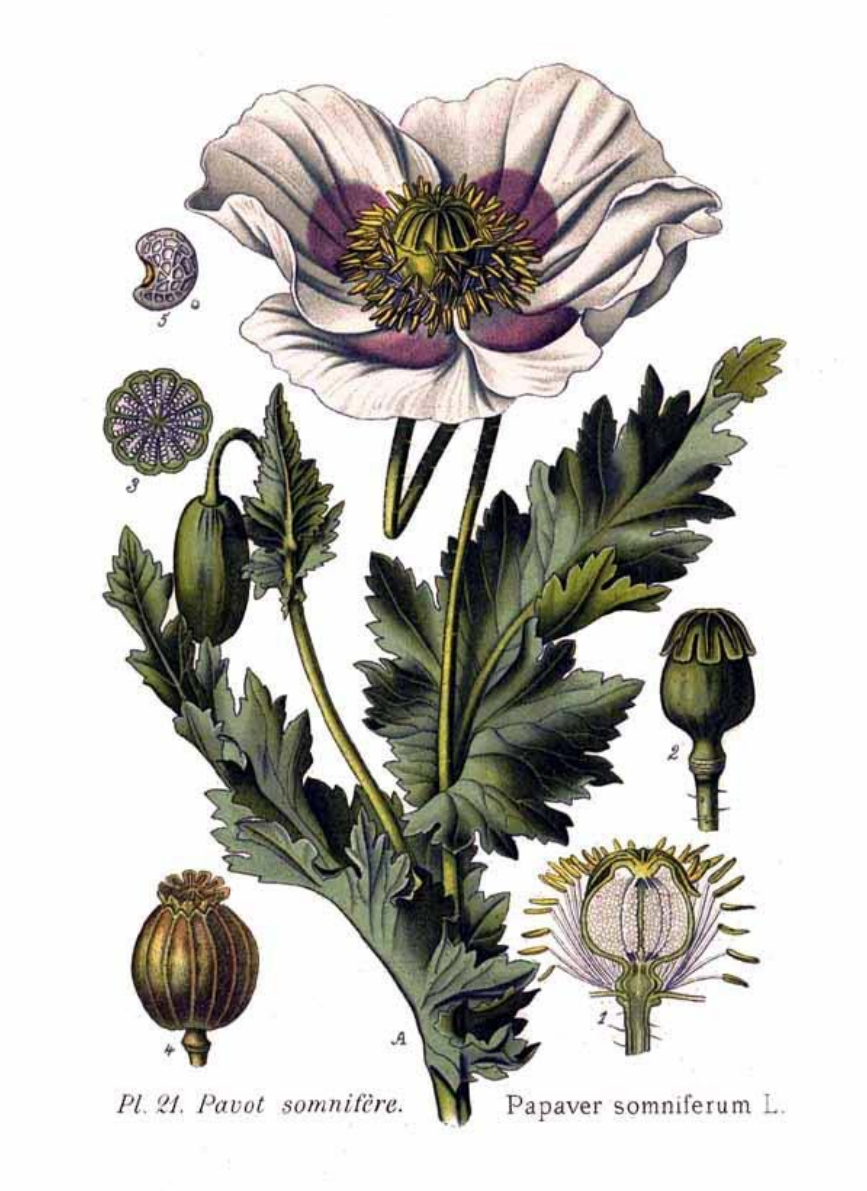

Figure 1. Planche botanique de Pavot Somnifère (*Papaver somniferum*) extrait de l'atlas des plantes de France, 1891 (4).

c. Utilisation des opioïdes depuis le XXe siècle

Une fois découverts, les opioïdes semi-synthétique et synthétiques disponibles sont rapidement identifiés pour la prise en charge de la douleur. Lors de la première guerre mondiale (1914-1918), la morphine est très largement mais aussi très mal utilisée pour soulager les blessés de guerre. Les effets indésirables, notamment de dépendance n'ont pas été anticipés, laissant après-guerre de nombreux soldats toxicomanes. Un problème rapidement devenu mondial et nécessitant une prise de position globale afin de structurer le marché des opioïdes et le limiter aux seuls besoins médicaux. Les indications médicales des opioïdes se précisent, dans la prise en charge des douleurs sévères notamment d'origine cancéreuses avec

Freud qui utilise la morphine pour lutter contre les douleurs de son cancer ORL (3). Dans les années 90, l'utilisation des analgésiques opioïdes s'élargie aux douleurs modérées à sévères chez tous types de patients (5).

Aujourd'hui, la prescription d'opioïdes est indiquée dans la prise en charge de la douleur d'intensité légère à sévère (6). Ils sont également utilisés en anesthésie, comme antitussifs, comme anti-diarrhéique et pour traiter la dépendance aux opioïdes (buprénorphine et méthadone) (6). Selon l'Organisation Mondiale de la Santé (OMS), les opioïdes antalgiques recommandés dans la prise en charge de la douleur sont graduellement, les opioïdes faibles (codéine, opium, hydrocodone, tramadol, dextropropoxyphène) puis, en cas d'inefficacité aux doses maximales tolérées, les opioïdes forts (morphine, hydromorphone, hydrocodone, oxycodone, oxymorphone, merepidine, tapentadol, fentanyl, pentazocine) (7).

1.2. CONTEXTE DE L'ETUDE

1.2.1. Un essor de la consommation d'opioïdes

a. Mondialement

Anciennement utilisés dans la prise en charge des douleurs sévères d'origine cancéreuse, dans les années 90, l'utilisation des analgésiques opioïdes s'est élargie aux douleurs modérées à sévères chez tous types de patients. Un essor de leur consommation a ainsi débuté, et ne cesse de continuer. En effet, la consommation mondiale d'opioïdes en équivalent morphine a augmenté de plus de dix fois entre 1990 et 2015, avec 42,69 millions de personnes utilisatrices d'opioïdes dans le monde en 2015 (8,9). La majorité de l'utilisation globale d'opioïdes semble se concentrer en Europe et en Amérique du Nord (10), notamment aux États-Unis et au Canada où une crise des opioïdes s'est installée depuis les années 2000 (10,11). En 2015, plus de 19% de la population consommait des opioïdes sur prescription aux États-Unis (8), 13,1 % au Canada (12) et 17,1% en France (13).

b. En France

La crise des opioïdes n'est pas encore arrivée en France, mais une augmentation de la consommation des opioïdes y est bien observée. En 2019, l'Agence Nationale de Sécurité du Médicament et des produits de santé (ANSM) publie un rapport sur la consommation des antalgiques opioïdes en France. Il s'inscrit dans une démarche de surveillance globale de l'utilisation des médicaments utilisés dans la prise en charge de la douleur. En 2015, 9 966 944 français (17,1 %) ont reçu un antalgique opioïde sur prescription (13). Entre 2006 et

2017, les tendances de consommations montraient que le tramadol est l'antalgique opioïde le plus consommé avec une augmentation de + 68 % entre 2006 et 2017 (13). L'oxycodone est cependant l'antalgique opioïde dont la consommation a connu la plus forte augmentation, soit +738% entre 2006 et 2017 (13).

1.2.2. Une amélioration de la prise en charge de la douleur

L'essor de la consommation d'antalgiques opioïdes observée est à considérer parallèlement à une amélioration de la considération du patient et de la prise en charge de sa douleur. La douleur est aujourd'hui correctement évaluée, reconnue et prise en charge dans de nombreuses situations médicales : aigues et chroniques. La lutte contre la douleur, qui peut sembler évidente découle pourtant d'une évolution des mentalités et des modalités de prise en charge débutée dans les années 90.

Le changement des mentalités est intervenu par la reconnaissance de la douleur et des droits du malade. Anciennement le soulagement de la douleur a pu être considéré comme secondaire lorsqu'elle était une « punition des dieux » dans l'antiquité ou encore rédemptrice au Moyen-Âge (3). Internationalement, un consensus s'établit pour définir la douleur comme « une expérience sensorielle et émotionnelle désagréable associée à une lésion tissulaire réelle ou potentielle, ou décrite en des termes évoquant une telle lésion » (14). Cette définition place le patient au premier plan et met l'accent sur le caractère subjectif de la perception douloureuse. En France, la loi n°2002-303 du 4 Mars 2002 relative aux droits de la personne malade et à la qualité du système de santé a notamment permis de conférer des droits aux patients spécifiquement liés à leur situation de malade (15).

Cela s'est accompagné d'une modification des pratiques diagnostiques avec un transfert de l'évaluation de la douleur du médecin vers le patient. La douleur étant alors mieux reconnue et évaluée, l'utilisation de l'arsenal thérapeutique dont les antalgiques opioïdes a alors été promue et facilitée.

a. Mondialement

Après la deuxième guerre mondiale, l'anesthésiste américain John Bonica (1917-1994) créé la première équipe pluridisciplinaire de lutte contre la douleur et le premier centre de la douleur « pain clinic » en 1978 (3). Depuis, l'OMS rapporte une dynamique mondiale pour la prise en charge de la douleur, largement considérée comme à la fois un droit du patient et un droit de l'homme. L'OMS ainsi que l'Organe International de Contrôle des Stupéfiants (OICS) encouragent les gouvernements à s'aligner sur la politique internationale. Une politique

équilibrée entre garantir la disponibilité et l'accessibilité aux antalgiques opioïdes et prévenir le risque d'abus et de dépendance. La convention unique des stupéfiants a été signée à ces fins en 1961. Ce traité international vise à encadrer le marché des opioïdes, limité aux usages médicaux et de recherche (16).

b. En France

En France, la lutte contre la douleur constitue depuis 1998 une priorité de santé publique en France, notamment avec la mise en place d'une succession de plans d'actions ministériels (17). Les actions ont notamment permis la mise à disposition et l'utilisation plus large des antalgiques opioïdes dans la prise en charge de la douleur. Trois principaux plans se sont succédés : 1998-2000, 2002-2005 et 2006-2011 (17). Ils ont notamment permis : l'amélioration de la prise en compte de la demande du patient et de son information concernant la prise en charge de sa douleur ; la mise en place de structures dédiées à la prise en charge de la douleur ; la sensibilisation et la formation des professionnels de santé ; l'évaluation des pratiques professionnelles et l'intégration d'indicateurs de prise en charge de la douleur dans la certification des établissements de santé (17).

1.2.3. Une balance bénéfices/risques complexe

Les opioïdes ont un intérêt majeur et incontestable dans la prise en charge de la douleur. Leur essor est donc en partie justifié. Mais s'ils sont la plupart du temps justement prescrits, ils font de par leurs effets indésirables et le potentiel d'abus et de dépendance, l'objet de dommages sanitaires importants (18).

Désormais, les traitements opioïdes sont prescrits essentiellement pour leurs propriétés analgésiques dans la prise en charge de la douleur intense, modérée et même légère (12,13). Différents profils d'utilisation se dégagent, avec une majorité d'utilisateurs ponctuels, mais pour une minorité, le traitement par opioïdes se prolonge et l'on voit apparaitre des utilisateurs à long terme (19). Hors selon les recommandations internationales actuelles, la prescription d'opioïdes à long terme n'est indiquée que dans la prise en charge de la douleur d'origine cancéreuse (20). Sorti du cadre de la prise en charge du cancer, le rapport bénéfices/risques d'une prescription à long-terme est fortement remis en cause. Il est estimé qu'environ un patient sur quatre, traité par un opioïde, aura un soulagement conséquent de la douleur à long terme. Un traitement par opioïdes ne devrait donc être poursuivi que dans les cas où il apporte un bénéfice notable sur la douleur et/ou la qualité de vie du patient (21,22).

1.3. JUSTIFICATION DE L'ETUDE

Les bénéfices d'une prescription à long terme d'opioïdes sont largement controversés, avec des résultats d'études très contradictoires (18). A l'inverse, les risques sont beaucoup mieux connus avec de nombreux effets indésirables attendus et un risque majeur de troubles liés à l'usage d'opioïdes. Il s'agit du risque de dépendance, d'abus et d'intoxication aigues, pouvant mener à syndromes de sevrage et des décès (18). La Société Française d'étude et de traitement de la douleur (SFDT) rapporte que des effets indésirables apparaissaient chez plus de 60% des patients traités par opioïdes, et étaient responsables d'environ 20% d'arrêts de traitement (21). Une étude menée entre 2006 et 2011 au Canada, a montré que plus de 2/3 des hospitalisations pour effets indésirables liés aux opioïdes survenaient au-delà d'un mois de traitement, les effets majoritaires étant respectivement la constipation, le delirium et la désorientation (23). Concernant le risque majeur de troubles liés à l'usage, le nombre de décès par intoxication aigue aux opioïdes a augmenté au cours des dernières années (24). Dans le monde, on estime à 27 millions le nombre de personnes qui souffraient de troubles liés à l'usage d'opioïdes en 2016, et environ 118 000 décès y seraient attribuables 2015 (24). Un patient sur 550 chez qui un traitement par opioïde a été initié en Ontario, Canada, est décédé de causes liées aux opioïdes environ 2,6 ans après sa première prescription d'opioïdes (25).

Le risque de troubles liés à l'usage a fait l'objet de plusieurs publications alarmantes aux États-Unis, ce qui a relancé la controverse sur l'utilisation à long terme d'opioïdes. Les autorités sanitaires ont alors mis en place des mesures de minimisation de risque. En Juillet 2012, la FDA approuve une stratégie d'évaluation et d'atténuation des risques (REMS) destinées aux opioïdes libération prolongée et à action prolongée, élargie en 2018 aux opioïdes à libération immédiate. La composante principale de la REMS est l'éducation des prescripteurs d'opioïdes, étendue à tout professionnel de santé impliqué dans la prise en charge de la douleur (26). Au Canada, un plan de gestion de risque est désormais obligatoire pour les industriels commercialisant des opioïdes (27). En Europe, la France a mis en place un système d'ordonnances sécurisées et a récemment inscrit tous les médicaments contenant de la codéine sur la liste des médicaments disponibles sur ordonnance uniquement (28), et la Grande-Bretagne a élargi l'accès à la naloxone (29).

Afin de s'intéresser davantage à ce problème il est donc nécessaire d'estimer l'incidence de la prescription à long terme d'opioïdes au sein d'une population non cancéreuse. Les facteurs associés à la dépendance et à l'abus ont été identifiés (sexe masculin, âge jeune, troubles psychiatriques, antécédent d'addiction à l'alcool etc) (30). En revanche, ceux associés à

l’utilisation à long terme demeurent peu connus. Il semble donc désormais utile de comprendre quels sont les facteurs associés à la prescription à long terme d’opioïdes. Les cliniciens pourraient ainsi les considérer lorsqu’ils seront amenés à initier ou réviser un traitement par opioïdes. Afin d’identifier de potentiels facteurs associés, il est nécessaire d’étudier une population hétérogène et la plus représentative de la population réellement utilisatrice. Il semble donc plus approprié de se concentrer sur les données d’utilisation en vie réelle, issues d’études observationnelles.

1.4. QUESTION DE RECHERCHE ET OBJECTIFS

1.4.1. Question de recherche

1. Quelle est l'incidence de la prescription à long terme d'opioïdes au sein d'une population non cancéreuse ?
2. Quels sont les facteurs associés à la prescription à long terme d'opioïdes au sein d'une population non cancéreuse ?

1.4.2. Objectif principal

Estimer l'incidence de la prescription à long terme des opioïdes et identifier les facteurs associés au sein d'une population non cancéreuse.

1.4.3. Objectifs spécifiques

1.4.3.1. Estimer l'incidence de la prescription à long terme des opioïdes

- Dans la population non cancéreuse globale ;
- Dans des sous-populations définies selon les différentes indications des opioïdes (ex. péri-opératoire, douleur dentaire, douleur chronique non cancéreuse etc.).

1.4.3.2. Identifier les facteurs associés à la prescription à long terme d'opioïdes

- Identifier les caractéristiques des patients associées à la prescription à long terme (âge, sexe, contexte d'utilisation, comorbidités etc.);
- Identifier les caractéristiques du traitement par opioïdes associées à la prescription à long terme (classe et nombre d'opioïdes, dose, durée du traitement, spécialité du prescripteur, traitements associés etc.).
- Identifier les facteurs associés selon les différentes indications des opioïdes (ex. péri-opératoire, douleur dentaire, douleur aigue ou chronique non cancéreuse etc.).

1.4.4. Objectifs secondaires

Rapporter les différentes définitions de la prescription à long terme d'opioïdes disponibles dans la littérature.

2. ARTICLE

2.1. TITLE PAGE

Incidence and factors associated with long-term prescription opioid use in the non-cancer population: a systematic review and meta-analysis of observational studies.

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2.2. KEY POINTS

Question: What is the incidence of long-term prescription opioid use and associated factors in the non-cancer population?

Findings: According to this systematic review that included 64 observational studies, the incidence of long-term prescription opioid use among those who initiate a treatment ranged from 0.2 to 703.4 per 10,000 person-years. Obesity, tobacco use, anxiety and "any pain" indication were found to increase the risk of becoming a long-term prescription opioid user.

Meaning: Long-term prescription opioid use is a known predictor of opioid-related harms. The identification of determinants of long-term prescription opioid use may be used as a decision-making tool for clinicians when initiating or continuing treatment.

2.3. ABSTRACT

Importance: Long-term prescription opioid use in the non-cancer population is highly controversial as it is a known risk factor for opioid-related harms (adverse events including substance use disorders). The identification of factors associated with long-term prescription may be useful as a decision-making tool for clinicians when initiating or continuing treatment.

Objective: This study aimed to estimate the incidence of progressing to long-term prescription opioid use in patients without cancer who initiate a treatment and, to identify associated factors.

Design: Systematic review and meta-analysis.

Data Sources: Medline and Embase electronic databases were searched from 01 January 2009 to 15 January 2020. Additional sources were sought through pragmatic searches.

Study Selection: Observational studies on long-term prescription opioid use in the non-cancer population from all ages, community-dwelling or institutionalized and reporting a definition for long-term use, incidence estimates and/or associated factors were eligible. Two authors independently screened titles and abstracts, with conflicts resolved by a third author.

Data Extraction and Synthesis: Data were extracted by one author and validated by a second author. Methodological quality of individual studies was assessed using the Joanna Briggs Institute critical appraisal tools. For potential risk factors investigated in a least two studies, a meta-analysis of adjusted measures of association was conducted using a random effect model, and expressed as an odds ratio (OR) with corresponding 95% confidence interval (95%CI). Statistical heterogeneity of estimates was assessed using the I^2 statistics.

Main Outcome(s) and Measure(s): Long-term prescription opioid use.

Results: A total of 64 observational studies including from 96 to 1,353,902 patients without cancer were included in the review. Among prescription opioid users, the incidence of progressing to long-term use ranged from 0.2 to 703.4 per 10,000 person-years (median: 41.6), with the highest incidence found in the post-surgery setting. Factors associated with long-term use were: obesity (OR 1.32, 95%CI 1.23-1.42), tobacco use (1.60, 1.42-1.80), anxiety (1.36, 1.14-1.61) and prescription for “any pain” (1.64, 1.39-1.95), with no evidence

of statistical heterogeneity across studies. In subgroup analysis based on sociodemographic characteristics, LTPO definition and quality assessment, male gender, psychiatric disorder, pre-existing substance use disorder and back pain indication were also associated factors.

Conclusions and Relevance: This review demonstrated that long-term prescription opioid use is frequent, especially in post-surgical patients. Tangible risk factors have been identified, some of which are actionable at the point of care.

2.4. INTRODUCTION

Previously restricted to severe non-cancer pain, opioid use expanded in the 1990s in mild to severe pain for all types of patients. Opioid consumption increased more than tenfold between 1990 and 2015 to reach 43 million users worldwide in 2015 (1, 2). The highest use is found in North America, where the opioid crisis has been particularly devastating, accounting for a surge in opioid-related harms, including accidental death due to unintentional overdose (3, 4). Opioids are mainly used for analgesia, but also as antitussive or antidiarrheal (5). The majority of users are occasional users but a minority extends their treatment and progress to long-term prescription opioid (LTPO) use (6). According to international guidelines, the benefit-risk of LTPO use is highly controversial, except for cancer management (7, 8). Benefits remain uncertain, while risks are well known. Opioid-related harms are opioids AEs including opioid use disorders (9). It has been reported that AEs have occurred in more than 60% of French patients treated with opioids (7). In Canada, more than 2/3 of hospitalizations for opioid-related AEs occurred beyond the first month of treatment, with constipation, delirium and disorientation being commonly reported (10). Opioid use disorders include addiction, abuse and overdose, which can lead to withdrawal syndrome or death (11). The World Health Organization (WHO) estimates that 27 million people worldwide suffered from opioid use disorders in 2016, which were also related to approximately 118,000 deaths in 2015 (11). In Ontario, Canada, one in 550 patients initiating opioids died of opioid-related causes 2.6 years after their first opioid prescription (12).

Although LTPO use is a known risk factor for opioid-related harms, to our knowledge, a synthesis of knowledge on the frequency of LTPO use in the non-cancer population has not been conducted. It is also not known in which sub-populations LTPO use is most frequent. The identification of factors associated with LTPO use may be the backdrop against which a typical profile of at-risk patients could be defined and used as a decision-making tool for clinicians when initiating or continuing treatment. This study focused on the progression to long-term use among patients who initiated a prescription, and not on the potential opioid use disorders resulting from such use.

2.5. METHODS

A systematic review was conducted to identify estimates of the incidence of progression to LTPO use in the non-cancer population as well as a meta-analysis to identify associated factors. The definitions of LTPO use in the selected sources were also determined. A study protocol was developed a priori and registered in PROSPERO (CRD42019122617) in February 2019.

Search strategy

The literature search was conducted in Medline and Embase electronic databases from 01 January 2009 to 15 January 2020 with a language restriction to English and French. The search strategy included terms relating to the population (non-cancer, all age groups, community-dwelling or institutionalized), the intervention (opioids), the outcome (long-term prescription opioid use) and the study type (observational studies) (full search strategy is available in Tables 1 and 2 of the Supplement). Additional sources were sought through pragmatic searches, including: (i) searches with Google Scholar and in the System for Information on Grey Literature in Europe (OpenGrey), (ii) screening of the list of references of the retained publications ("snowballing"), (iii) search of abstracts of unpublished studies presented in relevant conferences or seminars. Bibliographic references were imported into the EndNote software (Version X7.0.1).

Study selection

Studies were included in the systematic review if they met the following selection criteria: (i) *Population*: non-cancer population, all ages, community-dwelling or institutionalized; (ii) *Intervention*: opioid receptor agonists; studies including methadone and buprenorphine were considered only if these products accounted for less than 5% of opioid use in the study population or if a subgroup analysis excluding those products was conducted; (iii) *Outcome*: LTPO use with an incidence estimate or a LTPO definition; (iv) *Study type*: Observational studies defined as cross-sectional studies (CSS), prospective or retrospective cohort, case-control (CC) or self-controlled designs. Studies were considered for the meta-analysis if they met the following additional eligibility criteria: (i) At least one factor potentially associated with long-term prescription opioid use was investigated, (ii) study included a comparator group of short-term users, (iii) and reported an adjusted measure of association such as a relative risk (RR), odds ratio (OR), or hazard ratio (HR) with associated time intervals. There was no contact with study authors to access or seek further data. Two authors independently

screened titles and abstracts of search outputs. In case of discrepancies, a third author determined the final eligibility (YM). For studies published in full text articles and retained after screening, the full text was reviewed to confirm eligibility; reasons for excluding studies at this stage were documented. A flow chart for the selection of studies was developed according to the international PRISMA recommendations (13).

Data extraction

Data extraction was performed in a standardized data extraction form previously piloted on a random sample of five studies and conducted independently by two authors (IP, AB). Data extraction for all retained studies was performed by one author (IP), and validated independently by a second author (AB or GC). Any disagreement was resolved by consensus or by a third author (YM), if necessary. From each retrieved study, the following information was extracted: *Source:* Search type, study reference, study acronym (if applicable), publication date, publication type, geographical region, country, funding source; *Study methods:* Design, setting, study period, study duration, maximal duration of follow-up, data source(s), opioid exposure (incident or prevalent use, opioid products included/excluded, definition of LTPO use), statistical methods, comparator (if applicable), confounder(s) (if applicable); *Populations:* Target population (age, specific sub-population), study population (non-cancer definition, inclusion and exclusion criteria, number of patients who initiated an opioid, mean (or median) duration of follow-up); *Study results:* Sociodemographic characteristics (age, gender distribution), opioid characteristics (proportion of new opioid user(s), most frequent indications), LTPO use (number of LTPO users, incidence of LTPO use), factors associated with LTPO use (reference used, measure of association, adjusted estimate with 95% CI and adjustment variables). Data extraction was carried out using Excel software (version 2010, Microsoft, Redmond, Washington, DC).

Quality assessment

The methodological quality of studies was assessed only for those included in the meta-analysis because the results of the meta-analysis are the most critical. The Joanna Briggs Institute (JBI) critical appraisal tools were used, developed for cohort (11 items), case-control (10 items) and cross-sectional studies (8 items) (14). For each item the answer options are yes, no or, uncertain (i.e., not explicitly described in the publication). The quality of the studies was performed independently by one author (IP), and any doubt was resolved by discussion with a second author (FS), if necessary. A study was considered at high risk of bias

if the scores included: at least one “no” (≥ 1) or more than two “uncertain” (> 2), else study was considered to be at low risk of bias.

Statistical analysis

For the systematic review, estimates of LTPO use incidence were extracted and standardized to a 10,000 person-years denominator of patients who initiated an opioid treatment. For each study, the total person-years was calculated based on the reported mean or median follow-up time period. For studies that included naloxone and/or treatments for opioid addiction (i.e., methadone and buprenorphine) but with subgroup analysis, the number of LTPO patients was calculated only using data from patients with the eligible opioids. Estimates of incidence were qualitatively synthesized using a range (lowest and highest estimates) as well as median (i.e., the exact middle value in the set of incidences estimates with as many estimates greater and less than the median).

Factors potentially associated with LTPO use that were investigated in at least two studies were eligible for inclusion in the meta-analysis. In order to minimize confounding, only studies reporting an adjusted measure of association (RR, OR or HR with associated time interval) were considered for the meta-analysis. A pooled estimate of OR with a 95% CI was estimated assigning weights to each study based on the inverse of the overall study error variance. A random-effects model was used, as it is the most suitable in the presence of heterogeneous study designs, such as those of observational studies (15). Statistical heterogeneity of estimates obtained from individual studies was assessed using the Cochran Q test (with p-value < 0.10 considered to be statistically significant; (16)) and quantified by the I^2 statistics. Heterogeneity was considered low if I^2[25%;50%]; moderate if I^2]50%;75%] and high if I^2 >75% (17)). When heterogeneity was high, estimates were not pooled. In this case, potential sources of heterogeneity were investigated and subgroups were created according to study population (adults (18-64 years), elderly (≥ 65 years), pediatric (<18 years), mixed or unknown; sex ratio: >50% women or >50% males), study design (CSS, CC, PC or RC and, follow-up time for cohorts ≤12 months or >12 months), LTPO use definition (≥90 continuous days; ≥120 cumulative days during 12 months follow-up or, other definitions) as well as study quality (high risk of bias). All analyses were performed using RevMan® software (version 5.3, Nordic Cochrane Centre, Cochrane Collaboration). The systematic review and meta-analysis were developed and reported according to international PRISMA recommendations (13).

2.6. RESULTS

Study selection and study characteristics

The systematic review yielded 4,092 records (1,472 from Medline and 2,620 from Embase), 984 of which were duplicates and thus, removed. Screening of titles and abstracts led to the exclusion of 2,759 records. An additional five records were retrieved by pragmatic searches (3 conferences abstracts) and by "snowballing" (two references). The remaining 354 records underwent full text examination; 64 studies were finally included in the systematic review (reasons for exclusion are available in Table 3 of the Supplement; (18-81)) and 21 of these were included in the meta-analysis to determine factors associated with LTPO (22, 26, 28, 29, 33, 36, 40, 45, 50-52, 56, 57, 60, 64, 66, 69, 72, 74, 75, 77). There were 43 studies included in the systematic review that were not eligible for inclusion in the meta-analysis. Reasons for exclusion were: inappropriate comparator group (13 studies) (19, 23, 25, 30, 31, 34, 35, 41, 42, 46, 53, 62, 80); descriptive (non-comparative) analysis (15 studies) (18, 20, 24, 32, 38, 39, 43, 44, 58, 59, 63, 65, 68, 70, 76, 81); ineligible or unadjusted measure of association (8 studies) (27, 54, 55, 61, 67, 71, 73, 82); associated factor studied in one study only (2 studies) (21, 47); ineligible intervention (3 studies) (48, 49, 78); ineligible outcome (2 studies) (37, 79) (Figure 2).

The characteristics of the 64 studies included in the systematic review are summarized in Table 1. These consisted of: two prospective cohort studies (49, 79), one case-control study (44) and 12 cross-sectional studies (18, 24, 29, 32, 36, 38, 39, 43, 56, 59, 63, 72), the 49 other studies were retrospective cohort studies. Eight studies were conducted in Europe (20, 24, 31, 32, 42, 70, 74, 75), four in Australia (33, 49, 60, 64) and the remaining 52 others in North America (46 United States and 4 Canada). Data sources were administrative claims database for 46 studies, electronic medical records (EMRs) for nine studies (23, 24, 26, 45, 59, 67, 73, 75, 76), medical chart review for two studies (35, 38) mixed with questionnaires or registry for five studies (25, 36, 50, 65, 77) and ad hoc data collection for two studies (49, 79). The total sample size ranged from 96 to 1,353,902 patients and the follow-up period from 3 to 120 months (mean 29.0 months; median 12 months). One study targeted pediatrics patients (<18 years) (29) and five elderly patients (≥65 years) (21, 56, 59, 68, 78). In five studies, the population included more than 75% males and three studied females only (45, 72, 81). For sub-populations based on setting, 22 studies targeted post-surgery patients (21, 28, 31, 34, 35, 41, 46, 49, 51, 52, 54, 55, 58, 61, 62, 65, 67, 69, 71, 79-81), 18 non-cancer chronic pain (18, 19, 22, 25, 30, 32, 33, 36, 42, 45, 47, 50, 56, 57, 63, 70, 72, 73), three non-cancer acute pain

or traumatic injuries (40, 53, 74) or inflammatory disease (29, 44, 77) and one post-kidney transplantation (26).

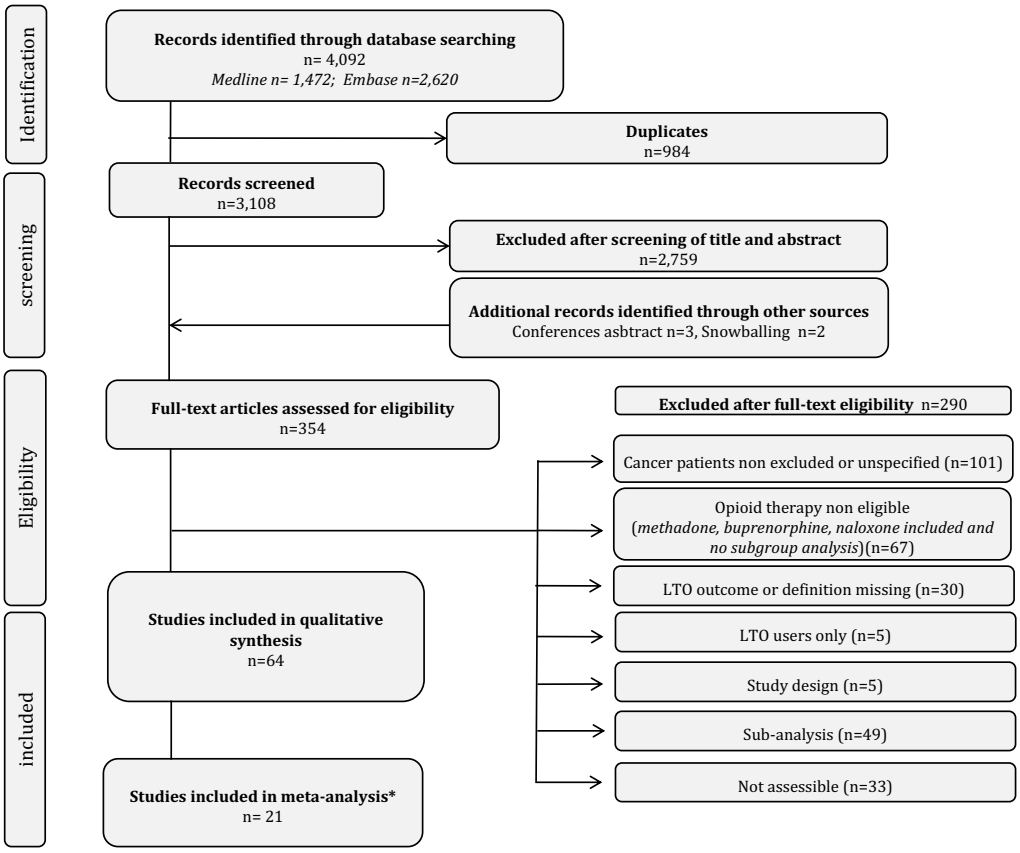

Figure 2. PRISMA flow diagram for study identification, selection and inclusion.

*Reasons for studies included in the qualitative synthesis of estimates but excluded from the meta-analysis of measures of association for the identification of risk factors were: Inappropriate comparator group (n=13); Descriptive analysis (n=15); Inappropriate or unadjusted risk measure (n=8); Associated factor studied only in this study (n=2); Inappropriate intervention (n=3); Inappropriate outcome (n=2).

Table 1. Characteristics of included studies (N=64)

Study reference	Country	Year	Design	Study period	Average follow-up (months)	Data collection method	Data source	Sample size: number of opioid users	Targeted age	Male,%*
Boudreau et al. (18)	US	2009	CSS	1997 -2006	108	Administrative Claims Database	Kaiser Permanente Northern California (KPNC); Group Health Cooperative (GH)	338,645 (KPNC: 46,475; GH: 292,170)	Adults and elderly (≥18)	42.0*
Deyo et al. (19)	US	2011	RC	2003 - 2005	6	Administrative Claims Database	Kaiser Permanente, Northwest (KPNW) health care system in Portland, Oregon.	26,014	Adults and elderly (≥18)	43.5
Skurtveit et al. (20)	Norway	2011	RC	2004 - 2008	48	Administrative Claims Database	Norwegian Prescription Database (NorPD)	245,006	*Unknown*	53.4
Alam et al. (21)	Canada	2012	RC	1997 - 2008	35	Administrative Claims Database	Health administrative databases in Ontario and Ontario Drug Benefit database	391,139 (Non-early opioid users: 363,503; Early opioid users: 27,636)	Elderly (≥65)	38.3*
Richardson et al. (22)	US	2012	RC	2001-2008	18	Administrative Claims Database	Medicare- and Medicaid-certified NHs	59,077	Mixed	44.6*
Dobscha et al. (23)	US	2013	RC	2007-2009	12	Electronic Medical Records (EMRs)	Veterans Affairs (VA) medical care database	5,871†	Adults and elderly (≥18)	NA
Chevalier et al. (24)	Germany UK	2014	CSS	2006-2016	60	Electronic Medical Records (EMRs)	UK: CPRD and HES; Germany: IMS Disease Analyzer	UK: 46,027† Germany: 149,808	Adults and elderly (≥18)	UK: 28.1* Ger: 36.7*
Fredheim et al. (25)	US	2014	RC	2006 - 2011	36	Mixed	Veterans Affairs (VA) medical care database	45,837 (CNCP: 14,477)	Adults and elderly (≥18)	46.0
Kulshrestha et al. (26)	US	2014	RC	2004-2012	12	Electronic Medical Records (EMRs)	EMRs of Veterans Health Administration (VHA)	59,865	Adults and elderly (≥18)	61.8
Morden et al. (27)	US	2014	RC	2007 - 2011	60	Administrative Claims Database	Medicare NHs	61,071	Adults (19-64)	51.1
Anderson et al. (28)	US	2015	RC	1993-2013	36	Administrative Claims Database	Ohio Bureau of Workers' Compensation (BWC)	1,002	*Unknown*	66.0*
Buckley et al. (29)	US	2015	CSS	2010-2011	24	Administrative Claims Database	Truven Health MarketScan® Commercial Claims and Encounters database	26,064 (Controls: 4,344; IBD: 21,720)	Pediatrics (≤18)	55.5*
Halbert et al. (30)	US	2015	RC	2006 - 2011	12	Administrative Claims Database	Veterans Affairs (VA) medical care database	54,237 (MHD: 3,983; non-MHD: 50,254)	Adults and elderly (≥18)	43.6*
Al Dabbagh et al (31).	Sweden	2016	RC	2005 -2008	24	Administrative Claims Database	Swedish National Hospital Discharge Register (SNHDR)	1,471	Mixed	44.0
Bedson et al. (32)	United Kingdom	2016	CSS	2002 -2013	12	Administrative Claims Database	CPRD	From 1,253,300 in 2002 to 1,379,217 in 2011	Adults and elderly (≥18)	Unknown
Heins et al. (33)	Australia	2016	RC	1999-2012	51	Administrative Claims Database	St Vincent's Private Hospital, Sydney	125,096 (Back injuries: 92,814; Shoulder injuries: 32,282)	Adults and elderly (≥18)	65.3*
Inacio et al. (34)	US	2016	RC	2001 - 2013	12	Administrative Claims Database	Veterans Affairs (VA) medical care database	45,837	Adults and elderly (≥18)	48.7

Study reference	Country	Year	Design	Study period	Average follow-up (months)	Data collection method	Data source	Sample size: number of opioid users	Targeted age	Male,%*
Kim et al. (35)	US	2016	RC	2015 - 2016	6	Medical Chart Review	Medicare- and Medicaid-certified NHs	707	*Unknown*	81.7
Lovejoy et al. (36)	US	2016	CSS	2009-2011	CSS	Mixed	Veterans Affairs (VA) medical care database and one interview	159	Mixed	92.9
Mudumbai et al. (37)	US	2016	RC	2010-2011	12	Administrative Claims Database	Veterans Affairs (VA) medical care database	61,071†	*Unknown*	NA
Sani et al. (38)	US	2016	CSS	2013 - 2015	36	Medical Chart Review	EMRs of Veterans Health Administration (VHA)	96	*Unknown*	Unknown
Smolina et al. (39)	Canada	2016	CSS	2005 -2012	108	Administrative Claims Database	Linked health datasets provided by Population Data British Columbia	200,974	*Unknown*	45.2*
Alghnam et al. (40)	US	2017	RC	2009-2012	24	Interviews	Medical Expenditure Panel Survey (MEPS)	36,824	Adults and elderly (≥18)	52.5
Anthony et al. (41)	US	2017	RC	2007 - 2014	12	Administrative Claims Database	PearlDriver Program, Humana administrative claims database	4,946	*Unknown*	Unknown
Birke et al. (42)	Denmark	2017	RC	2000 -2013	*Unknown*	Questionnaire	Danish National Cohort Study (DANCOS)	2,015	Mixed	46.0
Callinan et al. (43)	US	2017	CSS	July 2015	6	Interviews	Penn Pain Medicine Center	109	*Unknown*	39.1
Chen et al. (44)	US	2017	CC	2003 - 2014	12	Administrative Claims Database	Truven MarketScan	265,851 (RA: 181,922; SLE: 45,879; PSA: 30,346; AS: 7,704)	Adults and elderly (≥18)	Unknown
Cichowski et al. (45)	US	2017	RC	2002-2012	120	Electronic Medical Records (EMRs)	Medicare- and Medicaid-certified NHs	49,601	Adults and elderly (≥18)	*Female only*
Connolly et al. (46)	US	2017	RC	2009 - 2012	24	Administrative Claims Database	Veterans Affairs (VA) medical care database	8,377	Adults (19-64)	43.9
Deyo et al. (47)	US	2017	RC	2012 - 2013	12	Administrative Claims Database	Kaiser Permanente Northwest (KPNW) health care system in Portland, Oregon.	536,767	Mixed	Unknown
Shah et al. (48)	US	2017	RC	2006 - 2015	110	Administrative Claims Database	IMS Lifelink database	1,353,902	Mixed	Unknown
Stark et al. (49)	Australia	2017	PC	2015 - 2016	5	Cohort with Ad Hoc Data Collection	St Vincent's Private Hospital, Sydney	950	Adults and elderly (≥18)	NA
Thielke et al. (50)	US	2017	RC	2010-2013	12	Mixed	Veterans Health Administration (VHA)	762	Mixed	39.0
Adogwa et al. (51)	US	2018	RC	2007 - 2016	24	Administrative Claims Database	HORTHO Database (Medicare advantages beneficiaries with an orthopedic diagnosis)	13,257	Adults and elderly (≥18)	40.6
Anciano et al. (52)	US	2018	RC	2007-2015	6	Administrative Claims Database	PearlDiver patient records database	1,708	*Unknown*	Unknown
Bertenthal et al. (53)	US	2018	RC	2007 - 2015	12	Administrative Claims Database	Comprehensive Traumatic Brain Injury Evaluation (CTBIE) database from VA healthcare	53,124	*Unknown*	93.1
Bolarinwa et al. (54)	US	2018	RC	2007 - 2015	108	Administrative Claims Database	PearlDriver Program, Humana administrative claims database	55,354	*Unknown*	41.6
Cancienne et al.	US	2018	RC	2007 - 2015	108	Administrative	PearlDriver Program, Humana administrative	113,337	*Unknown*	36.5

Study reference	Country	Year	Design	Study period	Average follow-up (months)	Data collection method	Data source	Sample size: number of opioid users	Targeted age	Male,%*
(55)						Claims Database	claims database			
Chui et al. (56)	US	2018	CSS	2008-2010	36	Administrative Claims Database	Veterans Affairs (VA) medical care database	21,111 (Both: 1430; CMS: 5596; VHA: 14,085)	Elderly (≥65)	98.2*
Fritz et al. (57)	US	2018	RC	2012-2015	12	Administrative Claims Database	Medicare- and Medicaid-certified NHs	707	Adults (19-64)	32.2
Hernandez et al. (58)	US	2018	RC	2012 - 2014	32	Disease Registry	Prospective institutional total joint registry	159	*Unknown*	38%
Hunnicutt et al. (59)	US	2018	CSS	2012	4	Electronic Medical Records (EMRs)	Medicare- and Medicaid-certified NHs	297,734†	Elderly (≥65)	NA
Lalic et al. (60)	Australia	2018	RC	2013-2015	12	Administrative Claims Database	St Vincent's Private Hospital, Sydney	125,096	Adults and elderly (≥18)	47.0
Politzer et al. (61)	US	2018	RC	2007 - 2015	24	Administrative Claims Database	Veterans Affairs (VA) medical care database	950	*Unknown*	36.6
Steiner et al. (62)	US	2018	RC	2007 - 2016	6	Administrative Claims Database	Veterans Affairs (VA) medical care database	75,372	*Unknown*	45.4
Taqi et al. (63)	US	2018	CSS	2000 - 2015	12	Administrative Claims Database	Medicare- and Medicaid-certified NHs	89,521	Adults and elderly (≥18)	Unknown
Thornton et al. (64)	Australia	2018	RC	2006-2015	4	Administrative Claims Database	St Vincent's Private Hospital, Sydney	491,442	Mixed	47.5
Barham et al. (65)	US	2019	RC	2017-2018	6	Mixed	Medical Chart Review of the Urology Clinic at Tripler Army Medical Center + Statewide pharmacy claims database	228 (Pre-vasectomy opioid users: 102; Pre-vasectomy non-opioid users: 126)	*Unknown*	*Male only*
Barnett et al. (66)	US	2019	RC	2012-2013	12	Administrative Claims Database	Veterans Affairs (VA) medical care database	304,601 (Low intensity prescribers: 215,678; High intensity prescribers: 161,951)	*Unknown*	90.5*
Basilico et al. (67)	US	2019	RC	2002-2015	3	Electronic Medical Records (EMRs)	Trauma center Enterprise Data Warehouse + Research Patient Data Registry	17,961	Adults and elderly (≥18)	49.8
Beliveau et al. (68)	Canada	2019	RC	2014-2016	12	Administrative Claims Database	Quebec administrative claims database (*RAMQ*)	34,779	Elderly (≥65)	Unknown
Bennett et al. (69)	US	2019	RC	2002-2014	6	Administrative Claims Database	Clinformatics Optum Database	11,257	Adults (19-64)	0.8
Birke et al. (70)	Norway	2019	RC	2010-2016	48	Administrative Claims Database	Complete national Norwegian Prescription Database (NorPD)	64,792	Adults and elderly (≥18)	45.7
Desai et al. (71)	US	2019	RC	2010-2014	12	Administrative Claims Database	Medicare NHs	358,121	Adults (19-64)	33.2
Gibson et al. (72)	US	2019	CSS	2014-2015	CSS	Administrative Claims Database	Veterans Affairs (VA) medical care database	104,984	Mixed	*Female only*
Goplen et al. (73)	Canada	2019	RC	2013-2015	12	Electronic Medical Records (EMRs)	Surgical data were obtained from the Alberta Bone and Joint Health Institute + Pharmaceutical	14,252	Adults and elderly (≥18)	39.6

Study reference	Country	Year	Design	Study period	Average follow-up (months)	Data collection method	Data source	Sample size: number of opioid users	Targeted age	Male,%*
							Information Network			
Harris et al. (74)	Ireland	2019	RC	2015-2016	9	Administrative Claims Database	Optum Clinformatics DataMart	3,983	Adults and elderly (≥18)	47.0
Hedenmalm et al. (75)	Germany France	2019	RC	2006-2016	120	Electronic Medical Records (EMRs)	IMS Disease Analyzer	France: 90,987 Germany: 97,809	Adults and elderly (≥18)	Fr: 47.8 Ger: 42.4
Hirji et al. (76)	US	2019	RC	2016	12	Electronic Medical Records (EMRs)	Healthcare Research Patient Data Registry (RPDR)	330	*Unknown*	70.6
Lee et al. (77)	US	2019	RC	2002-2016	15	Questionnaire	Consortium of Rheumatology Researchers of North America (CORRONA)	26,288	Adults and elderly (≥18)	24.1
Musich et al. (78)	US	2019	RC	2016-2017	12	Administrative Claims Database	Medicare NHs	180,498	Elderly (≥65)	39.1
Rogero et al. (79)	US	2019	PC	2016-2017	6	Cohort with Ad Hoc Data Collection	Recorded by 5 fellowship-trained foot and ankle orthopedic surgeons	137	Adults and elderly (≥18)	14.0
Agarwalla et al. (80)	US	2020	RC	2008-2017	6	Administrative Claims Database	PearlDriver Program, Humana administrative claims database	7,204 (Fracture: 1,801; OA: 5,403)	*Unknown*	31.0
Young et al. (81)	US	2020	RC	2005-2015	12	Administrative Claims Database	Truven MarketScan database	331,322	Adults and elderly (≥18)	*Female only*

BWC: Bureau of Workers' Compensation; CC: Case-control; CPRD: Clinical Practice Research Datalink; CORRONA: Consortium of Rheumatology Researchers of North America; CSS: Cross-sectional study; CTBIE: Comprehensive Traumatic Brain Injury Evaluation; DANCOS: Danish National Cohort Study; EMRs: Electronic Medical Records; GH: Group Health; HES: Hospital Episode Statistics; IMS: Information Management System; KPNC: Kaiser Permanente Northern California; KPNW: Kaiser Permanente Northwest; MEPS: Medical Expenditure Panel Survey; NA: Non-applicable; NHs: National health service; NorPD: Norwegian Prescription Database; PC: Prospective cohort; RAMQ: *Régie de l'Assurance Maladie du Québec*; RC: Retrospective cohort; RPDR: Research Patient Data Registry; UK: United-Kingdom; US: United-States; VA: Veterans Affairs; VHA: Veterans Health Administration;*for male %, it represents studies including non-appropriate opioids as methadone and with no subgroup analysis). Studies in grey are the 21 studies included in the meta-analysis. †For studies including naloxone and/or treatments for opioid dependence (i.e., methadone and buprenorphine) but with subgroup analysis, the number of LTPO patients was calculated selecting only patients with appropriate intervention. *When the average sex ratio was reported by group, the estimate has been calculated as a weighted average (in %).

Quality assessment

The 21 studies included in the meta-analysis consisted of 16 cohort studies (22, 26, 28, 33, 45, 50-52, 57, 60, 64, 66, 69, 74, 75, 77), four CSS (29, 36, 56, 72) and one case control study (40). The overall risk of bias for these 21 studies was rated as low for ten studies (26, 33, 36, 56, 60, 66, 69, 72, 74, 75) and high for 11 studies (22, 28, 29, 40, 45, 50-52, 57, 64, 77) (Table 2; details of the quality assessment for each study are available in Table 4 of the Supplement). For 81.0% (17/21) of the studies, the validity of the exposure assessment (item 3) was considered uncertain as no details were found on the validity of codes used in claims databases or the gold standard used in other data sources (Figure 3). For the four cross-sectional studies, the reliability of LTPO use as an outcome (item 7) was considered to be "no" or uncertain because it was partially or not based on existing definition of LTPO use. For the only case-control study included, cases and controls were not matched appropriately (item 2) and hence, the two groups may not be comparable (40). For the 16 cohort studies, strategies to address incomplete follow-up (item 10) was considered to "not applicable" for 68.8% (11/16) of the studies because LTPO outcome assessment was closely related to follow-up and "no" for 18.8% (3/16) because the length of follow-up was not taken into account in the data analysis (Figure 3; details in Table 4 of the Supplement).

Table 2. Quality assessment by study using JBI critical appraisal tools (n=21)

		JBI Score											Study risk of bias
Study author	**Design**	1	2	3	4	5	6	7	8	9	10	11	
Buckley et al. 2015 (29)	CSS	Yes	Yes	UC	Yes	Yes	Yes	No	Yes	-	-	-	**High**
Lovejoy et al. 2016 (36)	CSS	Yes	Yes	UC	Yes	Yes	Yes	UC	Yes	-	-	-	**Low**
Chui et al. 2018 (56)	CSS	Yes	Yes	UC	Yes	Yes	Yes	UC	Yes	-	-	-	**Low**
Gibson et al. 2019 (72)	CSS	Yes	Yes	UC	Yes	Yes	Yes	UC	Yes	-	-	-	**Low**
Alghnam et al.2017 (40)	CC	No	No	Yes	Yes	Yes	Yes	Yes	UC	Yes	Yes	-	**High**
Richardson et al. 2012 (22)	RC	Yes	No	UC	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	**High**
Kulshrestha et al. 2014 (26)	PC	Yes	Yes	UC	Yes	Yes	UC	Yes	Yes	Yes	NA	Yes	**Low**
Anderson et al. 2015 (28)	RC	Yes	No	UC	Yes	Yes	No	Yes	Yes	UC	No	UC	**High**
Heins et al. 2016 (33)	RC	Yes	Yes	UC	Yes	Yes	UC	Yes	Yes	Yes	Yes	Yes	**Low**
Cicowski et al. 2017 (45)	RC	Yes	No	UC	Yes	Yes	No	Yes	Yes	UC	No	Yes	**High**
Adogwa et al. 2018 (51)	RC	Yes	Yes	UC	Yes	Yes	No	Yes	Yes	Yes	NA	Yes	**High**
Anciano et al. 2018 (52)	RC	UC	Yes	UC	Yes	Yes	No	Yes	Yes	Yes	NA	Yes	**High**
Fritz et al.2018 (57)	RC	Yes	No	UC	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	**High**
Thielke et al. 2017 (50)	RC	Yes	No	UC	UC	Yes	Yes	Yes	Yes	Yes	NA	Yes	**High**
Lalic et al. 2018 (60)	RC	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	**Low**
Thornton et al. 2018 (64)	RC	Yes	UC	UC	Yes	Yes	Yes	Yes	UC	Yes	NA	Yes	**High**
Barnett et al.2019 (66)	RC	Yes	Yes	UC	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	**Low**
Bennett et al.2019 (69)	RC	Yes	Yes	UC	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	**Low**
Harris et al. 2019 (74)	RC	Yes	Yes	UC	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	**Low**
Hedenmalm et al. 2019 (75)	RC	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	UC	No	Yes	**Low**
Lee et al. 2019 (77)	RC	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**High**

CC: Case-control; CSS: Cross-sectional study; NA: Non-applicable; PC: Prospective cohort; RC: Retrospective cohort; UC: Uncertain.

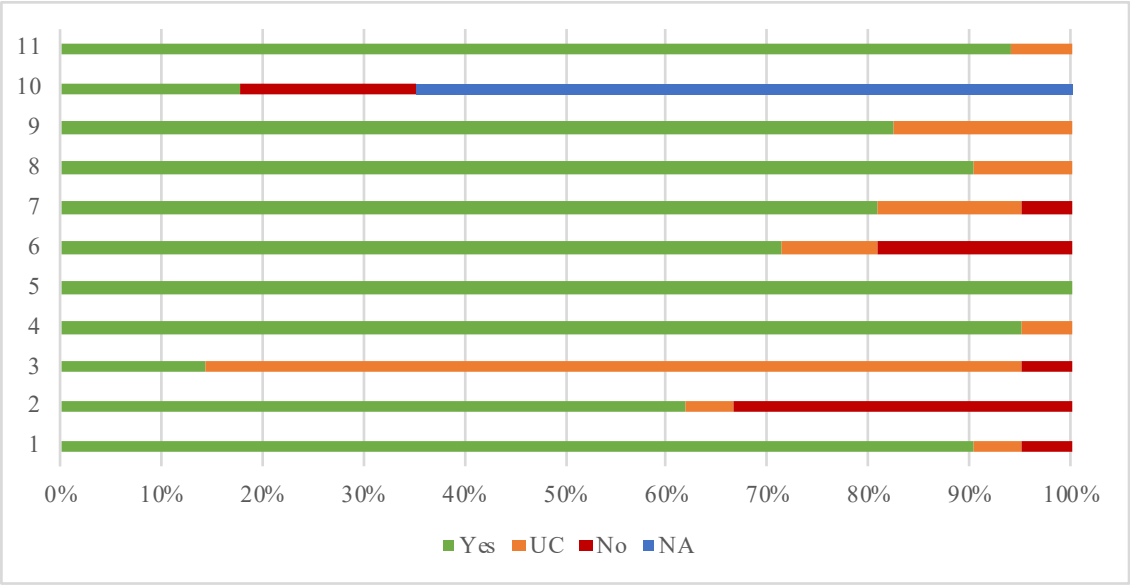

Figure 3. Risk of bias graphic with author's judgement for each JBI risk of bias item (1 to 11) presented as percentage across all included studies.
Author's judgement is presented in different colors: green "Yes"; orange "Uncertain"; red "No" and blue "Not applicable".

Long-term prescription opioid use incidence and definition

Results of the 64 studies included in the systematic review are summarized in the Table 5 of the Supplement. The primary objective of this systematic review was to estimate the incidence of LTPO use, and the secondary objective was to report the definitions used. Sixty studies reported incidence estimates, and four reported prevalence estimate instead (18, 36, 72, 77). Among patients who initiated a prescription opioid, the incidence of LTPO use ranged from 0.2 to 703.4 per 10,000 person-years (median: 41.6 per 10,000 person-years). In sub-populations, it ranged from 0.2 to 688.3 per 10,000 person-years for post-surgery patients (22 studies; median: 102.2), 3.0 to 387.1 for non-cancer chronic pain (15 studies; median: 26.6), 7.5 to 89.3 per 10,000 person-years for non-cancer acute pain or traumatic injuries (three studies; median: 27.7), 9.4 to 208.3 per 10,000 person-years for inflammatory disease (two studies; median: 129.3) and of 94.9 per 10,000 person-years for transplantation (one study). For four studies, incidence was calculated by subtracting patients with excluded opioid exposure (naloxone, methadone etc.) (23, 24, 37, 59).

The 64 studies reported a definition for LTPO use. In 23 (35.9%) studies, LTPO use was defined as ≥90 continuous or ≥120 cumulative days during 12 months of follow-up (18, 22, 23, 34, 36, 37, 39, 43-45, 47, 53, 56, 57, 59, 64-66, 68, 71-74). A total of 16 (25.0%) studies focused on the number of drug claims/prescriptions during follow-up (19, 21, 27, 29-33, 40-42, 48, 51, 63, 70, 78), 15 (23.4%) studies had a definition on opioid use remaining 1 to 12

months post-surgery (28, 35, 46, 49, 52, 54, 55, 61, 62, 67, 69, 76, 79-81) and three (4.7%) studies developed definitions on daily dose (20, 25) or serum concentration (38). The Lalic *et al*. study developed a trajectory model to determine persistent users. The remaining six (9.4%) studies had wider definitions (24, 26, 50, 58, 75, 77).

Factors associated with long-term opioid use

The 21 studies included in the meta-analysis represented 1,772,154 patients, and all reported an OR as the measure of association. Factors that were potentially associated with LTPO and thus included in the meta-analysis were classified into three groups: sociodemographic characteristics, patient characteristics with medical history and comorbidities and, potential indications for opioid treatment. These are called "potential" indications because they are mainly deduced from medical diagnoses competing with opioid prescription, particularly in claims databases.

Sociodemographic characteristics

These included: age as a continuous variable (seven studies; (22, 33, 36, 57, 64, 72, 74)) and sex with male (nine studies; (22, 29, 33, 51, 52, 60, 64, 69, 74)) and female (six studies; (36, 40, 56, 57, 75, 77)). Sex was not found to be a risk factor for LTPO (OR for female gender 1.04, 95% CI: 0.90-1.19; $p<0.05$, $I^2=68\%$; Supplementary Figure 1). Heterogeneity across studies was too high to pool estimates for age and male factors ($p<0.05$; $I^2= 95\%, 91\%$). In the subgroup of studies including patients from age groups mixed or unspecified (three studies;(22, 52, 64)), male sex was a risk factor for LTPO use (OR 1.51, 95% CI: 1.39-1.65) with no heterogeneity across studies ($p=0.46$, $I^2=0\%$).

Patient characteristics

These included: depression (10 studies; (28, 36, 40, 50, 52, 56, 57, 60, 66, 77)), anxiety (3 studies; (57, 66, 69)), other psychiatric disorders (nine studies; (22, 26, 29, 36, 56, 57, 60, 69, 72)), obesity (three studies; (52, 57, 72)), tobacco use (six studies; (26, 45, 52, 57, 60, 69)) and pre-existing substance use disorder (six studies; (26, 36, 52, 56, 57, 64)). Obesity and tobacco use were risk factors for LTPO use with OR of 1.32 (95% CI: 1.23-1.42; $p=0.31$, $I^2=14\%$; Figure 4) and 1.60 (95% CI: 1.42-1.80; $p<0.10$, $I^2=72\%$; Figure 4). Anxiety was also a risk factor for LTPO use with OR of 1.36 (95% CI: 1.14-1.61; $p=0.26$, $I^2=26\%$; Figure 4). In the subgroup of studies including patient from age groups mixed or unspecified (three studies;(22, 36, 72)), having other psychiatric disorder was a risk factor (OR 1.65, 95% CI:

1.40-1.95) with no heterogeneity across studies (p=0.25, I^2=28%). In the subgroup analysis of studies using a different LTPO definition from the one commonly used (four studies;(26, 29, 52, 60)), having other psychiatric disorder (OR 2.22, 95% CI: 1.82-2.70; p=0.14, I^2=49%) and pre-existing substance use disorder (OR 1.56, 95% CI: 1.00-2.42) were risk factors for LTPO use, with little heterogeneity across studies (p=0.23, I^2=30%).

Potential indications for opioid therapy

These included: back pain (six studies; (33, 45, 52, 66, 75)), injuries (5 studies; (29, 33, 40, 66, 75)), headache (five studies; (22, 29, 45, 52, 75)); fibromyalgia (two studies; (45, 52)), arthritis (five studies; (22, 52, 64, 69, 75)) and any other pain including severe pain, likely chronic pain and "any pain" (four studies, (64, 69, 75, 77)). Indication for "any pain" was a risk factor for LTPO use with odds ratio of 1.64 (95% CI: 1.39-1.95; p<0.10, I^2=75%; Figure 4), especially in the subgroup of low risk of bias studies (OR 1.43; 95% CI: 1.26-1.63; p=0.55, I^2=0%). Headache was not a significant risk factor (OR 1.18; 95% CI: 0.95-1.45; p<0.10, I^2=70%; Supplementary Figure 2). Back pain indication was significantly associated with LTPO use in the subgroup analysis of studies with female sex ratio over 50% (OR 1.30; 95% CI: 1.25-1.35; p=0.09, I^2=0%; two studies;(22, 45)) and using the definition commonly used (≥90 continuous or ≥120 cumulative days during 12 months) (OR 1.30; 95% CI: 1.25-1.35; p=0.71, I^2=0%; three studies;(22, 45, 66)). For other potential indication, statistical heterogeneity across the studies was too high for all factors ($p < 0.05$; I^2 >75%). According to subgroup analysis, heterogeneity was not due to study design or follow-up duration.

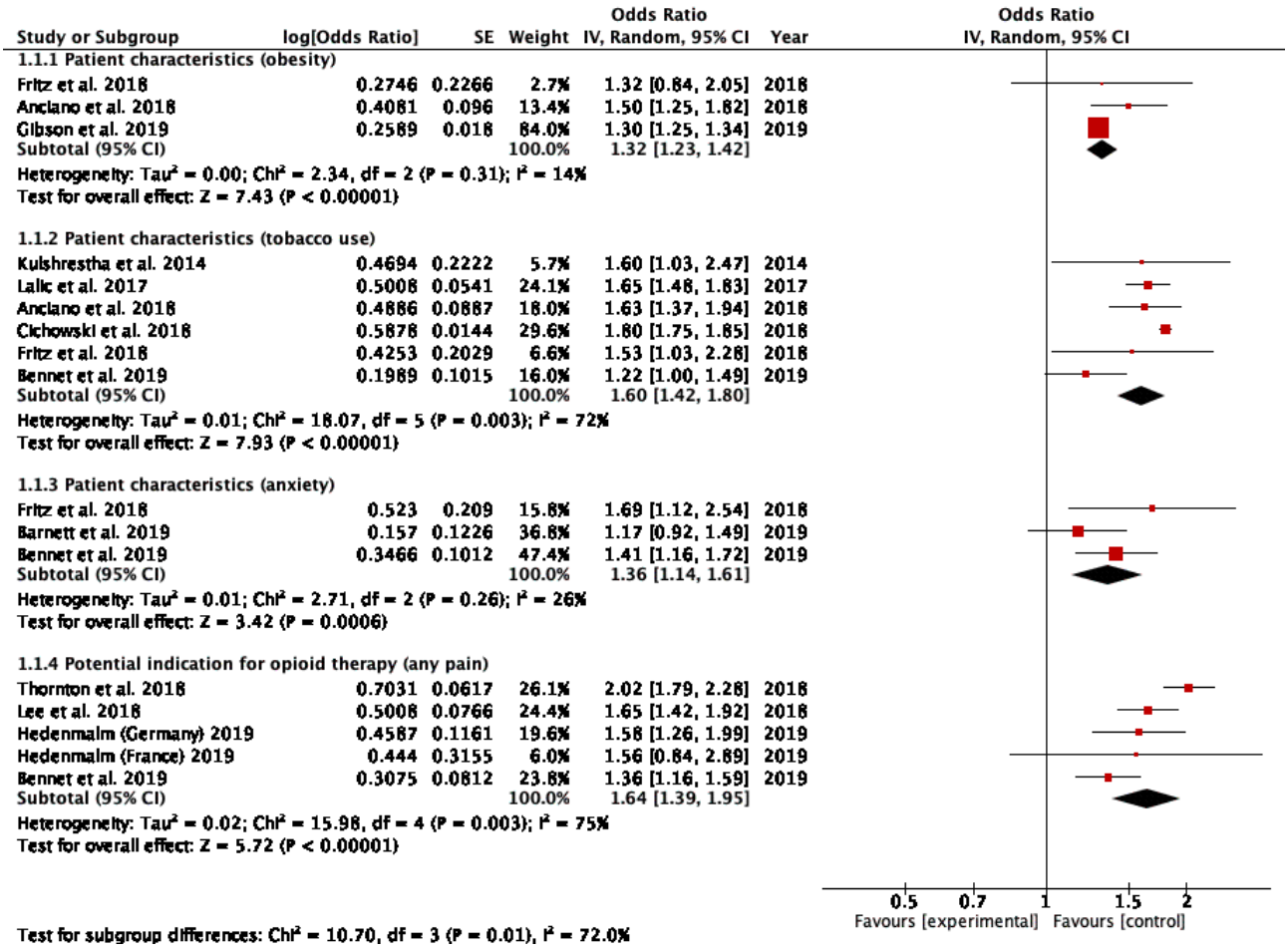

Figure 4. Forest plot of factors associated with LTPO use vs non-LTPO use (obesity, tobacco use, anxiety and potential indication for opioid therapy "any pain").
Odds Ratio (OR) calculated for individual observational studies with 95% confidence interval (CI) is presented; arrows indicate the CI exceeding the limits of the graph. An estimate of the weight of each observational study on pooled ORs is reported as a percentage and graphically (black square size); pooled OR is presented by a black diamond; statistical heterogeneity among studies was evaluated using Q statistic ($p<0.10$ considered significant), and the proportion of total variation contributed by between-study variance was estimated using I^2 index.

2.7. DISCUSSION

In this systematic review of 64 observational studies allows, the incidence of LTPO use was highly variable, ranging from 0.2 to 703.4 per 10,000 person-years (median: 41.6 per 10,000 person-years). Post-surgery patients were identified as those with the highest incidence, from 0.2 to 688.3 per 10,000 person-years (median: 102.2). More than 35% of studies used the most frequent definition for LTPO use, i.e., number of days supply of at least 90 continuous days or ≥120 cumulative days during 12 months of follow-up. Opioids can be prescribed on an as-needed basis, and to integrate cumulative days to the definition is aligned with clinical practice. The meta-analysis of 21 observational studies found an increased risk of LTPO use associated with obesity, tobacco use and anxiety. Prescribing opioids for "any pain" also increased the risk of LTPO use. In the subgroup analysis, heterogeneity across studies was mainly due to age groups, sex ratio and definition of LTPO use. Heterogeneity was highest across studies that used the most commonly used definition (≥90 continuous or ≥120 cumulative days during 12 months of follow-up). A possible explanation could be that the data management and programming requirements to implement this definition may differ.

The strengths of our study lie in five keys aspects. First, to our knowledge, this systematic review is the largest to synthetize estimates of incidence and definitions of LTPO use. The systematic review used data from 64 observational studies from 1993 to 2018 and pooled data of more than 8 million patients. Second, it covered a diverse population with patients included worldwide, across all age groups, from pediatrics to elderly patients and different settings for of opioid use (post-surgical, non-cancer chronic pain and acute pain, inflammatory diseases, transplantation etc.). Third, this meta-analysis is the first to study factors associated with LTPO use. Although strict inclusion criteria were used in the meta-analysis, 21 studies were included and 15 potential associated factors were assessed. Fourth, pooled ORs were available for six of these factors despite a strict rule to pool estimates. The choice to pool measures of association only when heterogeneity between the estimates was low or moderate (≤ 75%) ensures that the information disseminated on factors associated with LTPO outcome is reliable and robust. And finally, the quality of each study included was assessed according to JBI tools; eleven of the 21 studies presented a high risk of bias, but the pooled estimates were still significant or even higher when they were excluded.

Associated factors identified by the meta-analysis have a strong plausibility. Obesity and tobacco use associated with LTPO use are clinically plausible as both are comorbidities highly related to dependence. Both nicotine and opioids are able to increase levels of dopamine in discrete brain regions and nicotine pre-treatment has been shown to reinforce

morphine-induced dopamine release (83). Not surprisingly, pre-existing substance use disorder was also identified in the subgroup analyses. For anxiety, it is known that anxiety or a psychiatric diagnosis lead to poorer pain management diagnoses, which can explain a longer duration of opioid use (84). Furthermore, the prevalence of anxiety in chronic pain patients is higher than in the general population (85, 86). According to an Israeli study, mood disorders double the risk of opioid addiction or misuse (OR: 2.18; 95% CI: 1.37-4.17), so one should be prudent when prescribing opioids to anxious people (86). Finally, the finding of "any pain" indication as an associated factor reinforces that opioid prescription outside of chronic cancer pain may be at risk. This is further supported by the factor identified in the subgroup analysis: opioid prescribed for back pain in studies including mainly women and rated as low risk of bias.

Finally, the study had some limitations that may affect the interpretation of results. First, only 32.8% (21/64) of studies could be included in the meta-analysis. Nevertheless, this represents over 1 million patients and the two main reasons for exclusion were descriptive analysis or inappropriate comparator group for 65.1% of studies (28/43). Second, even if measures of association included in the meta-analysis were only derived from adjusted models to reduce potential confounding, level of adjustment differed for each study and residual confounding may remain. Third, a strict rule was used for pooling estimates in the meta-analysis, it was not performed when heterogeneity across studies was high. This avoids presenting results potentially biased by heterogeneity, but limits the amount of results reported. Important heterogeneity between studies in meta-analysis of observational studies is well known (87). Fourth, most of the studies included in our meta-analysis collected data from data claims or electronic medical records (EMRs). These data do not distinguish between what is prescribed or dispensed from what is actually administered to the patient, especially as-needed opioids for pain treatment.

2.8. CONCLUSION

This study revealed a variable heterogeneity in the incidence of long-term prescription opioid use all over the world, with the highest in post-surgical patients. The identification of associated factors including obesity, tobacco use, anxiety and potential indication of “any pain”, may be used to identify which patients will likely progress to LTPO use. This could be used as a decision-making tool for clinicians when initiating or continuing treatment. It is also important to consider the balance between “not to let a patient suffer” and the opioid-related harms s/he will be exposed to. That balance needs to be continually reassessed and adjusted.

2.9. ARTICLE REFERENCES

1. Opioid users worldwide number by region 2015-2016 | Statistic [Available from: https://www.statista.com/statistics/721265/number-of-worldwide-users-of-opioids-by-region/.

2. Global Opioid Consumption. Pain & Policy Studies Group, University of Wisconsin/WHO Collaborating Center; 2015 2018/11/30.

3. Fischer B, Rehm J, Tyndall M. Effective Canadian policy to reduce harms from prescription opioids: learning from past failures. CMAJ : Canadian Medical Association Journal. 2016;188(17-18):1240-4.

4. Manjiani D, Paul DB, Kunnumpurath S, Kaye AD, Vadivelu N. Availability and Utilization of Opioids for Pain Management: Global Issues. The Ochsner Journal. 2014;14(2):208-15.

5. Availability of Internationally Controlled Drugs: Ensuring Adequate Access for Medical and Scientific Purposes. International Narcotics Control Board, United Nations; 2011 2018/12/06.

6. Lalic S, Gisev N, Bell JS, Korhonen MJ, Ilomäki J. Predictors of persistent prescription opioid analgesic use among people without cancer in Australia. British Journal of Clinical Pharmacology. 2018;84(6):1267-78.

7. Utilisation des opioïdes forts dans la douleur chronique non cancéreuse chez l'adulte. Société Française d'Evaluation et de Traitement de la Douleur; 2016 2018/11/08.

8. CDC Guideline for Prescribing Opioids for Chronic Pain, Drug Overdose CDC Injury Center; 2018. Contract No.: 2018/12/06.

9. WHO. Troubles liés à l'utilisation de substances psychoactives [Available from: http://www.who.int/substance_abuse/terminology/definition4/fr/.

10. Canadian Institute for Health I. Hospitalisations liées aux réactions indésirables aux médicaments chez les personnes âgées, de 2006 à 2011. 2013 2018/11/07/20:44:34.

11. WHO. Information sheet on opioid overdose [Available from: http://www.who.int/substance_abuse/information-sheet/en/

https://www.who.int/substance_abuse/information-sheet/en/.

12. Bekkering GE, Soares-Weiser K, Reid K, Kessels AG, Dahan A, Treede RD, et al. Can morphine still be considered to be the standard for treating chronic pain? A systematic review including pair-wise and network meta-analyses. Current Medical Research and Opinion. 2011;27(7):1477-91.

13. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015;350:g7647.

14. Joanna Briggs I. Critical Appraisal Tools - JBI [Available from: http://joannabriggs.org/research/critical-appraisal-tools.html.

15. DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled Clinical Trials. 1986;7(3):177-88.

16. Cochran WG. The comparison of percentages in matched samples. Biometrika. 1950;37(3-4):256-66.

17. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557-60.

18. Boudreau D, Von Korff M, Rutter CM, Saunders K, Ray GT, Sullivan MD, et al. Trends in long-term opioid therapy for chronic non-cancer pain. Pharmacoepidemiology & Drug Safety. 2009;18(12):1166-75.

19. Deyo RA, Smith DH, Johnson ES, Donovan M, Tillotson CJ, Yang X, et al. Opioids for back pain patients: primary care prescribing patterns and use of services. Journal of the American Board of Family Medicine: JABFM. 2011;24(6):717-27.

20. Skurtveit S, Furu K, Borchgrevink P, Handal M, Fredheim O. To what extent does a cohort of new users of weak opioids develop persistent or probable problematic opioid use? Pain. 2011;152(7):1555-61.

21. Alam A, Gomes T, Zheng H, Mamdani MM, Juurlink DN, Bell CM. Long-term analgesic use after low-risk surgery: a retrospective cohort study. Archives of Internal Medicine. 2012;172(5):425-30.

22. Richardson LP, Russo JE, Katon W, McCarty CA, DeVries A, Edlund MJ, et al. Mental health disorders and long-term opioid use among adolescents and young adults with chronic pain. Journal of Adolescent Health. 2012;50(6):553-8.

23. Dobscha SK, Morasco BJ, Duckart JP, Macey T, Deyo RA. Correlates of prescription opioid initiation and long-term opioid use in veterans with persistent pain. Clinical Journal of Pain. 2013;29(2):102-8.

24. Chevalier P, Smulders M, Chavoshi S, Sostek M, LoCasale R. A description of clinical characteristics and treatment patterns observed within prescribed opioid users in Germany and the UK. Pain Management. 2014;4(4):267-76.

25. Fredheim OM, Mahic M, Skurtveit S, Dale O, Romundstad P, Borchgrevink PC. Chronic pain and use of opioids: a population-based pharmacoepidemiological study from the Norwegian prescription database and the Nord-Trondelag health study. Pain. 2014;155(7):1213-21.

26. Kulshrestha S, Barrantes F, Samaniego M, Luan FL. Chronic opioid analgesic usage post-kidney transplantation and clinical outcomes. Clinical Transplantation. 2014;28(9):1041-6.

27. Morden NE, Munson JC, Colla CH, Skinner JS, Bynum JP, Zhou W, et al. Prescription opioid use among disabled Medicare beneficiaries: intensity, trends, and regional variation. Medical Care. 2014;52(9):852-9.

28. Anderson JT, Haas AR, Percy R, Woods ST, Ahn UM, Ahn NU. Chronic Opioid Therapy After Lumbar Fusion Surgery for Degenerative Disc Disease in a Workers' Compensation Setting. Spine. 2015;40(22):1775-84.

29. Buckley JP, Cook SF, Allen JK, Kappelman MD. Prevalence of chronic narcotic use among children with inflammatory bowel disease. Clinical Gastroenterology & Hepatology. 2015;13(2):310-5.e2.

30. Halbert B, Chiodi SN, Davis RB, Wee CC. Opioid use with mental health disorders: Are we over-prescribing? Journal of General Internal Medicine. 2015;2):S216-S7.

31. Al Dabbagh Z, Jansson KA, Stiller CO, Montgomery S, Weiss RJ. Long-term pattern of opioid prescriptions after femoral shaft fractures. Acta Anaesthesiologica Scandinavica. 2016;60(5):634-41.

32. Bedson J, Chen Y, Hayward RA, Ashworth J, Walters K, Dunn KM, et al. Trends in long-term opioid prescribing in primary care patients with musculoskeletal conditions: an observational database study. Pain. 2016;157(7):1525-31.

33. Heins SE, Feldman DR, Bodycombe D, Wegener ST, Castillo RC. Early opioid prescription and risk of long-term opioid use among US workers with back and shoulder injuries: a retrospective cohort study. Injury Prevention. 2016;22(3):211-5.

34. Inacio MC, Hansen C, Pratt NL, Graves SE, Roughead EE. Risk factors for persistent and new chronic opioid use in patients undergoing total hip arthroplasty: a retrospective cohort study. BMJ Open. 2016;6(4):e010664.

35. Kim KY, Anoushiravani AA, Chen KK, Roof M, Long WJ, Schwarzkopf R. Preoperative Chronic Opioid Users in Total Knee Arthroplasty-Which Patients Persistently Abuse Opiates Following Surgery? Journal of Arthroplasty. 2018;33(1):107-12.

36. Lovejoy TI, Dobscha SK, Turk DC, Weimer MB, Morasco BJ. Correlates of prescription opioid therapy in Veterans with chronic pain and history of substance use disorder. Journal of Rehabilitation Research & Development. 2016;53(1):25-36.

37. Mudumbai SC, Oliva EM, Lewis ET, Trafton J, Posner D, Mariano ER, et al. Time-to-Cessation of Postoperative Opioids: A Population-Level Analysis of the Veterans Affairs Health Care System. Pain Medicine. 2016;17(9):1732-43.

38. Sani AR, Zin CS, Noor ZM, Mohamed AH, Nissen LM. Differential patterns of persistent opioid use in patients with cancer and non-cancer pain. Value in Health. 2016;19 (7):A814.

39. Smolina K, Gladstone EJ, Rutherford K, Morgan SG. Patterns and trends in long-term opioid use for non-cancer pain in British Columbia, 2005-2012. Canadian Journal of Public Health Revue Canadienne de Sante Publique. 2016;107(4-5):e404-e9.

40. Alghnam S, Castillo R. Traumatic injuries and persistent opioid use in the USA: findings from a nationally representative survey. Injury Prevention. 2017;23(2):87-92.

41. Anthony CA, Westermann RW, Bedard N, Glass N, Bollier M, Hettrich CM, et al. Opioid Demand Before and After Anterior Cruciate Ligament Reconstruction. American Journal of Sports Medicine. 2017;45(13):3098-103.

42. Birke H, Ekholm O, Sjogren P, Kurita GP, Hojsted J. Long-term opioid therapy in Denmark: A disappointing journey. European Journal of Pain. 2017;21(9):1516-27.

43. Callinan CE, Neuman MD, Lacy KE, Gabison C, Ashburn MA. The Initiation of Chronic Opioids: A Survey of Chronic Pain Patients. Journal of Pain. 2017;18(4):360-5.

44. Chen S, Feldman CH, Brill G, Lee YC, Desai RJ, Kim SC. Use of prescription opioids among patients with systemic inflammatory diseases (SID) versus patients with hypertension but no SID. Arthritis and Rheumatology Conference: American College of Rheumatology/Association of Rheumatology Health Professionals Annual Scientific Meeting, ACR/ARHP. 2017;69(Supplement 10).

45. Cichowski S, Rogers R, Murata A, Murata E, Murata G. A 10 year analysis of chronic pelvic pain (CPP) and chronic narcotic use (CNU) in the female veteran population. Obstetrics and Gynecology. 2017;129 (Supplement 1):83S-4S.

46. Connolly J, 3rd, Javed Z, Raji MA, Chan W, Kuo YF, Baillargeon J. Predictors of Long-term Opioid Use Following Lumbar Fusion Surgery. Spine. 2017;42(18):1405-11.

47. Deyo RA, Hallvik SE, Hildebran C, Marino M, Dexter E, Irvine JM, et al. Association Between Initial Opioid Prescribing Patterns and Subsequent Long-Term Use Among Opioid-Naive Patients: A Statewide Retrospective Cohort Study. Journal of General Internal Medicine. 2017;32(1):21-7.

48. Shah A, Hayes CJ, Martin BC. Factors Influencing Long-Term Opioid Use Among Opioid Naive Patients: An Examination of Initial Prescription Characteristics and Pain Etiologies. Journal of Pain. 2017;18(11):1374-83.

49. Stark N, Kerr S, Stevens J. Prevalence and predictors of persistent post-surgical opioid use: a prospective observational cohort study. Anaesthesia & Intensive Care. 2017;45(6):700-6.

50. Thielke SM, Shortreed SM, Saunders K, Turner JA, LeResche L, Von Korff M. A Prospective Study of Predictors of Long-term Opioid Use Among Patients With Chronic Noncancer Pain. Clinical Journal of Pain. 2017;33(3):198-204.

51. Adogwa O, Davison MA, Vuong VD, Desai SA, Lilly DT, Moreno J, et al. Regional Variation in Opioid Use After Lumbar Spine Surgery. World Neurosurgery. 2018.

52. Anciano Granadillo V, Cancienne JM, Gwathmey FW, Werner BC. Perioperative Opioid Analgesics and Hip Arthroscopy: Trends, Risk Factors for Prolonged Use, and Complications. Arthroscopy. 2018;34(8):2359-67.

53. Bertenthal D, Yaffe K, Barnes DE, Byers AL, Gibson CJ, Seal KH, et al. Do postconcussive symptoms from traumatic brain injury in combat veterans predict risk for receiving opioid therapy for chronic pain? Brain Injury. 2018;32(10):1188-96.

54. Bolarinwa S, Casp AA, Cancienne JM, Werner BC, Browne JA. Narcotic use and total hip arthroplasty. HIP International. 2018.

55. Cancienne JM, Patel KJ, Browne JA, Werner BC. Narcotic Use and Total Knee Arthroplasty. Journal of Arthroplasty. 2018;33(1):113-8.

56. Chui PW, Bastian LA, DeRycke E, Brandt CA, Becker WC, Goulet JL. Dual Use of Department of Veterans Affairs and Medicare Benefits on High-Risk Opioid Prescriptions in Veterans Aged 65 Years and Older: Insights from the VA Musculoskeletal Disorders Cohort. Health Services Research. 2018;53 Suppl 3:5402-18.

57. Fritz JM, King JB, McAdams-Marx C. Associations Between Early Care Decisions and the Risk for Long-term Opioid Use for Patients With Low Back Pain With a New Physician Consultation and Initiation of Opioid Therapy. Clinical Journal of Pain. 2018;34(6):552-8.

58. Hernandez NM, Parry JA, Mabry TM, Taunton MJ. Patients at Risk: Preoperative Opioid Use Affects Opioid Prescribing, Refills, and Outcomes After Total Knee Arthroplasty. Journal of Arthroplasty. 2018;33(7S):S142-S6.

59. Hunnicutt JN, Chrysanthopoulou SA, Ulbricht CM, Hume AL, Tjia J, Lapane KL. Prevalence of Long-Term Opioid Use in Long-Stay Nursing Home Residents. Journal of the American Geriatrics Society. 2018;66(1):48-55.

60. Lalic S, Gisev N, Bell JS, Korhonen MJ, Ilomaki J. Predictors of persistent prescription opioid analgesic use among people without cancer in Australia. British Journal of Clinical Pharmacology. 2018;84(6):1267-78.

61. Politzer CS, Kildow BJ, Goltz DE, Green CL, Bolognesi MP, Seyler TM. Trends in Opioid Utilization Before and After Total Knee Arthroplasty. Journal of Arthroplasty. 2018;33(7S):S147-S53.e1.

62. Steiner SRH, Cancienne JM, Werner BC. Narcotics and Knee Arthroscopy: Trends in Use and Factors Associated With Prolonged Use and Postoperative Complications. Arthroscopy. 2018;34(6):1931-9.

63. Taqi A, Otete H, Knaggs R. Opioid prescription patterns in UK primary care patients with knee osteoarthritis: A population-based study. Pharmacoepidemiology and Drug Safety. 2018;27 (Supplement 2):324-5.

64. Thornton JD, Dwibedi N, Scott V, Ponte CD, Ziedonis D, Sambamoorthi N, et al. Predictors of Transitioning to Incident Chronic Opioid Therapy Among Working-Age Adults in the United States. American Health & Drug Benefits. 2018;11(1):12-21.

65. Barham DW, McMann LP, Musser JE, Schisler JQ, Speir RW, Olcese SP, et al. Routine Prescription of Opioids for Post-Vasectomy Pain Control Associated with Persistent Use. The Journal of urology. 2019;202(4):806-10.

66. Barnett ML, Zhao X, Fine MJ, Thorpe CT, Sileanu FE, Cashy JP, et al. Emergency Physician Opioid Prescribing and Risk of Long-term Use in the Veterans Health Administration: an Observational Analysis. Journal of general internal medicine. 2019;34(8):1522-9.

67. Basilico M, Bhashyam AR, Harris MB, Heng M. Prescription Opioid Type and the Likelihood of Prolonged Opioid Use After Orthopaedic Surgery. The Journal of the American Academy of Orthopaedic Surgeons. 2019;27(9):e423-e9.

68. Beliveau A, Castilloux AM, Tanenbaum C, Vincent P, De Moura CS, Bernatsky S, et al. Incidence of chronic opioid use in seniors. Pharmacoepidemiology and Drug Safety. 2019;28(Supplement 2):329.

69. Bennett KG, Kelley BP, Vick AD, Lee JS, Gunaseelan V, Brummett CM, et al. Persistent Opioid Use and High-Risk Prescribing in Body Contouring Patients. Plastic and reconstructive surgery. 2019;143(1):87-96.

70. Birke H, Ekholm O, Sjogren P, Fredheim O, Clausen T, Skurtveit S. Tramadol use in Norway: A register-based population study. Pharmacoepidemiology and drug safety. 2019;28(1):54-61.

71. Desai RJ, Jin Y, Franklin PD, Lee YC, Bateman BT, Lii J, et al. Association of Geography and Access to Health Care Providers With Long-Term Prescription Opioid Use in Medicare Patients With Severe Osteoarthritis: A Cohort Study. Arthritis & rheumatology (Hoboken, NJ). 2019;71(5):712-21.

72. Gibson CJ, Li Y, Huang AJ, Rife T, Seal KH. Menopausal Symptoms and Higher Risk Opioid Prescribing in a National Sample of Women Veterans with Chronic Pain. Journal of general internal medicine. 2019;34(10):2159-66.

73. Goplen CM, Randall JR, Kang SH, Vakilian F, Jones CA, Voaklander DC, et al. The Influence of Allowable Refill Gaps on Detecting Long-Term Opioid Therapy: An Analysis of Population-Based Administrative Dispensing Data Among Patients with Knee Arthritis Awaiting Total Knee Arthroplasty. Journal of managed care & specialty pharmacy. 2019;25(10):1064-72.

74. Harris RA, Kranzler HR, Chang K-M, Doubeni CA, Gross R. Long-term use of hydrocodone vs. oxycodone in primary care. Drug and alcohol dependence. 2019;205:107524.

75. Hedenmalm K, Slattery J, Skibicka-Stepien I, Kurz X, Morales D. Prescribing patterns of tramadol in adults in IMS primary care databases in France and Germany between 1 January 2006 and 30 June 2016. European journal of clinical pharmacology. 2019;75(5):707-16.

76. Hirji SA, Landino S, Cote C, Lee J, Orhurhu V, Shah RM, et al. Chronic opioid use after coronary bypass surgery. Journal of cardiac surgery. 2019;34(2):67-73.

77. Lee YC, Kremer J, Guan H, Greenberg J, Solomon DH. Chronic Opioid Use in Rheumatoid Arthritis: Prevalence and Predictors. Arthritis & rheumatology (Hoboken, NJ). 2019;71(5):670-7.

78. Musich S, Wang SS, Slindee L, Kraemer S, Yeh CS. Characteristics associated with transition from opioid initiation to chronic opioid use among opioid-naive older adults. Geriatric nursing (New York, NY). 2019;40(2):190-6.

79. Rogero R, Fuchs D, Nicholson K, Shakked RJ, Winters BS, Pedowitz DI, et al. Postoperative Opioid Consumption in Opioid-Naive Patients Undergoing Hallux Valgus Correction. Foot & ankle international. 2019;40(11):1267-72.

80. Agarwalla A, Liu JN, Gowd AK, Amin NH, Werner BC. Differential Use of Narcotics in Total Hip Arthroplasty: A Comparative Matched Analysis Between Osteoarthritis and Femoral Neck Fracture. The Journal of arthroplasty. 2020;35(2):471-6.

81. Young JC, Wu JM, Willis-Gray M, Pate V, Jonsson Funk M. Persistent Opioid Use After Hysterectomy in the United States, 2005-2015. Obstetrics and gynecology. 2020;135(1):123-32.

82. Bolarinwa SA, Casp AA, Cancienne JM, Werner BC, Browne JA. Narcotic use and total hip arthroplasty. Hip international : the journal of clinical and experimental research on hip pathology and therapy. 2019;29(4):379-84.

83. Skurtveit S, Furu K, Selmer R, Handal M, Tverdal A. Nicotine dependence predicts problematic use of prescribed opioids. Prospective population based cohort study. Pharmacoepidemiology and Drug Safety (PDS). 2009;18 (S1):S246.

84. Hooten WM. Chronic Pain and Mental Health Disorders: Shared Neural Mechanisms, Epidemiology, and Treatment. Mayo Clin Proc. 2016;91(7):955-70.

85. Wasan AD, Michna E, Edwards RR, Katz JN, Nedeljkovic SS, Dolman AJ, et al. Psychiatric Comorbidity Is Associated Prospectively with Diminished Opioid Analgesia and Increased Opioid Misuse in Patients with Chronic Low Back Pain. Anesthesiology. 2015;123(4):861-72.

86. Feingold D, Brill S, Goor-Aryeh I, Delayahu Y, Lev-Ran S. Misuse of prescription opioids among chronic pain patients suffering from anxiety: A cross-sectional analysis. Gen Hosp Psychiatry. 2017;47:36-42.

87. Metelli S, Chaimani A. Challenges in meta-analyses with observational studies. Evid Based Ment Health. 2020;23(2):83-7.

3. CONCLUSION GENERALE

La revue systématique a permis de rapporter une incidence importante de la prescription d'opioïdes à long terme dans le monde entier, en particulier chez les patients en post-chirurgie. L'identification de facteurs associés comme l'obésité, le tabagisme, l'anxiété et la prescription pour indication "douleur non caractérisée" pourrait-être utilisée afin de prédire quels patients passeront le plus souvent à prescription d'opioïdes à long terme. Intégrer ces facteurs dans la pratique, en tant qu'outil de décision pour les prescripteurs au moment d'initier ou de poursuivre un traitement par opioïdes, pourrait contribuer à prévenir la progression vers la prescription à long-terme et ses conséquences. Il est également important de garder à l'esprit cet équilibre entre : "ne pas laisser un patient souffrir" et les méfaits liés aux opioïdes auxquels on l'expose. Un équilibre qui doit être constamment révisé et ajusté.

Les antalgiques opioïdes sont identités mondialement comme le traitement efficace et peu couteux de prise en charge de la douleur. Une enquête réalisée par l'OMS dans 81 pays et 25 états indiens, révèle cependant qu'il reste dans certains pays émergeants des difficultés de prise en charge médicamenteuse de la douleur (31). L'OMS estime que 5 billions de personnes dans le monde ont peu ou pas d'accès aux antalgiques opioïdes (31).

BIBLIOGRAPHIE

1. Douleur [Internet]. Inserm - La science pour la santé. [cité 3 sept 2020]. Disponible sur: https://www.inserm.fr/information-en-sante/dossiers-information/douleur

2. Stoelting RK, Hillier SC. Pharmacology and Physiology in Anesthetic Practice. Lippincott Williams & Wilkins; 2012. 2828 p.

3. Gomas JM. Petite histoire de la douleur et de la morphine... ... Ou tout ce que vous avez toujours voulu savoir sur l histoire des antalgiques et de la douleur sans oser le demander... ! 2004;(2):8.

4. atlas des plantes de france de a masclef - AbeBooks [Internet]. [cité 5 sept 2020]. Disponible sur: https://www.abebooks.fr/rechercher-livre/titre/atlas-des-plantes-de-france/auteur/a-masclef/

5. Committee Report No. 6 - HESA (42-1) - House of Commons of Canada [Internet]. [cité 4 sept 2020]. Disponible sur: https://www.ourcommons.ca/DocumentViewer/en/42-1/HESA/report-6/

6. International Narcotics Control Board, éditeur. Report of the International Narcotics Control Board on the Availability of Internationally Controlled Drugs: Ensuring Adequate Access for Medical and Scientific Purposes. New York: United Nations; 2011. 74 p.

7. Cancer pain relief. 1st impr., repr. Geneva: WHO; 1987. 74 p.

8. Opioid users worldwide number by region 2015-2016 | Statistic [Internet]. Statista. [cité 30 nov 2018]. Disponible sur: https://www.statista.com/statistics/721265/number-of-worldwide-users-of-opioids-by-region/

9. Pain and Policy Studies Group: Two Decades of Working to Address Regulatory Barriers to Improve Opioid Availability and Accessibility Around the World - Journal of Pain and Symptom Management [Internet]. [cité 5 sept 2020]. Disponible sur: https://www.jpsmjournal.com/article/S0885-3924(17)30373-1/fulltext

10. Manjiani D, Paul DB, Kunnumpurath S, Kaye AD, Vadivelu N. Availability and Utilization of Opioids for Pain Management: Global Issues. Ochsner J. 2014;14(2):208-15.

11. Fischer B, Rehm J, Tyndall M. Effective Canadian policy to reduce harms from prescription opioids: learning from past failures. CMAJ Can Med Assoc J. 6 déc 2016;188(17-18):1240-4.

12. Opioïdes d'ordonnance (Sommaire canadien sur la drogue) | Centre canadien sur les dépendances et l'usage de substances [Internet]. [cité 5 sept 2020]. Disponible sur: https://www.ccsa.ca/fr/opioides-dordonnance-sommaire-canadien-sur-la-drogue

13. Etat des lieux de la consommation des antalgiques opioïdes et leurs usages problematiques. :52.

14. DGOS. La douleur [Internet]. Ministère des Solidarités et de la Santé. 2020 [cité 3 sept 2020]. Disponible sur: https://solidarites-sante.gouv.fr/soins-et-maladies/prises-en-charge-specialisees/douleur/article/la-douleur

15. LOI n° 2002-303 du 4 mars 2002 relative aux droits des malades et à la qualité du système de santé. 2002-303 mars 4, 2002.

16. United Nations Treaty Collection [Internet]. [cité 4 sept 2020]. Disponible sur: https://treaties.un.org/pages/ViewDetails.aspx?src=TREATY&mtdsg_no=VI-15&chapter=6&clang=_fr

17. DGOS. Douleur : l'action des pouvoirs publics [Internet]. Ministère des Solidarités et de la Santé. 2020 [cité 5 sept 2020]. Disponible sur: https://solidarites-sante.gouv.fr/soins-et-maladies/prises-en-charge-specialisees/douleur/article/douleur-l-action-des-pouvoirs-publics

18. OMS | Troubles liés à l'utilisation de substances psychoactives [Internet]. WHO. [cité 30 nov 2018]. Disponible sur: http://www.who.int/substance_abuse/terminology/definition4/fr/

19. Lalic S, Gisev N, Bell JS, Korhonen MJ, Ilomäki J. Predictors of persistent prescription opioid analgesic use among people without cancer in Australia. Br J Clin Pharmacol. 2018;84(6):1267-78.

20. Ripamonti CI, Santini D, Maranzano E, Berti M, Roila F, ESMO Guidelines Working Group. Management of cancer pain: ESMO Clinical Practice Guidelines. Ann Oncol Off J Eur Soc Med Oncol. oct 2012;23 Suppl 7:vii139-154.

21. recos_opioides_forts_sfetd_version_longue.compressed.pdf [Internet]. [cité 4 sept 2020]. Disponible sur: https://www.sfetd-douleur.org/wp-content/uploads/2019/06/recos_opioides_forts_sfetd_version_longue.compressed.pdf

22. CDC Guideline for Prescribing Opioids for Chronic Pain | Drug Overdose | CDC Injury Center [Internet]. 2019 [cité 5 sept 2020]. Disponible sur: https://www.cdc.gov/drugoverdose/prescribing/guideline.html

23. Hospitalisations liées aux réactions indésirables aux médicaments chez les personnes âgées, de 2006 à 2011. 2006;26.

24. Opioid overdose [Internet]. [cité 5 sept 2020]. Disponible sur: https://www.who.int/news-room/fact-sheets/detail/opioid-overdose

25. Bekkering GE, Soares-Weiser K, Reid K, Kessels AG, Dahan A, Treede RD, et al. Can morphine still be considered to be the standard for treating chronic pain? A systematic review including pair-wise and network meta-analyses. Curr Med Res Opin. juill 2011;27(7):1477-91.

26. Research C for DE and. Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS). FDA [Internet]. 29 avr 2019 [cité 5 sept 2020]; Disponible sur: https://www.fda.gov/drugs/information-drug-class/opioid-analgesic-risk-evaluation-and-mitigation-strategy-rems

27. Canada H. Submission of targeted risk management plans and follow-up commitments for prescription opioid-containing products - Guidance for industry - Summary [Internet]. aem. 2018 [cité 4 sept 2020]. Disponible sur: https://www.canada.ca/en/health-canada/services/drugs-health-products/reports-publications/medeffect-canada/submission-targeted-rm-plans-commitments-prescription-opioid-containing-products-guidance-industry.html

28. L'ANSM publie la liste des médicaments contenant de la codéine, du dextrométhorphane, de l'éthylmorphine ou de la noscapine désormais disponibles uniquement sur ordonnance - Point d'Information - ANSM : Agence nationale de sécurité du médicament et des produits de santé [Internet]. [cité 6 déc 2018]. Disponible sur: https://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/L-ANSM-publie-la-liste-des-medicaments-contenant-de-la-codeine-du-dextromethorphane-de-l-ethylmorphine-ou-de-la-noscapine-desormais-disponibles-uniquement-sur-ordonnance-Point-d-Information

29. Widening the availability of naloxone [Internet]. GOV.UK. [cité 6 déc 2018]. Disponible sur: https://www.gov.uk/government/publications/widening-the-availability-of-naloxone/widening-the-availability-of-naloxone

30. Edlund MJ, Martin BC, Fan M-Y, Devries A, Braden JB, Sullivan MD. Risks for opioid abuse and dependence among recipients of chronic opioid therapy: results from the TROUP study. Drug Alcohol Depend. 1 nov 2010;112(1-2):90-8.

31. UICC_Palliative_Care_backgrounder_Nov2013.pdf [Internet]. [cité 4 sept 2020]. Disponible sur: https://www.esmo.org/content/download/30697/609667/file/UICC_Palliative_Care_backgrounder_Nov2013.pdf

ANNEXES (*SUPPLEMENTARY FILE*)

TABLES

Table 1. Concepts plan and full search strategy used in MEDLINE and EMBASE.

Concept	Description du concept	Mots-clés et MeSH	Énoncés de recherche (Indiquer si PubMed, Medline, EMBASE)	Notes
			MEDLINE (OVID)	EMBASE
A	**Population**			
A1	Population non cancéreuse	*Non cancer*	(non-cancer* OR noncancer* OR "without cancer" OR non-malignant* OR cancer-free OR non-tumor*).ti,ab,kw.	OK
A2		*Non-cancer pain*	((pain/exp not "cancer pain"/exp) or "Pain Management"/ or pain.ti,ab.) or ("headache disorders"/ or "Arthritis"/ or "Diabetic Neuropathies"/ or "Inflammatory Bowel Diseases"/ or "Perioperative Period"/) or (rachialgia or neuralgia or cephalgia or fibromyalgia or myasthenia or polymyalgia or knee or hip or ankle or elbow or hand or arthritis or "rheumatoid arthritis" or gonarthrosis or osteomyelitis or postherpetic or phantom or neuropath* or polyneuropath* or musculoskeletal or "globus syndrome" or pancreatitis or "irritable bowel" or "irritable colon" or "reflex sympathetic dystrophy" or surgery or surgical or postsurgical or injury* or trauma or dental or "tooth extraction").ti,ab,kw.	
A3		*Other indication(s)*	(anesthesia OR cough* OR diarrhea).ti,ab,kw.	OK
B	**Intervention**			
B1		Opioid	("Analgesics, Opioid"/exp or Narcotics/exp or "Opiate Alkaloids"/exp or Morphinans/exp) or (opioid* or opioate* or narcotic* or morphine or ethylmorphine or opium or hydromorphone or levorphanol or oxycodone or codeine or dihydrocodeine or tramadol or tapentadol or pethidine or meperidin or fentanyl or dextropropoxyphene or pentazocine or butorphanol or nalbuphine).ti,ab.	(Opioate/exp OR "Opioate agonist"/exp OR "Narcotic analgesic agent"/exp OR "Narcotic agent"/exp) or (opioid* or opioate* or narcotic* or morphine or ethylmorphine or opium or hydromorphone or levorphanol or oxycodone or codeine or dihydrocodeine or tramadol or tapentadol or pethidine or meperidin or fentanyl or dextropropoxyphene or pentazocine or butorphanol or nalbuphine).ti,ab.
B2		*NOT dependance drugs*	not (naloxone or buprenorphine or methadone).ti.	
C	**Outcome**			
	Utilisation à long terme	*Long term*	((long-term or longterm or "long term" or persistent or chronic* or prolonged or regular) ADJ3 (5 or use* or medication or prescription or prescrib* or utili* or therapy) or "long course" or overus* or overutili*).ti,ab.	OK
D	**Study**			
D1	**Etudes observationnelles**	Observational studies Prospective : cohort, SCCS Retrospective : case control, CSO Cross-sectional studies	("Epidemiologic Studies"/ OR "Case-Control Studies"/exp OR "Cohort Studies"/exp OR "Cross-Sectional Studies"/ OR pharmacoepidemiology/ OR Drug Utilization/sn, td) OR (epidemiologic ADJ (study or studies)) OR "case control" OR (cohort adj (study or studies)) OR "cohort analy$" OR "cross sectional" OR ("follow up" ADJ (study or studies)) OR longitudinal OR retrospective$ OR prospective$ OR (observ$ adj3 (study or studies)) OR "population based" OR survey* OR database* OR (logistic ADJ (regression OR model)) OR (propensity ADJ (score or scores)) or trajector*	("Epidemiologic Studies"/ OR "Case-Control Study"/exp OR "Cohort analysis"/exp OR "cross-sectional study"/ OR pharmacoepidemiology/) OR (epidemiologic ADJ (study or studies)).ti,ab,kw. OR "case control".ti,ab,kw. OR (cohort adj (study or studies)).ti,ab,kw. OR "cohort analy$".ti,ab,kw. OR "cross sectional".ti,ab,kw. OR ("follow up" ADJ (study or studies)).ti,ab,kw. OR longitudinal.ti,ab,kw. OR retrospective$.ti,ab,kw. OR prospective$.ti,ab,kw. OR (observ$ adj3 (study or studies)).ti,ab,kw. OR "population based".ti,ab,kw. OR survey*.ti,ab,kw. OR database*.ti,ab,kw. OR (logistic ADJ (regression OR model)).ti,ab,kw. OR (propensity ADJ (score or scores)).ti,ab,kw. or trajector*.ti,ab,kw.
D2	NOT		**NOT** ("systematic review" or meta-analysis or "randomized controlled trial"* or "case report" or protocol* or guideline).ti,kw.	OK

Table 2. Search strategies on Ovid and Medline

Database(s): All Ovid MEDLINE(R) 1946 to Present

#	Searches
1	(non-cancer* or noncancer* or "without cancer" or non-malignant* or cancer-free or non-tumor*).ti,ab,kw.
2	(pain/exp not "cancer pain"/exp) or "Pain Management"/ or pain.ti,ab. or ("headache disorders"/ or "Arthritis"/ or "Diabetic Neuropathies"/ or "Inflammatory Bowel Diseases"/ or "Perioperative Period"/) or (rachialgia or neuralgia or cephalgia or fibromyalgia or myasthenia or polymyalgia or knee or hip or ankle or elbow or hand or arthritis or "rheumatoid arthritis" or gonarthrosis or osteomyelitis or postherpetic or phantom or neuropath* or polyneuropath* or musculoskeletal or "globus syndrome" or pancreatitis or "irritable bowel" or "irritable colon" or "reflex sympathetic dystrophy" or surgery or surgical or postsurgical or injury* or trauma or dental or "tooth extraction").ti,ab,kw.
3	(anesthesia or cough* or diarrhea).ti,ab,kw.
4	1 or 2 or 3
5	"Analgesics, Opioid"/exp or Narcotics/exp or "Opiate Alkaloids"/exp or Morphinans/exp or (opioid* or opioate* or narcotic* or morphine or ethylmorphine or opium or hydromorphone or levorphanol or oxycodone or codeine or dihydrocodeine or tramadol or tapentadol or pethidine or meperidin or fentanyl or dextropropoxyphene or pentazocine or butorphanol or nalbuphine).ti,ab.
6	5 not (naloxone or buprenorphine or methadone).ti.
7	(((long-term or longterm or "long term" or persistent or chronic* or prolonged or regular) adj3 ("Analgesics, Opioid" or Narcotics or "Opiate Alkaloids" or Morphinans or (opioid* or opioate* or narcotic* or morphine or ethylmorphine or opium or hydromorphone or levorphanol or oxycodone or codeine or dihydrocodeine or tramadol or tapentadol or pethidine or meperidin or fentanyl or dextropropoxyphene or pentazocine or butorphanol or nalbuphine) or use* or medication or prescription or prescrib* or utili* or therapy)) or "long course" or overus* or overutili*).ti,ab,kw.
8	"Epidemiologic Studies"/ or "Case-Control Studies"/exp or "Cohort Studies"/exp or "Cross-Sectional Studies"/ or pharmacoepidemiology/ or Drug Utilization/sn, td or (epidemiologic adj (study or studies)).mp. or "case control".mp. or (cohort adj (study or studies)).mp. or "cohort analy$".mp. or "cross sectional".mp. or ("follow up" adj (study or studies)).mp. or longitudinal.mp. or retrospective$.mp. or prospective$.mp. or (observ$ adj3 (study or studies)).mp. or "population based".mp. or survey*.mp. or database*.mp. or (logistic adj (regression or model)).mp. or (propensity adj (score or scores)).mp. or trajector*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
9	8 not ("systematic review" or meta-analysis or "randomized controlled trial*" or "case report" or protocol* or guideline*).ti,kw.
10	4 and 6 and 7 and 9
11	limit 10 to (yr="2009 -Current" and (english or french))

Database(s): Embase 1974 to 2019 January 15

#	Searches
1	(non-cancer* or noncancer* or "without cancer" or non-malignant* or cancer-free or non-tumor*).ti,ab,kw.
2	(pain/exp not "cancer pain"/exp) or "Pain Management"/ or pain.ti,ab. or ("headache disorders"/ or "Arthritis"/ or "Diabetic Neuropathies"/ or "Inflammatory Bowel Diseases"/ or "Perioperative Period"/) or (rachialgia or neuralgia or cephalgia or fibromyalgia or myasthenia or polymyalgia or knee or hip or ankle or elbow or hand or arthritis or "rheumatoid arthritis" or gonarthrosis or osteomyelitis or postherpetic or phantom or neuropath* or polyneuropath* or musculoskeletal or "globus syndrome" or pancreatitis or "irritable bowel" or "irritable colon" or "reflex sympathetic dystrophy" or surgery or surgical or postsurgical or injury* or trauma or dental or "tooth extraction").ti,ab,kw.
3	(anesthesia or cough* or diarrhea).ti,ab,kw.
4	1 or 2 or 3
5	Opioate/exp or Opioate agonist/exp or Narcotic analgesic agent/exp or Narcotic agent/exp or (opioid* or opioate* or narcotic* or morphine or ethylmorphine or opium or hydromorphone or levorphanol or oxycodone or codeine or dihydrocodeine or tramadol or

	tapentadol or pethidine or meperidin or fentanyl or dextropropoxyphene or pentazocine or butorphanol or nalbuphine).ti,ab.
6	5 not (naloxone or buprenorphine or methadone).ti.
7	(((long-term or longterm or "long term" or persistent or chronic* or prolonged or regular) adj3 (Opioate or Opioate agonist or Narcotic analgesic agent or Narcotic agent or (opioid* or opioate* or narcotic* or morphine or ethylmorphine or opium or hydromorphone or levorphanol or oxycodone or codeine or dihydrocodeine or tramadol or tapentadol or pethidine or meperidin or fentanyl or dextropropoxyphene or pentazocine or butorphanol or nalbuphine) or use* or medication or prescription or prescrib* or utili* or therapy)) or "long course" or overus* or overutili*).ti,ab.
8	"Epidemiologic Studies"/ or "Case-Control Study"/exp or "Cohort analysis"/exp or "cross-sectional study"/ or pharmacoepidemiology/ or (epidemiologic adj (study or studies)).ti,ab,kw. or "case control".ti,ab,kw. or (cohort adj (study or studies)).ti,ab,kw. or "cohort analy$".ti,ab,kw. or "cross sectional".ti,ab,kw. or ("follow up" adj (study or studies)).ti,ab,kw. or longitudinal.ti,ab,kw. or retrospective$.ti,ab,kw. or prospective$.ti,ab,kw. or (observ$ adj3 (study or studies)).ti,ab,kw. or "population based".ti,ab,kw. or survey*.ti,ab,kw. or database*.ti,ab,kw. or (logistic adj (regression or model)).ti,ab,kw. or (propensity adj (score or scores)).ti,ab,kw. or trajector*.ti,ab,kw.
9	8 not ("systematic review" or meta-analysis or "randomized controlled trial*" or "case report" or protocol* or guideline).ti.
10	4 and 6 and 7 and 9
11	limit 10 to (yr="2009 -Current" and (english or french))
12	limit 11 to (conference abstracts or embase)

Table 3. Reasons for excluding references from systematic literature review.

A total of 290 studies were excluded because: cancer patients non excluded or unspecified (101 studies) (1-101); opioid therapy non eligible (*methadone, buprenorphine, naloxone included and no subgroup analysis*) (67 studies) (102-168); long-term opioid outcome or definition missing (30 studies) (169-198); long-term opioid users only (5 studies) (199-203); inappropriate study design (5 studies) (204-208); sub-analysis of a main study (49 studies) (209-257); full-text no assessable (33 studies) (258-290).

Table 4. Details on study quality assessment using the JBI tools.

Study author	Design	JBI Score								
		1	Details	2	Details	3	Details	4	Details	5
Alghnam et al.	CC	No	The two groups were not comparable because of the absence of matching cases and controls: injury-free group is of 32,111 patients while injured group is of 4,713 patients	No	The source population is clearly defined and appropriate but no matching of cases and controls was perfomed	Yes	Controls fulfiled all the eligibility criteria defined for the cases except for those relating to injury status	Yes	Method of measurement of opioid use clearly defined	Yes
Anciano et al.	RC	UC	Inclusion and exclusion criteria were detailed but targeted age criteria is missing	Yes	Exposure is clearly defined and the information on opioid included and excluded is available	UC	No details on validity of codes used for exposure assessment	Yes	Counfounder were identified and measured	Yes
Anderson et al.	RC	Yes	Inclusion and exclusion criteria were clearly defined	No	Exposure is not clearly defined as the information on opioid included is not available	UC	No details on validity of codes used for exposure assessment	Yes	Counfounder were identified and measured	Yes
Buckley et al.	CSS	Yes	Inclusion and exclusion criteria were clearly defined	Yes	Clear description of the population including demographics, location and time period	UC	No details on validity of codes used for exposure assessment	Yes	Chronic user definition was clearly defined	Yes
Fritz et al.	RC	Yes	Inclusion and exclusion criteria were clearly defined	No	Exposure is not clearly defined as the information on opioid included is not available	UC	No details on validity of codes used for exposure assessment	Yes	Counfounder were identified and measured	Yes
Heins et al.	RC	Yes	Inclusion and exclusion criteria were clearly defined	Yes	Exposure is clearly defined and the information on opioid included is available	UC	No details on validity of codes used for exposure assessment	Yes	Counfounder were identified and measured	Yes
Kulshrestha et al.	PC	Yes	Inclusion and exclusion criteria were clearly defined	Yes	Exposure is clearly defined and the information on opioid included and excluded is available (supplementary file)	UC	No details on validity of codes used for exposure assessment	Yes	Counfounder were identified and measured	Yes
Lalic et al.	RC	Yes	Inclusion and exclusion criteria were clearly defined	Yes	Exposure is clearly defined and the information on opioid included and excluded is available (molecules, road of adminiostration, doses)	Yes	We used a validated tool, the RxRisk-V tool, which has been shown to predict mortality in both Australian and interna- tional studies	Yes	Counfounder were identified and measured	Yes
Richardson et al.	RC	Yes	Inclusion and exclusion criteria were clearly defined	No	Exposure is not clearly defined as the information on opioid selected is not available	UC	No details on validity of codes used for exposure assessment	Yes	Counfounder were identified and measured	Yes
Thielke et al.	RC	Yes	Inclusion and exclusion criteria were clearly defined	No	Exposure is not clearly defined as the information on opioid selected is not available	UC	No details on validity of codes used for exposure assessment	UC	Somes counfounder were identified and measured, but comorbidity or potential indication for opioid use were not measured	Yes
Thornton et al.	RC	Yes	Inclusion and exclusion criteria were clearly defined	UC	Exposure is defined and the information on opioid excluded (methadone) and included is available but incomplete: composition of the "other opioids" group is not specified	UC	No details on validity of codes used for exposure assessment	Yes	Counfounder were identified and measured	Yes
Barnett et al.	RC	Yes	Inclusion and exclusion criteria were clearly defined	Yes	Exposure is clearly defined and details on distribution of 5 most common opioid prescriptions by prescribers available in Supplementary file S2	UC	No details on validity of drug product names extraction for exposure assessment	Yes	Counfounder were identified and measured	Yes
Bennett et al.	RC	Yes	Inclusion and exclusion criteria were clearly defined	Yes	Exposure is clearly defined and the information on opioid included is available	UC	No details on validity of codes used for exposure assessment	Yes	Counfounder were identified and measured	Yes
Gibson et al.	CSS	Yes	Inclusion and exclusion criteria were clearly defined	Yes	Clear description of the population including demographics and comorbidities	UC	No details on validity of codes used for exposure assessment	Yes	Long-term opioid use definition was clearly defined	Yes

Harris et al.	RC	Yes	Inclusion and exclusion criteria were clearly defined	Yes	Exposure is clearly defined and the information on opioid included is available	UC	No details on validity of codes used for exposure assessment	Yes	Somes counfounder were identified and measured, but comorbidity or potential indication for opioid use were not measured	Yes
Hedenmalm et al.	RC	Yes	Inclusion and exclusion criteria were clearly defined	Yes	Exposure is clearly defined and the information on opioid included is available	Yes	To increase the validity of exposure data, daily doses (France and Germany) and duration (France only) recorded by IMS® were reviewed against data contained within physi- cian free text fields of the prescription.	Yes	Counfounder were identified and measured	Yes
Chui et al.	CSS	Yes	Inclusion and exclusion criteria were clearly defined	Yes	Clear description of the population including demographics and comorbidities	UC	No details on validity of codes used for exposure assessment	Yes	Long-term opioid use definition was clearly defined	Yes
Lovejoy et al.	CSS	Yes	Inclusion and exclusion criteria were clearly defined	Yes	Clear description of the population including demographics and comorbidities	UC	No details on validity of codes used for exposure assessment	Yes	Long-term opioid use definition was clearly defined	Yes
Lee et al.	RC	Yes	Inclusion and exclusion criteria were clearly defined	No	It is not clearly defined how exposure was reported with questionnaires	No	Exposure was identifed by questionnaires, a validity analysis of exposure assessment is needed	Yes	Counfounder were identified and measured	Yes
Adogwa et al.	RC	Yes	Inclusion and exclusion criteria were clearly defined	Yes	Exposure is clearly defined and the information on opioid included is available	UC	No details on validity of codes used for exposure assessment	Yes	Counfounder were identified and measured	Yes
Cicowski et al.	RC	Yes	Inclusion and exclusion criteria were clearly defined	No	Exposure is not clearly defined as the information on opioid included is not available	UC	No details on validity of codes used for exposure assessment	Yes	Counfounder were identified and measured	Yes

Study author	6	Details	7	Details	8	Details	9	Details	10	Details	11	Details
Alghnam et al.	Yes	Counfounder were identified and measured	Yes	Logistic regressions were performed adjusting for identified counfounders	UC	No details on outcome assessment validity or training	Yes	Two years of follow-up is meaningfull for long-term opioid use	Yes	Reference groups and adjustment variables are clearly defined	-	-
Anciano et al.	No	It is not specified is participants were naive for long-term opioid at the start of the study	Yes	Preoperative and Postoperative groups definitions were clearly defined	Yes	6 months of follow-up is meaningfull according to long-term opioid use definition	Yes	6 months follow-up require to assess long-term outcome	NA	6 months follow-up required to assess long-term outcome	Yes	Appropriate statistical analysis
Anderson et al.	No	It is not specified if participants were naive for long-term opioid at the start of the study	Yes	Temporary opioid and chronic opioid and Postoperative groups definitions were clearly defined	Yes	Three years of follow-up is meaningfull for long-term opioid use	UC	No informations on follow-up completion	No	Analysis not considering the lenght of follow-up	UC	The authors decided to do not use a stepwise regression model, no justification support this decision
Buckley et al.	Yes	Stratification and logistic regression model were performed adjusting for identified confounders	No	Definition used is "chronic users if they had at least 3 narcotic drug claims during the 2-year study period", not based on existing defintion	Yes	Appropriate statistical analysis	-	-	-	-	-	-
Fritz et al.	Yes	Exclusion of patients with a claim for an opioid prescription in the 90 days preceding the index visit	Yes	Acute/episodic opioid and long-term opioid groups definitions were clearly defined	Yes	12 months of follow-up is meaningfull according to long-term opioid use definition	Yes	12 months follow-up require to assess long-term outcome. The, is is specidied that "the most common reason for exclusion was not having a second LBP-related ICD-9 code in the 1-year follow-up period"	NA	Not having 12 months of follow-up was an exclusion criteria	Yes	Appropriate statistical analysis
Heins et al.	UC	"Exclusion of patients in order to focus on a group of claimants for whom early opioid use" is controversial, not according to select patients naive for long-term opioid use	Yes	Long-term, short-term opioid use and non-users groups definitions were clearly defined	Yes	4,25 years of average follow-up is meaningfull according to long-term opioid use definition	Yes	4,25 years (51 months) of average duration of follow-up	Yes	Adjusting for time in system potential (used to control for possible non-random data censoring) (supplementary file)	Yes	Appropriate statistical analysis
Kulshrestha et al.	UC	Effort was made to include only those who had unequivocal documen-tation of continued opioid analgesic use. Exclusion was not performed to select patient naive for long-term opioid use	Yes	Chronic opioid use and non chronic opioid use groups definitions were clearly defined	Yes	12 months of follow-up is meaningfull according to long-term opioid use definition	Yes	12 months follow-up require to assess long-term outcome	NA	12 months follow-up required to assess long-term outcome	Yes	Appropriate statistical analysis
Lalic et al.	Yes	Naive users only: "no preceding opioid dispensings in the 12 months prior to the initial opioid dispensing"	Yes	Persitent opioid users and non persistent users groups definitions were clearly defined	Yes	12 months of follow-up is meaningfull according to long-term opioid use definition	Yes	12 months follow-up require to assess long-term outcome	NA	12 months follow-up required to assess long-term outcome	Yes	Appropriate statistical analysis
Richardson et al.	Yes	Naive users only: "no use of opioids in the 6 months prior to the first qualifying pain diagnosis"	Yes	Chronic, non-chronic use and non-users groups definitions were clearly defined	Yes	18 months of follow-up is meaningfull according to long-term opioid use definition	Yes	18 months follow-up require to assess long-term outcome	NA	18 months follow-up required to assess long-term outcome	Yes	Appropriate statistical analysis
Thielke et al.	Yes	Confirmed opioid initiators by interviews and by pharmacy claims "must not have filled an opioid prescriptio with a days' supply that extended into the 30-day period before the date of the index prescription"	Yes	Continuing opiois users and non-continuing opiois users groups definitions were clearly defined	Yes	12 months of follow-up is meaningfull according to long-term opioid use definition	Yes	12 months follow-up require to assess long-term outcome	NA	12 months follow-up required to assess long-term outcome	Yes	Appropriate statistical analysis
Thornton et al.	Yes	To ensure that we captured individuals who were free of opioid use at baseline, we used the first prescription date between January 2007 and May 2015.	Yes	Incident chronic opioid therapy group and non-incident chronic opioid therapy group were clearly identified	UC	4 months of follow-up is meaning-full according the main definition of long-term use (90 or 120 days), but not according other definitions	Yes	4 months follow-up require to assess long-term outcome	NA	4 months follow-up required to assess long-term outcome	Yes	Appropriate statistical analysis

Barnett et al.	Yes	No fills of prescription opioid within 6 months visible in the VA system prior to the index ED visit	Yes	Low and high-intensity prescribers groups were clearly defined	Yes	12 months of follow-up is meaningfull according to long-term opioid use definition, a sensitivity analysis on 18 months was also performed	Yes	12 months follow-up require to assess long-term outcome	NA	12 months follow-up required to assess long-term outcome	Yes	Appropriate statistical analysis
Bennett et al.	Yes	Only to patients who did not fill an opioid prescription in the 11 months prior to the perioperative period	Yes	Persitent opioid users and non persistent users groups definitions were clearly defined	Yes	6 months of follow-up is meaningfull according to long-term opioid use definition	Yes	6 months follow-up require to assess long-term outcome	NA	6 months follow-up required to assess long-term outcome	Yes	Appropriate statistical analysis
Gibson et al.	Yes	Logistic regression model were performed adjusting for important confounders	UC	Definition is based on the commonly used definition of long-term use (≥ 90 days continuoulsy) but do not take into account cumulative days definition	Yes	Statistical analysis appropriate	-	-	-	-	-	-
Harris et al.	Yes	Exclusion of patients who had filled an opioid prescription or received a diagnosis of aBP in the 3 months prior to the index visit	Yes	Long-term and non long-term opioid users groups definitions were clearly defined	Yes	9 months of follow-up is meaningfull according to long-term opioid use definition	Yes	270 days (9 months) of average duration of follow-up	NA	120 days of follow-up required to assess long-term outcome	Yes	Appropriate statistical analysis
Hedenmalm et al.	Yes	Incident tramadol exposure was defined as a prescription for tramadol in a patient with at least 365 days of observation with no prescription within the previous 365 days	Yes	Long-term and non long-term opioid users groups definitions were clearly defined	Yes	120 months of follow-up is meaningfull according to long-term opioid use definition	UC	No informations on follow-up completion	No	Analysis not considering the lenght of follow-up	Yes	Appropriate statistical analysis
Chui et al.	Yes	Logistic regression model were performed adjusting for identified confounders	UC	Definition is based on the commonly used definition of long-term use (≥ 90 days continuoulsy) but do not take into account cumulative days definition	Yes	Statistical analysis appropriate	-	-	-	-	-	-
Lovejoy et al.	Yes	Logistic regression model were performed adjusting for identified confounders	UC	Definition is based on the commonly used definition of long-term use (≥ 90 days continuoulsy) but do not take into account cumulative days definition	Yes	Statistical analysis appropriate	-	-	-	-	-	-
Lee et al.	Yes	For the analyses examining predictors of chronic opioid use, we excluded those who reported prevalent opioid use at study entry	Yes	Chronic opioid use and non chronic opioid use groups definitions were clearly defined	Yes	15 months of follow-up is meaningfull according to long-term opioid use definition	Yes	3.1 years (37.2 months) of average duration of follow-up	Yes	Exclusion criteria: all participants of Corrona cohort with RA who had ≥ 90 days of follow-up.	Yes	Appropriate statistical analysis
Adogwa et al.	No	It is not specified if participants were naive for long-term opioid at the start of the study	Yes	Prolonged opioid users and non prolonged opioid users groups definitions were clearly defined	Yes	24 months of follow-up is meaningfull according to long-term opioid use definition	Yes	24 months follow-up require to assess long-term outcome	NA	24 months follow-up require to assess long-term outcome	Yes	Appropriate statistical analysis
Cicowski et al.	No	It is not specified if participants were naive for long-term opioid at the start of the study	Yes	Chronic opioid use and non chronic opioid use groups definitions were clearly defined	Yes	120 months of follow-up is meaningfull according to long-term opioid use definition	UC	No informations on follow-up completion	No	Analysis not considering the lenght of follow-up	Yes	Appropriate statistical analysis

Table 5. Results of prevalence and/or incidence estimates and LTPO use definitions of included studies (N=64)

Study reference	Targeted population	Long-term use definition	Naive opioid users (Yes/No)	Incidence per 10,000 person year	Prevalence per 10,000 person
Boudreau et al. (291)	Noncancer pain	Episodes lasting longer than 90 days that had 120+ total days supply of dispensed medication or 10+ opioid prescriptions dispensed within a given year were classified as long-term opioid episodes.	Yes		From 1997-2005 GH: 468 /10,000 KPNC: 392 /10,000
Deyo et al. (292)	Noncancer and non palliative care	Patients with at least six fills during this period were considered to have initiated long-term opioid use.	Yes	41.6	
Skurtveit et al. (293)	New users of weak opioid for nonmalignant pain	Persistent users of opioids if they received opioids each year from 2005 to 2008 and, in addition, in 2008 received more than 365 DDDs of opioids, which means 1 DDD/day all days.	Yes	0.6	
Alam et al. (294)	Patients discharged alive after low-pain short-stay surgery hospitalizations	Long-term opioid use was defined as an additional claim for any opioid within 60 days of the 1-year anniversary date (eg, 305-425 days after the index date)	Yes	Early opioid users: 30.4 Non-early opioid users: 21.4	
Richardson et al. (295)	Adolescents and young adults with chronic pain	>90 days of opioid use within a 6-month period with no gap in use of >30 days.	No	3.0	
Dobscha et al. (296)	Patients with Persistent Non-Cancer Pain	Patients prescribed opioid medications for 90 or more consecutive days (COT)	Yes	40.7	
Chevalier et al. (297)	Non cancer population in UK and Germany	Chronic users (183 days and above)	Yes	UK: 35.6 Germany: 10.5	
Fredheim et al. (298)	People with chronic nonmalignant pain	Wide definition: an opioid quantity of >180 DDD or 4500 OMEQ during 365 days, with prescriptions in at least 3 of 4 quarters of the year. Strict definition**:** an opioid quantity >730 DDD or 18,000 OMEQ with at least 10 prescriptions distributed in all quarters of the year.	No	Complete population: 3.1 CNCP: 9.2	
Kulshrestha et al. (299)	Post-kidney transplantation	Active use of opioid analgesics at all the three time intervals or first two time intervals if the patient had an event (death and/or graft loss) between three and 12 months.	No	94.9	
Morden et al. (300)	Disabled Medicare Beneficiaries	Chronic opioid users: 6 or more fills.	No	39.2	
Anderson et al. (301)	Lumbar fusion surgery for degenerative disc disease (DDD) and discogenic low back pain (LBP)	Chronic opioid therapy (COT) as being supplied opioid analgesics for more than 1 year after the immediate 6-week postoperative period.	No	159.4	
Buckley et al. (302)	Children with/without Inflammatory Bowel Disease (IBD)	At least 3 drug claims during the 2-year study period	No	Controls: 9.4 IBD: 23.1	
Halbert et al. (303)	Population with and without Mental Health Disorders (MHD)	Long term opioid therapy as having >=3 opioid prescriptions	Yes	MHD: 181.3 non-MHD: 108.3	
Al Dabbagh et al. (304)	Femoral shaft fracture	Patients continued to receive dispensed prescriptions for opioids for over 6, 12 months or 18 months	No	6 months: 364.8 12 months: 129.7 18 months: 56.7	

				24 months: 26.6	
Bedson et al. (305)	Musculoskeletal condition	At least 3 opioid prescriptions issued within a 90-day period from the date of the new opioid prescription. An episode of long-term opioid use ended when there was a gap of 6 months or more without an opioid prescription. The end date of a long-term opioid episode was set at 28 days after the issue of the last prescription	Yes	2002 : 42.4 (41.2-43.6) 2013: 55.8 (54.5-57.1)	
Heins et al. (306)	US workers with back injuries or shoulder injuries	Average of at least one prescription per month for 3 months or at least three consecutive prescription refills with less than 1 month between refill	No	Back injuries: 25.3 Shoulder injuries: 26.2	
Inacio et al. (307)	Total hip arthroplasty	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. New chronic users: were those who did not have chronic use prior to their THA. Persistent chronic opioid users: were those with chronic opioid use before and after surgery.	No	43.0	
Kim et al. (308)	Total Knee Arthroplasty	Patients who were identified as persistent chronic opioid users at 6 months after TKA	No	113.4	
Lovejoy et al. (309)	Veterans with chronic pain and history of substance use disorder	≥90 d duration	No		2290
Mudumbai et al. (310)	Veterans post surgery	Short-acting opioid group with total day supply>90 days)	No	153.6	
Sani et al. (311)	non-cancer pain	Persistence pattern is defined based on different levels of dispensed opioid amounts, number of prescriptions and the number of quarters out of the year in which prescriptions were dispensed. The strict definition describes a typical patient using opioids to achieve a continuous serum concentration in the therapeutic range, the intermediate definition represents a typical patient using opioid daily but not around the clock and the wide definition describes a typical patient who uses opioids for at least half of the days in a year.	No	37.5	
Smolina et al. (312)	NonCancer Non Palliative Care	A patient had to have filled one or more prescriptions containing at least 90 days of opioid therapy, with no gaps in prescriptions (periods during which previous prescriptions would have run out if taken consecutively) lasting longer than 182 days (six months). Episode start: At dispense of a first prescription of opioid with no opioid in the previous 6 months. Episode end: the date when the dispensed supply would have run out for the last prescription after which there was a minimum of six months with no further opioid dispensations. Episode category defined frequency of use by percentage of days covered: chronic users (50%–89%); every-day users (≥90%).	Yes	28.7	

Alghnam et al. (313)	Patient with /without incident traumatic injury	Opioid use in more than one round (at least 8 months) following round 2 (ie, opioid use in rounds 3, 4, etc)	Yes	7.5
Anthony et al. (314)	Anterior Cruciate Ligament Reconstruction	Those who had filled an opioid prescription 3, 9 or 12 months after ACLR	Yes	3 months: 241.3 9 months: 55.2 12 months: 39.3
Birke et al. (315)	Adult (16 years or older) Danish citizens	Individuals, who had been dispensed at least one prescription in six separate months within a year	Yes	CNCP: 90 Non CNCP: 20
Callinan et al. (316)	Non cancer pain opioid users	>90 days	No	703.4
Chen et al. (317)	Systemic Inflammatory Diseases (SID); Rheumatoid arthritis (RA); Systemic lupus Eythematosus (SLE); Ankylosing spondylitis (AS); Psoriatic arthritis (PsA)	> 90 days	No	RA: 158.3 SLE: 133.3 PSA: 125.0 AS: 208.3
Cichowski et al. (318)	Chronic Pelvic Pain (CPP) in the women veteran population	The use of opioids on a daily or intermittent basis for 90 or more calendar days.	No	24.0
Connolly et al. (319)	Lumbar Fusion Surgery for degenerative spine conditions, post-laminectomy or as a refusion procedure	Long-term opioid use: ≥365 days of opioid prescriptions dispensed in the two years following surgery	No	122.3
Deyo et al. (320)	Back Pain Patients	≥120 days or >90 days with 10 or more fills	No	312.8
Shah et al. (321)	Opioid naive patients	Patients who continued opioid use for ≥12 months were those who did not meet our definition of opioid discontinuation prior to the 12 months period following their first opioid prescription.	Yes	38.9
Stark et al. (322)	Post-surgical	Persistent post-surgical opioid use was defined as prescription or over-the-counter opioid use greater than 90 days after surgery	Yes	172.6
Thielke et al. (323)	Patients with chronic noncancer pain	Continuing opioid use at 1 year from electronic pharmacy data. This was defined as 30 or more days' supply of opioids dispensed during the 120 days before the 12-month time point.	Yes	387.1
Adogwa et al. (324)	Degenerative conditions of the lumbosacral spine who underwent lumbar decompression and fusion procedure	Patients with prolonged (>1 year) opioid use after fusion	No	274.7
Anciano et al. (325)	total Hip Arthroscopy (THA)	New prescription for an opioid pain medication between 3 and 6 months following the procedure.	No	456.7
Bertenthal et al. (326)	Postconcussive symptoms from traumatic brain injury in combat veterans	Long-term opioid therapy was defined as being prescribed ≥90 consecutive days of opioid medications during any 110-day period in the year following CTBIE. (p*atients with episodic patterns of opioid use who had received 90 or more days of opioids, but lacked 90 continuous days of prescribed opioids during the year following CTBIE*)	Yes	27.7
Bolarinwa et al. (327)	Patient who underwent primary THA	Prolonged postoperative narcotic use was defined as a patient filling a prescription for a narcotic pain medicate between 3 and 6 months postoperatively.	No	25.1

Cancienne et al. (328)	Total Knee Arthroplasty	Prolonged postoperative narcotic use was defined as a patient filling a prescription for a narcotic pain medicate between 3 and 6 months postoperatively.	No	29.2
Chui et al. (329)	Musculoskeletal disorders in payer groups: both CMS and VHA/ only CMS/only VHA claims	Long-term opioid prescriptions, defined by >90 days of prescribed opioid therapy and overlap of concurrent opioid prescriptions in 2010.	No	Both: 3.9 CMS: 12.6 VHA: 6.5
Fritz et al. (330)	Low Back Pain (LBP) with a new physician consultation	≥ 120 days or > 90 days with 10 or more fills during the 1-year follow-up period	Yes	202.7
Hernandez et al. (331)	Total Knee Arthroplasty in opioid naive users and non-naive opioid users	Remaining on opioids at latest follow-up	Yes/No	51.1
Hunnicutt et al. (332)	Long-stay nursing homes (NHs) residents	Long-term: ≥90 days cumulative use during the 120 days	No	269.4
Lalic et al. (333)	Non-cancer patients	Patients dispensed opioids only at baseline were all categorized as non-persistent users; Groupe based trajectory modelling undertaken on cohort of people with > 1 month covered in the 12 months follow-up period to determine persistent users.	Yes	21.8
Politzer et al. (334)	Total Knee Arthroplasty in opioid naive users and non-naive opioid users	Chronic opioid users were defined as those patients who were prescribed any opioids for over 6 contiguous months postoperatively in each cohort.	Yes	88.8
Steiner et al. (335)	Knee Arthroscopy	Prolonged postoperative narcotic use was defined as having at least 1 new narcotic prescription provided between 3 and 6 months after knee arthroscopy	No	376.8
Taqi et al. (336)	Knee Osteoarthritis	An episode of long-term opioid prescribing was defined as at least 3 prescriptions issued within a 90-day period from the date of opioid initiation (date of first opioid prescription after the incident KOA diagnosis, or the date of first prescription in a treatment episode inclusive of diagnosis date).	Yes	288.3
Thornton et al. (337)	Working-Age adults in the United States	At least a 90-day supply of opioids during the follow-up period (ie, 120 days after the index date).	Yes	33.4
Barham et al. (338)	Patients who underwent vasectomy, opiod users and non-opioid users	New persistent opioid use was defined as at least 1 opioid prescription between 90 and 180 days from vasectomy in patients who did not fill an opioid prescription within the 90 days prior to vasectomy and who received an opioid prescription for pain control after vasectomy.	Yes	Pre-vasectomy opioid users: 130.7 Pre-vasectomy nonopioid users: 26.5
Barnett et al.(339)	Opioid naive patient at ED visit	Long-term opioid use, defined as > 180 days of opioids supplied in the 12 months after an index ED visit, *excluding prescriptions within 30 days after the index visit since the likelihood of getting an opioid in that period is directly related to the OPR of the provider seen.*	Yes	Low intensity prescribers: 12.5 High intensity prescribers: 9.7
Basilico et al.(340)	Surgically treated traumatic musculoskeletal injuries patients	Prolonged opioid use: receipt of at least one opioid prescription within 90 days of injury presentation and another within 90 to 180 days postoperatively	Yes	688.3
Beliveau et al. (341)	Elderly opioid initiators	Chronic opioid use: 90 consecutive or 120 cumulative days with an active opioid prescription during the 12-month follow-up	Yes	38.4
Bennett et al. (342)	Patient who underwent a body contouring surgical procedure	Persistent opioid use was the primary outcome, defined as continued prescription fills between 90 and 180 days after discharge, among those patients who had filled an opioid prescription in the perioperative period	Yes	102.2
Birke et al.(343)	Adult (16 years or older) Danish citizens with	Individuals, who had been dispensed at least one prescription in six separate	Yes	11.2

	and without CNCP	months within a year.			
Desai et al. (344)	Patients who underwent total joint replacement (TJR): severe osteoarthritis patients	We defined long-term opioid use for each patient in a 360 days period immediately preceding TJR based on prescription dispensing for any opioid with day supply totaling ≥ 90 days	No	138.2	
Gibson et al. (345)	Women veterans aged 45-64 with chronic non-cancer pain	Long-term opioids were defined as prescribed oral opioid medications for ≥ 90 days over the observed period,	No		5,050
Goplen et al.(346)	Patients with chronic noncancer pain secondary to end-stage knee arthritis	Patients who had 90 days or more of continuous opioid dispensing within 180 days before TKA	Yes	Fixed model: from 36.7 to 121.7	
Harris et al.(347)	Primary care patients who were prescribed hydrocodone or oxycodone for acute back pain	Long term opioid use if the prescription dates spanned at least 90 days from the initial prescription to the run-out date of the last prescription, and included at least 120 days' supply or 10 fills	Yes	89.3	
Hedenmalm et al. (348)	Adult patients-prescribed tramadol	Continuous treatment episode of 366 days or longer	Yes	France: 24.1 Germany: 21.4	
Hirji et al.(349)	Opioid users	Chronic opioid usage was defined as having active opioid prescription beyond 90 days following the surgery	Yes	48.0	
Lee et al. (350)	Rheumatoid arthritis patients	Documentation of opioid use on patient questionnaires from ≥ 2 consecutive Corrona visits.	Yes (*for predictive analysis only)*		2012: 740 2015: 160
Musich et al.(351)	Elderly	Chronic opioid use was defined as ≥2 prescriptions and >90 days' supply of opioids	Yes	35.6	
Rogero et al. (352)	Patients undergoing outpatient Hallux Valgus correction procedures	Prolonged opioid use as a patient filling an opioid prescription 90 to 180 days after the index procedure	Yes	24.3	
Agarwalla et al. (353)	Patient who underwent primary THA due to Osteoarthitis (OA) or Hip Fracture (HF)	Prolonged postoperative narcotic usage was defined as a patient filling a narcotic prescription between 3 and 6 months postoperatively. Patients filling prescriptions beyond 6 months were excluded to avoid patients who may have had additional surgeries or injuries that required narcotic use that was unrelated to the THA. Furthermore, patients filling narcotic prescriptions prior to 3 months postoperatively were also excluded because acute periprosthetic joint infection typically occurs within 3 months of THA and patients may fill additional narcotic pain medications to provide pain relief from the infection	No	OA: 510.5 HF: 461.8	
Young et al. (354)	Pelvic organ prolapse (POP) and stress incontinence (SUI) surgery	Continuous: at least one monthly opioid prescription after surgery at 12 motnhs postop Sensitivity analysis: opioid prescription between 90 and 180 days after hysterectomy	Yes	Continuous: 0.2 Sensitivity: 65.7	

FIGURES

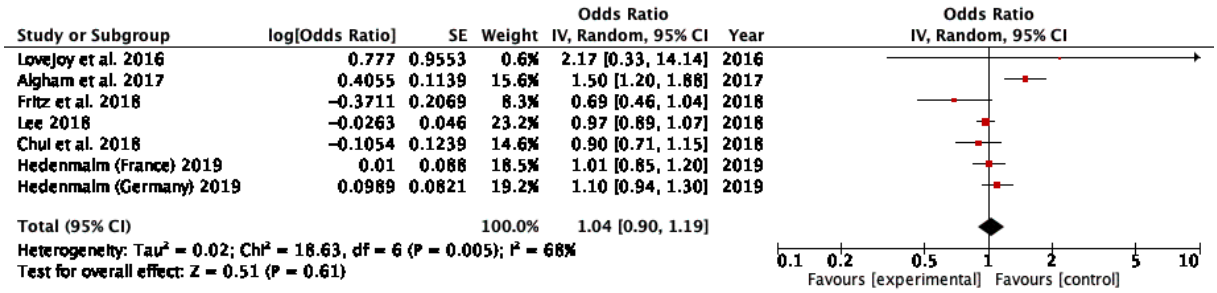

Figure 1. Forest plot of female sex associated with LTPO use vs non-LTPO use.

Odds Ratio (OR) for individual observational studies with 95% confidence interval (CI) is presented; arrow indicates that the CI exceeds the limits of the graph. An estimate of the weight of each observational study in pooled ORs is reported as a percentage and graphically (black square size); pooled OR is presented by a black diamond; statistical heterogeneity across studies was evaluated using the Q statistic ($p<0.10$ considered statistically significant), and the proportion of the total variation contributed by the between-study variance was estimated using I^2 statistics.

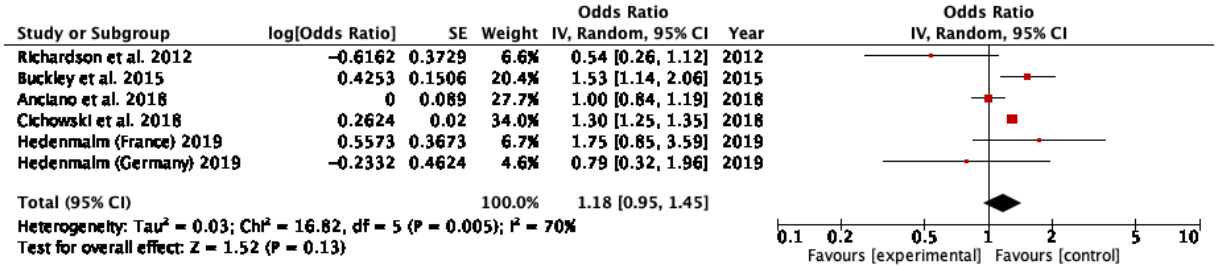

Figure 2. Forest plot of headache indication associated with LTPO use vs non-LTPO use.

Odds Ratio (OR) calculated for individual observational studies with 95% confidence interval (CI) is presented; arrows indicate that the CI exceeds the limits of the graph. An estimate of the weight of each observational study in pooled ORs is reported as a percentage and graphically (black square size); pooled OR is presented by a black diamond; statistical heterogeneity across studies was evaluated using the Q statistic ($p<0.10$ considered statistically significant), and the proportion of the total variation contributed by the between-study variance was estimated using I^2 statistics.

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REFERENCES ANNEXES

1. Young JC, Dasgupta N, Chidgey BA, Funk MJ. Post-surgical opioid prescriptions and risk of long-term use in the USA. Pharmacoepidemiology and Drug Safety. 2018;27 (Supplement 2):215.

2. Yenikomshian HA, Curtis EE, Carrougher GJ, Qiu Q, Gibran NS, Mandell SP. Outpatient opioid use in burn patients: A retrospective review. Journal of Burn Care and Research. 2018;39 (Supplement 1):S97.

3. Yaffe PB, Green RS, Butler MB, Witter T. Is Admission to the Intensive Care Unit Associated With Chronic Opioid Use? A 4-Year Follow-Up of Intensive Care Unit Survivors. Journal of Intensive Care Medicine. 2017;32(7):429-35.

4. Wu S, Zhang X, Boykin S, Scranton R, Tran MH. Incidence and persistence of opioid use after surgery among opioid-Naive adults in a large commercial US health plan. Pharmacoepidemiology and Drug Safety. 2019;28(Supplement 2):328-9.

5. Wright JD, Huang Y, Tergas AI, Collado FK, St. Clair CM, Hou JY, et al. Patterns of perioperative use and persistent use of opioids after gynecologic surgery. Gynecologic Oncology. 2019;154(Supplement 1):198.

6. Wright JD, Huang Y, Melamed A, Tergas AI, St Clair CM, Hou JY, et al. Use and Misuse of Opioids After Gynecologic Surgical Procedures. Obstetrics and gynecology. 2019;134(2):250-60.

7. Wright AK, Matt S, Leveque JC. Evaluating the impact of initial prescription on long-term opioid utilization following discectomy and laminectomy surgery. Journal of Neurosurgery. 2019;131(1):59.

8. Witter T, Brousseau C, Butler MB, Erdogan M, Mac Dougall PC, Green RS. Prolonged chronic use of opioids: A comparison between the critically ill and surgical populations. Intensive Care Medicine Experimental Conference: 29th Annual Congress of the European Society of Intensive Care Medicine, ESICM. 2016;4(Supplement 1).

9. Wen X, Matteson KA, Aroke H, Kogut S, Shireman T. Chronic use of opioids before and after hysterectomy: Patterns and predictors. Pharmacoepidemiology and Drug Safety. 2018;27 (Supplement 2):325.

10. Weiner SG, Chou SC, Chang YSC, Baker O. 227 Emergency Physician Opioid Prescriptions That Resulted in Chronic Use. Annals of Emergency Medicine. 2019;74(4 Supplement):S90.

11. Wei J, Ehrenfeld J, Woo E, Edwards D. Clinical predictors of persistent postoperative opioid use following lumbar spine surgery. Pain Medicine (United States). 2018;19 (4):877-8.

12. Wang H, Hill A, Fowler R, Pinto R, Gomes T, Wunsch H. Epidemiology of elderly opioid users admitted to intensive care units. American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS. 2017;195(no pagination).

13. Walco GA, Gove N, Phillips J, Weisman SJ. Opioid Analgesics Administered for Pain in the Inpatient Pediatric Setting. Journal of Pain. 2017;18(10):1270-6.

14. Vollstedt A, Ngon A, Meeks W, Pais V, Sites B. Incidence and predictors of repeated and prolonged opioid use after kidney stone diagnosis. Journal of Urology. 2019;201(4 Supplement 1):e170-e1.

15. Velazquez-Ramirez G, Krebs J, Stafford J, Ur R, Craven T, Bleyer A, et al. Prevalence of Chronic Opioid use in Patients With Peripheral Arterial Disease Undergoing Lower Extremity Interventions. Journal of Vascular Surgery. 2019;69(1):e13-e4.

16. Veal FC, Bereznicki LR, Thompson AJ, Peterson GM. Use of Opioid Analgesics in Older Australians.[Erratum appears in Pain Med. 2017 Apr 1;18(4):822; PMID: 28586446]. Pain Medicine. 2015;16(8):1519-27.

17. Thiels CA, Habermann EB, Hooten WM, Jeffery MM. Chronic use of tramadol after acute pain episode: cohort study. BMJ (Clinical research ed). 2019;365:l1849.

18. Theidel U, Mittendorf T, Mueller-Schwefe GHH, Ueberall MA. Utilization patterns for treatment with strong opioids for chronic back pain in Germany. Value in Health. 2013;16 (7):A390.

19. Tam CA, Dauw CA, Ghani KR, Gunaseelan V, Kim T, Leavitt DA, et al. New Persistent Opioid Use After Outpatient Ureteroscopy for Upper Tract Stone Treatment. Urology. 2019;134:103-8.

20. Swenson CW, Kamdar NS, Seiler K, Morgan DM, Lin P, As-Sanie S. Definition development and prevalence of new persistent opioid use following hysterectomy. American Journal of Obstetrics & Gynecology. 2018;219(5):486.e1-.e7.

21. Sun EC, Darnall BD, Baker LC, Mackey S. Incidence of and Risk Factors for Chronic Opioid Use Among Opioid-Naive Patients in the Postoperative Period.[Erratum appears in JAMA Intern Med. 2016 Sep 1;176(9):1412; PMID: 27533349]. JAMA Internal Medicine. 2016;176(9):1286-93.

22. Steen T, Lirk PB, Sigurdsson MI. The demographics of persistent opioid consumption following limb amputation. Acta Anaesthesiologica Scandinavica. 2019.

23. Stafford C, Francone T, Roberts PL, Ricciardi R. What factors are associated with increased risk for prolonged postoperative opioid usage after colorectal surgery? Surgical Endoscopy. 2018;32(8):3557-61.

24. Soneji N, Clarke HA, Ko DT, Wijeysundera DN. Risks of Developing Persistent Opioid Use After Major Surgery. JAMA Surgery. 2016;151(11):1083-4.

25. Somers EC, Lee J, Hassett AL, Zick SM, Harlow SD, Helmick CG, et al. Prescription Opioid Use in Patients With and Without Systemic Lupus Erythematosus - Michigan Lupus Epidemiology and Surveillance Program, 2014-2015. MMWR Morbidity and mortality weekly report. 2019;68(38):819-24.

26. Som A, Santosa K, Lapidus J, Skolnick G, Cho G, Waljee J, et al. Prolonged opioid use and prescription patterns in pediatric facial fracture surgery patients. Cleft Palate-Craniofacial Journal. 2019;56(1 Supplement):62.

27. Scaglione SJ, Aldrich D, Singh J, Park D, Mumtaz S, Afshar M, et al. Outcomes and reasons for chronic opioid use in patients with cirrhosis. Hepatology. 2018;68 (Supplement 1):465A.

28. Saraswathula A, Chen M, Whittemore A, Divi V. Postoperative opioid use in head and neck surgical patients. Otolaryngology - Head and Neck Surgery (United States). 2018;159 (1 Supplement 1):P96-P7.

29. Sanford Z, Turcotte J, Taylor H, Broda A, Speciale A, Patton C. Long-term opioid prescription fills in patients undergoing spine surgery. Journal of Neurosurgery. 2019;131(1):28.

30. Samuelsen PJ, Svendsen K, Wilsgaard T, Stubhaug A, Nielsen CS, Eggen AE. Persistent analgesic use and the association with chronic pain and other risk factors in the population-a longitudinal study from the Tromso Study and the Norwegian Prescription Database. European Journal of Clinical Pharmacology. 2016;72(8):977-85.

31. Said M, Patil D, Ogan K, Mehta A, Filson C, Lay A. Risk of prolonged opioid use among opioid-naive patients following urologic-minimally invasive surgery. Journal of Urology. 2019;201(4 Supplement 1):e197.

32. Said M, Leung A, Patil D, Ogan K, Mehta A, Filson C, et al. Risk of prolonged opioid use among opioid-naive patients following urologic stone surgery. Journal of Urology. 2019;201(4 Supplement 1):e325.

33. Roberts MH, Mapel DW, Hartry A, Von Worley A, Thomson H. Chronic pain and pain medication use in chronic obstructive pulmonary disease. A cross-sectional study. Annals of the American Thoracic Society. 2013;10(4):290-8.

34. Rice J, Samuelson T, Birnbaum H, Katz N. Characteristics and use patterns of chronic hydrocodone users. Journal of Pain. 2012;1):S80.

35. Rhon DI, Snodgrass SJ, Cleland JA, Cook CE. Comorbid Insomnia and Sleep Apnea are Associated with Greater Downstream Health Care Utilization and Chronic Opioid Use after Arthroscopic Hip Surgery. Pain physician. 2019;22(4):E351-E60.

36. Raman SR, Bush C, Karmali RN, Greenblatt LH, Roberts AW, Skinner AC. Characteristics of new opioid use among medicare beneficiaries: Identifying high-risk patterns. Journal of Managed Care and Specialty Pharmacy. 2019;25(9):966-72.

37. Pugely AJ, Bedard NA, Kalakoti P, Hendrickson NR, Shillingford JN, Laratta JL, et al. Opioid use following cervical spine surgery: trends and factors associated with long-term use. Spine Journal. 2018.

38. Puenpatom RA, Rubino M, Garvin R, Chieffo C. Opioid analgesics utilization in us children: A retrospective database analysis. Value in Health. 2013;16 (3):A125.

39. Pu T, Erali RA, Share M, Russell GB, Clark CJ, Levine E, et al. PERSISTENT OPIOID USE AFTER CURATIVE-INTENT HEPATECTOMY FOR NEOPLASTIC DISEASE. Gastroenterology. 2019;156(6 Supplement 1):S-1383.

40. Pensa MA, Galusha DH, Cantley LF. Patterns of Opioid Prescribing and Predictors of Chronic Opioid Use in an Industrial Cohort, 2003 to 2013. Journal of Occupational & Environmental Medicine. 2018;60(5):457-61.

41. Painter JT, Crofford LJ, Talbert J. Geographic variation of chronic opioid use in fibromyalgia. Clinical Therapeutics. 2013;35(3):303-11.

42. Owusu-Agyemang P, Cata JP, Meter AV, Kapoor R, Zavala AM, Williams UU, et al. Perioperative factors associated with persistent opioid use after extensive abdominal surgery in children and adolescents: A retrospective cohort study. Paediatric Anaesthesia. 2018;28(7):625-31.

43. Olds C, Spataro E, Li K, Kandathil C, Most SP. Assessment of Persistent and Prolonged Postoperative Opioid Use Among Patients Undergoing Plastic and Reconstructive Surgery. JAMA facial plastic surgery. 2019;21(4):286-91.

44. Oh G, Brouwer ES, Abner EL, Fardo DW, Freeman PR, Moga DC. Predictors of long-term opioid use in HIV patients who initiated antiretroviral therapy. Pharmacoepidemiology and Drug Safety. 2019;28(Supplement 2):325.

45. Nguyen A, Ross E, Westra J, Huang N, Nguyen C, Raji M, et al. Student presentation, encore presentation spinal surgery for degenerative spine disease-opioid prescription filling patterns in geriatric patients. Journal of the American Geriatrics Society. 2019;67(Supplement 1):S2.

46. Namba RS, Singh A, Paxton EW, Inacio MCS. Patient Factors Associated With Prolonged Postoperative Opioid Use After Total Knee Arthroplasty. Journal of Arthroplasty. 2018;33(8):2449-54.

47. Muller AE, Clausen T, Sjogren P, Odsbu I, Skurtveit S. Prescribed opioid analgesic use developments in three Nordic countries, 2006-2017. Scandinavian journal of pain. 2019;19(2):345-53.

48. Mitra A, Leon E, Dewey E, Ando Y, Englander H, Lhewa DY, et al. Characterizing opiate use in liver transplantation. Hepatology. 2018;68 (Supplement 1):672A.

49. Merlin JS, Tamhane A, Starrels JL, Kertesz S, Saag M, Cropsey K. Factors Associated with Prescription of Opioids and Co-prescription of Sedating Medications in Individuals with HIV. AIDS & Behavior. 2016;20(3):687-98.

50. Mehta HB, Kuo YF, Westra J, Goodwin JS, Raji M. ASSOCIATION OF DEMENTIA SEVERITY AND OPIOID USE IN LONG-TERM CARE NURSING HOME RESIDENTS WITH DEMENTIA. Alzheimer's and Dementia. 2019;15(7 Supplement):P1571.

51. Luu H, Slavova S. Long-term use of high-dose opioid analgesics in Kentucky from 2012 to 2016. Pharmacoepidemiology and Drug Safety. 2018;27 (Supplement 2):330.

52. Lindestrand AG, Christiansen ML, Jantzen C, van der Mark S, Andersen SE. Opioids in hip fracture patients: an analysis of mortality and post hospital opioid use. Injury. 2015;46(7):1341-5.

53. Lin C, Pujari A, Garlich J, Rosen S. Prolonged opioid use following geriatric hip fracture surgery. Journal of the American Geriatrics Society. 2019;67(Supplement 1):S21.

54. Lee SS, Choi Y, Pransky GS. Extent and Impact of Opioid Prescribing for Acute Occupational Low Back Pain in the Emergency Department. Journal of Emergency Medicine. 2016;50(3):376-84.e1-2.

55. Labaran L, Jain N, Puvanesarajah V, Jain A, Carmouche JJ, Hassanzadeh H. P147. Opioids and spinal cord stimulators: pre and postoperative opioid use pattern and factors associated with chronic postoperative opioid use. Spine Journal. 2019;19(9 Supplement):S226.

56. Kwok AK, O'Hara NN, Pollak AN, O'Hara LM, Herman A, Welsh CJ, et al. Are injured workers with higher rehabilitation service utilization less likely to be persistent opioid users? A cross-sectional study. BMC health services research. 2019;19(1):32.

57. Kurteva S, Weir D, Schmidt A, Lee T, Tamblyn R. Patterns of opioid utilization in the 90-days post-hospital discharge and risk of readmissions and emergency department visits. Pharmacoepidemiology and Drug Safety. 2018;27 (Supplement 2):326.

58. Kin C, Sceats LA, Kamdar N, Shelton A, Kirilcuk N, Gurland BH, et al. Prolonged opioid use after anorectal vs. abdominal colorectal operations: Who is at risk? Diseases of the Colon and Rectum. 2018;61 (5):e282.

59. Kennedy J, Seymour CW, Chang CH, Girard TD, Kim C, Lo-Ciganic J, et al. Patterns of inpatient, intensive care, and post-discharge opioid prescribing to opioid-naive patients in a large health system. American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS. 2018;197(MeetingAbstracts).

60. Karp JF, Lee CW, McGovern J, Stoehr G, Chang CC, Ganguli M. Clinical and demographic covariates of chronic opioid and non-opioid analgesic use in rural-dwelling older adults: the MoVIES project. International Psychogeriatrics. 2013;25(11):1801-10.

61. Karamchandani K, Pyati S, Bryan W, Pepin M, Lehman E, Raghunathan K. Persistent post-intensive care opioid use in US veterans after major abdominal surgery. Critical Care. 2019;23(Supplement 2).

62. Kang C, Shu X, Herrell SD, Miller NL, Hsi RS. Opiate Exposure and Predictors of Increased Opiate Use After Ureteroscopy. Journal of endourology. 2019;33(6):480-5.

63. Kalakoti P, Shamrock A, Eisenberg JM, Hendrickson NR, Laratta JL, Pugely AJ. 145. Opioid utilization in adult idiopathic scoliosis after multilevel deformity correction: postoperative trends and factors associated with long-term use. Spine Journal. 2019;19(9 Supplement):S70.

64. Kalakoti P, Hendrickson NR, Bedard NA, Pugely AJ. Opioid Utilization Following Lumbar Arthrodesis: Trends and Factors Associated With Long-term Use. Spine. 2018;43(17):1208-16.

65. Jiang X, Orton M, Feng R, Hossain E, Malhotra NR, Zager EL, et al. Chronic Opioid Usage in Surgical Patients in a Large Academic Center. Annals of Surgery. 2017;265(4):722-7.

66. Huang A, Azam A, Segal S, Pivovarov K, Katznelson G, Ladak SS, et al. Chronic postsurgical pain and persistent opioid use following surgery: the need for a transitional pain service. Pain Management. 2016;6(5):435-43.

67. Hsia HL, Takemoto S, van de Ven T, Pyati S, Buchheit T, Ray N, et al. Acute Pain Is Associated With Chronic Opioid Use After Total Knee Arthroplasty. Regional Anesthesia & Pain Medicine. 2018;43(7):705-11.

68. Hosier GW, McGregor T, Beiko D, Jaeger M, Booth C, Whitehead M, et al. Persistent Opioid Use Among Patients with Urolithiasis: A Population based Study. European Urology Focus. 2019.

69. Harbaugh CM, Nalliah RP, Hu HM, Englesbe MJ, Waljee JF, Brummett CM. Persistent opioid use after wisdom tooth extraction. JAMA - Journal of the American Medical Association. 2018;320(5):504-6.

70. Harbaugh CM, Lee JS, Hu HM, McCabe SE, Voepel-Lewis T, Englesbe MJ, et al. Persistent Opioid Use Among Pediatric Patients After Surgery. Pediatrics. 2018;141(1).

71. Hand BN, Krause JS, Simpson KN. Dose and Duration of Opioid Use in Propensity Score-Matched, Privately Insured Opioid Users With and Without Spinal Cord Injury. Archives of Physical Medicine & Rehabilitation. 2018;99(5):855-61.

72. Hadlandsmyth K, Vander Weg MW, McCoy KD, Mosher HJ, Vaughan-Sarrazin MS, Lund BC. Risk for Prolonged Opioid Use Following Total Knee Arthroplasty in Veterans. Journal of Arthroplasty. 2018;33(1):119-23.

73. Gibson CJ, Li Y, Bertenthal D, Huang AJ, Rife T, Seal KH. Are menopause symptoms related to increased risk for chronic pain and opioid use in midlife? Journal of General Internal Medicine. 2018;33 (2 Supplement 1):118.

74. Gibson C, Li Y, Bertenthal D, Huang A, Seal K. Chronic pain and high-risk opioid use in women veterans: Is there an association with menopause? Menopause. 2017;24 (12):1425.

75. Furlan AD, Hassan S, Famiyeh IM, Wang W, Dhanju J. Long-term opioid use after discharge from inpatient musculoskeletal rehabilitation. Journal of Rehabilitation Medicine. 2016;48(5):464-8.

76. Fields AC, Cavallaro PM, Correll DJ, Rubin MS, Sequist T, Khawaja A, et al. Predictors of Prolonged Opioid Use Following Colectomy. Diseases of the colon and rectum. 2019;62(9):1117-23.

77. Dunn LK, Yerra S, Fang S, Hanak MF, Leibowitz MK, Tsang S, et al. Incidence and Risk Factors for Chronic Postoperative Opioid Use After Major Spine Surgery: A Cross-Sectional Study With Longitudinal Outcome. Anesthesia & Analgesia. 2018;127(1):247-54.

78. Donohue JM, Kennedy JN, Seymour CW, Girard TD, Lo-Ciganic WH, Kim CH, et al. Patterns of opioid administration among opioid-naive inpatients and associations with postdischarge opioid use a cohort study. Annals of Internal Medicine. 2019;171(2):81-90.

79. DeVeaugh-Geiss A, Kadakia A, Chilcoat H, Alexander L, Coplan P. A retrospective cohort study of long-term immediate-release hydrocodone/acetaminophen use and acetaminophen dosing above the Food and Drug Administration recommended maximum daily limit among commercially insured individuals in the United States (2008-2013). Journal of Pain. 2015;16(6):569-79.e1.

80. DeVeaugh-Geiss A, Coplan P, Kadakia A. Dose and duration of use among commercially insured adults prescribed immediate-release (IR) or extended-release (ER) oxycodone. Pharmacoepidemiology and Drug Safety. 2015;1):130.

81. Daubs MD, Gaffney DL, Lawrence BD, Brodke DS, Patel AA, Higgins T. Long-term narcotic usage following spinal surgery. Spine Journal. 2012;1):121S-2S.

82. Curtis JR, Xie F, Smith C, Saag KG, Chen L, Beukelman T, et al. Changing Trends in Opioid Use Among Patients With Rheumatoid Arthritis in the United States. Arthritis & Rheumatology. 2017;69(9):1733-40.

83. Cron D, Hammoud A, Hu HM, Lee J, Brummett C, Waljee J, et al. Prevalence and patterns of opioid use before and after liver transplantation. American Journal of Transplantation. 2018;18 (Supplement 2):63.

84. Chieng LO, Madhavan K, Teferi NT, Wang MY, Vanni S. Prolonged use of narcotic following lumbar spine surgery: Predictive factors and outcome analysis. Clinical Neurosurgery. 2018;65 (Supplement 1):132.

85. Chen TC, Chen LC, Knaggs RD. Defining persistent tramadol utilization using a multiple-dimension algorithm-a cohort study in the United Kingdom primary care setting. International Journal of Pharmacy Practice. 2016;1):25.

86. Carroll K, Northrup T, Yolanda V, Zare M, Brian R, Michelle K, et al. Analysis of morphine milligram equivalents of opioids prescribed in a large urban safety net system. Postgraduate Medicine. 2016;128 (Supplement 2):14-5.

87. Carroll I, Barelka P, Wang CK, Wang BM, Gillespie MJ, McCue R, et al. A pilot cohort study of the determinants of longitudinal opioid use after surgery. Anesthesia & Analgesia. 2012;115(3):694-702.

88. Carey EP, Nolan C, Kerns RD, Ho PM, Frank JW. Association Between Facility-Level Utilization of Non-pharmacologic Chronic Pain Treatment and Subsequent Initiation of Long-Term Opioid Therapy. Journal of General Internal Medicine. 2018;33(Suppl 1):38-45.

89. Calcaterra SL, Yamashita TE, Min SJ, Keniston A, Frank JW, Binswanger IA. Opioid Prescribing at Hospital Discharge Contributes to Chronic Opioid Use. Journal of General Internal Medicine. 2016;31(5):478-85.

90. Calcaterra SL, Yamashita TE, Keniston A, Frank JW, Binswanger I. The role of the hospital physician in long term opioid use. Journal of General Internal Medicine. 2015;2):S281.

91. Calcaterra SL, Scarbro S, Binswanger IA, Colborn KL. Prediction of future chronic opioid use among hospitalized patients: A machine learning approach. Journal of General Internal Medicine. 2017;32 (2 Supplement 1):S280.

92. Brummett CM, Waljee JF, Goesling J, Moser S, Lin P, Englesbe MJ, et al. New Persistent Opioid Use After Minor and Major Surgical Procedures in US Adults. JAMA Surgery. 2017;152(6):e170504.

93. Brescia AA, Harrington CA, Mazurek AA, Ward ST, Lee JSJ, Hu HM, et al. Factors Associated With New Persistent Opioid Usage After Lung Resection. The Annals of thoracic surgery. 2019;107(2):363-8.

94. Birke H, Ekholm O, Sjogren P, Fredheim O, Clausen T, Skurtveit S. Tramadol use in Norway: A registerbased population study. Pharmacoepidemiology and Drug Safety. 2018;27 (Supplement 2):413.

95. Bicket MC, Murimi IB, Mansour O, Wu CL, Alexander GC. Association of new opioid continuation with surgical specialty and type in the United States. American journal of surgery. 2019;218(5):818-27.

96. Bartels K, Fernandez-Bustamante A, McWilliams SK, Hopfer CJ, Mikulich-Gilbertson SK. Long-term opioid use after inpatient surgery - A retrospective cohort study. Drug & Alcohol Dependence. 2018;187:61-5.

97. Barnett ML, Zhao X, Fine MJ, Thorpe CT, Thorpe JM, Sileanu F, et al. Are emergency physician opioid prescribing patterns associated with the risk of long-term use in veterans? Journal of General Internal Medicine. 2018;33 (2 Supplement 1):117-8.

98. Azad TD, Vail D, Bentley J, Han SS, Suarez P, Varshneya K, et al. Initial Provider Specialty Is Associated With Long-term Opiate Use in Patients With Newly Diagnosed Low Back and Lower Extremity Pain. Spine. 2019;44(3):211-8.

99. Aizen J, Ham S, Adamic B, Labbate C, Andolfi C, Faris S. Impact of urologic surgery on increased rates of persistent opioid use: A national sample. Journal of Urology. 2019;201(4 Supplement 1):e197-e8.

100. Abolfotouh S, Fogarty CA, Matera J, Berry AM, Abolfotouh MA, Choma TJ, et al. 84. Incidence and predictors of long-term opioid use following cervical spine fusion surgery. Spine Journal. 2019;19(9 Supplement):S41.

101. Hooten WM, St Sauver JL, McGree ME, Jacobson DJ, Warner DO. Incidence and Risk Factors for Progression From Short-term to Episodic or Long-term Opioid Prescribing: A Population-Based Study. Mayo Clin Proc. 2015;90(7):850-6.

102. Zin CS, Nazar NI, Rahman NSA, Ahmad WR, Rani NS, Ng KS. Patterns of initial opioid prescription and its association with short-term and long-term use among opioid-naive patients in Malaysia: A retrospective cohort study. BMJ Open. 2019;9(7):e027203.

103. Wu BU, Butler RK, Chen W. Factors Associated With Opioid Use in Patients Hospitalized for Acute Pancreatitis. JAMA network open. 2019;2(4):e191827.

104. Westermann RW, Mather RC, 3rd, Bedard NA, Anthony CA, Glass NA, Lynch TS, et al. Prescription Opioid Use Before and After Hip Arthroscopy: A Caution to Prescribers. Arthroscopy : the journal of arthroscopic & related surgery : official publication of the Arthroscopy Association of North America and the International Arthroscopy Association. 2019;35(2):453-60.

105. Smith ME, Lee JS, Bonham A, Varban OA, Finks JF, Carlin AM, et al. Effect of new persistent opioid use on physiologic and psychologic outcomes following bariatric surgery. Surgical endoscopy. 2019;33(8):2649-56.

106. Shah D, Zhao X, Wei W, Gandhi K, Dwibedi N, Webster L, et al. A Longitudinal Study of the Association of Opioid Use with Change in Pain Interference and Functional Limitations in a Nationally Representative Cohort of Adults with Osteoarthritis in the United States. Advances in Therapy. 2019.

107. Schroeder AR, Dehghan M, Newman TB, Bentley JP, Park KT. Association of Opioid Prescriptions From Dental Clinicians for US Adolescents and Young Adults With Subsequent Opioid Use and Abuse. JAMA internal medicine. 2019;179(2):145-52.

108. Roughead EE, Lim R, Ramsay E, Moffat AK, Pratt NL. Persistence with opioids post discharge from hospitalisation for surgery in Australian adults: a retrospective cohort study. BMJ open. 2019;9(4):e023990.

109. Reddy S, Orenstein LAV, Strunk A, Garg A. Incidence of Long-term Opioid Use among Opioid-Naive Patients with Hidradenitis Suppurativa in the United States. JAMA Dermatology. 2019;155(11):1284-90.

110. Prentice HA, Inacio MCS, Singh A, Namba RS, Paxton EW. Preoperative Risk Factors for Opioid Utilization After Total Hip Arthroplasty. The Journal of bone and joint surgery American volume. 2019;101(18):1670-8.

111. Peahl AF, Dalton VK, Montgomery JR, Lai Y-L, Hu HM, Waljee JF. Rates of New Persistent Opioid Use After Vaginal or Cesarean Birth Among US Women. JAMA network open. 2019;2(7):e197863.

112. Olopoenia A, Slejko J, Simoni-Wastila L, Camelo-Castillo W. Patterns of prescription opioid use among commercially insured United States youth and young adults with co-morbid chronic pain and mental health conditions. Pharmacoepidemiology and Drug Safety. 2019;28(Supplement 2):445-6.

113. Oh G, Abner EL, Fardo DW, Freeman PR, Moga DC. Patterns and predictors of chronic opioid use in older adults: A retrospective cohort study. PloS one. 2019;14(1):e0210341.

114. Noureldin M, Higgins PDR, Govani SM, Cohen-Mekelburg S, Kenney BC, Stidham RW, et al. Incidence and predictors of new persistent opioid use following inflammatory bowel disease flares treated with oral corticosteroids. Alimentary pharmacology & therapeutics. 2019;49(1):74-83.

115. Muller C, Watson AR, Blevins Peratikos MB, Morris LC, Stringer EA. Prevalence of preoperative high-dose chronic opioid use and opioid tapering in knee, shoulder, and spine surgery. Pain Medicine (United States)_1. 2019;20(3):594.

116. Mosher HJ, Hofmeyer BA, Hadlandsmyth K, Richardson KK, Lund BC. Predictors of Long-Term Opioid Use After Opioid Initiation at Discharge From Medical and Surgical Hospitalizations. Journal of Hospital Medicine (Online). 2018;13(4):243-8.

117. Meisel ZF, Lupulescu-Mann N, Charlesworth CJ, Kim H, Sun BC. Conversion to Persistent or High-Risk Opioid Use After a New Prescription From the Emergency Department: Evidence From Washington Medicaid Beneficiaries. Annals of emergency medicine. 2019;74(5):611-21.

118. Lund BC, Ohl ME, Hadlandsmyth K, Mosher HJ. Regional and Rural-Urban Variation in Opioid Prescribing in the Veterans Health Administration. Military medicine. 2019;184(11-12):894-900.

119. Leroux TS, Saltzman BM, Sumner SA, Maldonado-Rodriguez N, Agarwalla A, Ravi B, et al. Elective Shoulder Surgery in the Opioid Naive: Rates of and Risk Factors for Long-term Postoperative Opioid Use. The American journal of sports medicine. 2019;47(5):1051-6.

120. Kazis LE, Ameli O, Rothendler J, Garrity B, Cabral H, McDonough C, et al. Observational retrospective study of the association of initial healthcare provider for new-onset low back pain with early and long-term opioid use. BMJ open. 2019;9(9):e028633.

121. Karhade AV, Schwab JH, Bedair HS. Development of Machine Learning Algorithms for Prediction of Sustained Postoperative Opioid Prescriptions After Total Hip Arthroplasty. The Journal of arthroplasty. 2019;34(10):2272-7.e1.

122. Jildeh TR, Taylor KA, Khalil LS, Okoroha KR, Matar RN, Geisenhoff A, et al. Risk Factors for Postoperative Opioid Use in Arthroscopic Meniscal Surgery. Arthroscopy : the journal of arthroscopic & related surgery : official publication of the Arthroscopy Association of North America and the International Arthroscopy Association. 2019;35(2):575-80.

123. Harris AB, Marrache M, Jami M, Raad M, Puvanesarajah V, Hassanzadeh H, et al. Chronic opioid use following anterior cervical discectomy and fusion surgery for degenerative cervical pathology. The spine journal : official journal of the North American Spine Society. 2020;20(1):78-86.

124. Harbaugh CM, Lee JS, Chua K-P, Kenney B, Iwashyna TJ, Englesbe MJ, et al. Association Between Long-term Opioid Use in Family Members and Persistent Opioid Use After Surgery Among Adolescents and Young Adults. JAMA surgery. 2019;154(4):e185838.

125. Gossett TD, Finney FT, Hu HM, Waljee JF, Brummett CM, Walton DM, et al. New Persistent Opioid Use and Associated Risk Factors Following Treatment of Ankle Fractures. Foot & ankle international. 2019;40(9):1043-51.

126. Gil JA, Gunaseelan V, DeFroda SF, Brummett CM, Bedi A, Waljee JF. Risk of Prolonged Opioid Use Among Opioid-Naive Patients After Common Shoulder Arthroscopy Procedures. The American journal of sports medicine. 2019;47(5):1043-50.

127. Finney FT, Gossett TD, Hu HM, Waljee JF, Brummett CM, Talusan PG, et al. New Persistent Opioid Use Following Common Forefoot Procedures for the Treatment of Hallux Valgus. The Journal of bone and joint surgery American volume. 2019;101(8):722-9.

128. Dy CJ, Peacock K, Olsen MA, Ray WZ, Brogan DM. Frequency and Risk Factors for Prolonged Opioid Prescriptions After Surgery for Brachial Plexus Injury. The Journal of hand surgery. 2019;44(8):662-8.e1.

129. Durand Z, Nechuta S, Krishnaswami S, Hurwitz EL, McPheeters M. Prevalence and Risk Factors Associated With Long-term Opioid Use After Injury Among Previously Opioid-Free Workers. JAMA network open. 2019;2(7):e197222.

130. Dunn LK, Taylor DG, Smith SJ, Skojec AJ, Wang TR, Chung J, et al. Persistent post-discharge opioid prescribing after traumatic brain injury requiring intensive care unit admission: A cross-sectional study with longitudinal outcome. PloS one. 2019;14(11):e0225787.

131. Cook DJ, Kaskovich SW, Pirkle SC, Mica MAC, Shi LL, Lee MJ. Benchmarks of Duration and Magnitude of Opioid Consumption After Total Hip and Knee Arthroplasty: A Database Analysis of 69,368 Patients. The Journal of arthroplasty. 2019;34(4):638-44.e1.

132. Chitnavis MV, Baray M, Northup PG, Tuskey AG, Behm BW. Opioid use and misuse in ulcerative colitis. World journal of gastrointestinal pharmacology and therapeutics. 2019;10(1):22-8.

133. Chen SK, Feldman CH, Brill G, Lee YC, Desai RJ, Kim SC. Use of prescription opioids among patients with rheumatic diseases compared to patients with hypertension in the USA: a retrospective cohort study. BMJ open. 2019;9(6):e027495.

134. Chen EY, Lasky R, Dotterweich WA, Niu R, Tybor DJ, Smith EL. Chronic Prescription Opioid Use Before and After Total Hip and Knee Arthroplasty in Patients Younger Than 65 Years. The Journal of arthroplasty. 2019;34(10):2319-23.

135. Catchpool M, Knight J, Young JT, Clarke P, Barrington MJ, Choong PFM, et al. Opioid use prior to elective surgery is strongly associated with persistent use following surgery: an analysis of 14 354 Medicare patients. ANZ journal of surgery. 2019;89(11):1410-6.

136. Carey ET, Strassle PD, Moore KJ, Schiff LD, Louie M. Associations Between Preoperative Depression, Hysterectomy, and Postoperative Opioid Use. Journal of Minimally Invasive Gynecology. 2019;26(7 Supplement):S71.

137. Anoushiravani AA, Kim KY, Roof M, Chen K, O'Connor CM, Vigdorchik J, et al. Risk factors associated with persistent chronic opioid use following THA. European Journal of Orthopaedic Surgery and Traumatology. 2020.

138. Zarling BJ, Yokhana SS, Herzog DT, Markel DC. Preoperative and Postoperative Opiate Use by the Arthroplasty Patient. Journal of Arthroplasty. 2016;31(10):2081-4.

139. Zamora-Legoff JA, Achenbach SJ, Crowson CS, Krause ML, Davis JM, 3rd, Matteson EL. Opioid use in patients with rheumatoid arthritis 2005-2014: a population-based comparative study. Clinical Rheumatology. 2016;35(5):1137-44.

140. Thielke SM, Simoni-Wastila L, Edlund MJ, DeVries A, Martin BC, Braden JB, et al. Age and sex trends in long-term opioid use in two large American health systems between 2000 and 2005. Pain Medicine. 2010;11(2):248-56.

141. Slater ME, De Lima J, Campbell K, Lane L, Collins J. Opioids for the management of severe chronic nonmalignant pain in children: a retrospective 1-year practice survey in a children's hospital. Pain Medicine. 2010;11(2):207-14.

142. Schoenfeld AJ, Nwosu K, Jiang W, Yau AL, Chaudhary MA, Scully RE, et al. Risk Factors for Prolonged Opioid Use Following Spine Surgery, and the Association with Surgical Intensity, Among Opioid-Naive Patients. Journal of Bone & Joint Surgery - American Volume. 2017;99(15):1247-52.

143. Richter MD, Achenbach SJ, Zamora-Legoff JA, Crowson CS, Matteson EL. Opioid use in patients with polymyalgia rheumatica. Clinical & Experimental Rheumatology. 2017;35(6):1014-7.

144. Rhon DI, Snodgrass SJ, Cleland JA, Sissel CD, Cook CE. Predictors of chronic prescription opioid use after orthopedic surgery: derivation of a clinical prediction rule. Perioperative Medicine. 2018;7:25.

145. Raebel MA, Newcomer SR, Reifler LM, Boudreau D, Elliott TE, DeBar L, et al. Chronic use of opioid medications before and after bariatric surgery. JAMA. 2013;310(13):1369-76.

146. Qureshi R, Werner B, Puvanesarajah V, Horowitz JA, Jain A, Sciubba D, et al. Factors Affecting Long-Term Postoperative Narcotic Use in Discectomy Patients. World Neurosurgery. 2018;112:e640-e4.

147. Quinn PD, Hur K, Chang Z, Krebs EE, Bair MJ, Scott EL, et al. Incident and long-term opioid therapy among patients with psychiatric conditions and medications: a national study of commercial health care claims. Pain. 2017;158(1):140-8.

148. Pauly NJ, Michailidis L, Kindred MG, Flomenhoft D, Lofwall MR, Walsh SL, et al. Predictors of Chronic Opioid Use in Newly Diagnosed Crohn's Disease. Inflammatory Bowel Diseases. 2017;23(6):1004-10.

149. Oh G, Abner EL, Fardo DW, Freeman PR, Moga DC. Patterns and predictors of long-term opioid use in older adults. Pharmacoepidemiology and Drug Safety. 2018;27 (Supplement 2):327.

150. Mueller KG, Memtsoudis SG, Mariano ER, Baker LC, Mackey S, Sun EC. Lack of Association Between the Use of Nerve Blockade and the Risk of Persistent Opioid Use Among Patients Undergoing Shoulder Arthroplasty: Evidence From the Marketscan Database. Anesthesia & Analgesia. 2017;125(3):1014-20.

151. Marschall U, L'Hoest H, Radbruch L, Hauser W. Long-term opioid therapy for chronic non-cancer pain in Germany.[Erratum appears in Eur J Pain. 2017 Nov;21(10):1774; PMID: 28990730]. European Journal of Pain. 2016;20(5):767-76.

152. Macey TA, Morasco BJ, Duckart JP, Dobscha SK. Patterns and correlates of prescription opioid use in OEF/OIF veterans with chronic noncancer pain. Pain Medicine. 2011;12(10):1502-9.

153. Kimmel PL, Fwu CW, Abbott KC, Eggers AW, Kline PP, Eggers PW. Opioid Prescription, Morbidity, and Mortality in United States Dialysis Patients. Journal of the American Society of Nephrology. 2017;28(12):3658-70.

154. Kim SC, Choudhry N, Franklin JM, Bykov K, Eikermann M, Lii J, et al. Patterns and predictors of persistent opioid use following hip or knee arthroplasty. Osteoarthritis & Cartilage. 2017;25(9):1399-406.

155. Johnson SP, Chung KC, Zhong L, Shauver MJ, Engelsbe MJ, Brummett C, et al. Risk of Prolonged Opioid Use Among Opioid-Naive Patients Following Common Hand Surgery Procedures. Journal of Hand Surgery - American Volume. 2016;41(10):947-57.e3.

156. Hudson TJ, Painter JT, Martin BC, Austen MA, Williams JS, Fortney JC, et al. Pharmacoepidemiologic analyses of opioid use among OEF/OIF/OND veterans. Pain. 2017;158(6):1039-45.

157. Hoffman EM, Watson JC, St Sauver J, Staff NP, Klein CJ. Association of Long-term Opioid Therapy With Functional Status, Adverse Outcomes, and Mortality Among Patients With Polyneuropathy. JAMA Neurology. 2017;74(7):773-9.

158. Hansen CA, Inacio MCS, Pratt NL, Roughead EE, Graves SE. Chronic Use of Opioids Before and After Total Knee Arthroplasty: A Retrospective Cohort Study. Journal of Arthroplasty. 2017;32(3):811-7.e1.

159. Han L, Allore H, Goulet J, Bathulapali H, Skanderson M, Brandt C, et al. Opioid dosing trends over eight years among US Veterans with musculoskeletal disorders after returning from service in support of recent conflicts. Annals of epidemiology. 2017;27(9):563-9 e3.

160. Hamina A, Taipale H, Tanskanen A, Tolppanen AM, Karttunen N, Pylkkanen L, et al. Long-term use of opioids for nonmalignant pain among community-dwelling persons with and without Alzheimer disease in Finland: a nationwide register-based study. Pain. 2017;158(2):252-60.

161. Franklin GM, Rahman EA, Turner JA, Daniell WE, Fulton-Kehoe D. Opioid use for chronic low back pain: A prospective, population-based study among injured workers in Washington state, 2002-2005. Clinical Journal of Pain. 2009;25(9):743-51.

162. Edlund MJ, Austen MA, Sullivan MD, Martin BC, Williams JS, Fortney JC, et al. Patterns of opioid use for chronic noncancer pain in the Veterans Health Administration from 2009 to 2011. Pain. 2014;155(11):2337-43.

163. Dau JD, Lee M, Ward MM, Gensler LS, Brown MA, Learch TJ, et al. Opioid Analgesic Use in Patients with Ankylosing Spondylitis: An Analysis of the Prospective Study of Outcomes in an Ankylosing Spondylitis Cohort. Journal of Rheumatology. 2018;45(2):188-94.

164. Daoust R, Paquet J, Moore L, Gosselin S, Gelinas C, Rouleau DM, et al. Incidence and Risk Factors of Long-term Opioid Use in Elderly Trauma Patients. Annals of Surgery. 2018;268(6):985-91.

165. Clarke H, Soneji N, Ko DT, Yun L, Wijeysundera DN. Rates and risk factors for prolonged opioid use after major surgery: population based cohort study. BMJ. 2014;348:g1251.

166. Berecki-Gisolf J, Collie A, McClure RJ. Prescription opioids for occupational injury: results from workers' compensation claims records. Pain Medicine. 2014;15(9):1549-57.

167. Bedard NA, Pugely AJ, Westermann RW, Duchman KR, Glass NA, Callaghan JJ. Opioid Use After Total Knee Arthroplasty: Trends and Risk Factors for Prolonged Use. Journal of Arthroplasty. 2017;32(8):2390-4.

168. Bedard NA, Pugely AJ, Dowdle SB, Duchman KR, Glass NA, Callaghan JJ. Opioid Use Following Total Hip Arthroplasty: Trends and Risk Factors for Prolonged Use. Journal of Arthroplasty. 2017;32(12):3675-9.

169. Ahmedani BK, Peterson EL, Wells KE, Lanfear DE, Williams LK. Policies and events affecting prescription opioid use for non-cancer pain among an insured patient population. Pain Physician. 2014;17(3):205-16.

170. Almakadma YS, Simpson K. Opioid therapy in non-cancer chronic pain patients: Trends and efficacy in different types of pain, patients age and gender. Saudi journal of anaesthesia. 2013;7(3):291-5.

171. Azad T, Vail D, Bentley J, Han S, Veeravagu A, Desai M, et al. Initial provider type is associated with opiate use in patients with newly diagnosed low back pain. Journal of Neurosurgery. 2018;128 (4):69.

172. Azevedo LF, Costa-Pereira A, Mendonca L, Dias CC, Castro-Lopes JM. A population-based study on chronic pain and the use of opioids in Portugal. Pain. 2013;154(12):2844-52.

173. Ballas SK, Kanter J, Agodoa I, Howard R, Wade S, Noxon V, et al. Opioid utilization patterns in united states patients with sickle cell disease. Blood Conference: 59th Annual Meeting of the American Society of Hematology, ASH. 2017;130(Supplement 1).

174. Becker W, Edelman EJ, Gordon KS, Kerns R, Crystal S, Fiellin LE, et al. Trends and correlates of opioid analgesic receipt among veterans with and without HIV: 1999-2010. Journal of General Internal Medicine. 2013;1):S227.

175. Curtis HJ, Croker R, Walker AJ, Richards GC, Quinlan J, Goldacre B. Opioid prescribing trends and geographical variation in England, 1998-2018: a retrospective database study. The lancet Psychiatry. 2019;6(2):140-50.

176. Diasso PDK, Sjogren P, Hojsted J, Nielsen SD, Main KM, Kurita GP. Patient reported outcomes and neuropsychological testing in patients with chronic non-cancer pain in long-term opioid therapy: a pilot study. Scandinavian journal of pain. 2019;19(3):533-43.

177. Edlund MJ, Martin BC, Devries A, Fan MY, Braden JB, Sullivan MD. Trends in use of opioids for chronic noncancer pain among individuals with mental health and substance use disorders: the TROUP study. Clinical Journal of Pain. 2010;26(1):1-8.

178. Englett BM, Botts S, Talbert J, Lane M. Opiate use for chronic nonmalignant pain. Journal of Pharmacy Practice. 2011;24 (2):255.

179. Fuzier R, Serres I, Bourrel R, Palmaro A, Lapeyre-Mestre M. Analgesic Drug Prescription After Carpal Tunnel Surgery: A Pharmacoepidemiological Study Investigating Postoperative Pain. Regional Anesthesia & Pain Medicine. 2018;43(1):19-24.

180. Hozack BA, Rivlin M, Lutsky KF, Graham J, Lucenti L, Foltz C, et al. Preoperative Exposure to Benzodiazepines or Sedative/hypnotics Increases the Risk of Greater Filled Opioid Prescriptions After Surgery. Clinical orthopaedics and related research. 2019;477(6):1482-8.

181. Huffman KL, Sweis GW, Gase A, Scheman J, Covington EC. Opioid use 12 months following interdisciplinary pain rehabilitation with weaning. Pain Medicine. 2013;14(12):1908-17.

182. Jafari A, Shen SA, Bracken DJ, Pang J, DeConde AS. Incidence and predictive factors for additional opioid prescription after endoscopic sinus surgery. International Forum of Allergy and Rhinology. 2018;8(8):883-9.

183. Jakubow P, Lotowska-Cwiklewska AM, Kosciuczuk U. The use of opioid analgesics in chronic pain therapy - A retrospective, single-center study. Palliative Medicine in Practice. 2019;13(1):11-6.

184. Jorgensen CC, Petersen M, Kehlet H, Aasvang EK. Analgesic consumption trajectories in 8975 patients 1 year after fast-track total hip or knee arthroplasty. European Journal of Pain (United Kingdom). 2018;22(8):1428-38.

185. Khazi ZM, Lu Y, Patel BH, Cancienne JM, Werner B, Forsythe B. Risk factors for opioid use after total shoulder arthroplasty. Journal of Shoulder and Elbow Surgery. 2019.

186. Khazi ZM, Lu Y, Shamrock AG, Duchman KR, Westermann RW, Wolf BR. Opioid use following shoulder stabilization surgery: risk factors for prolonged use. Journal of shoulder and elbow surgery. 2019;28(10):1928-35.

187. Korner D, Ahrend MD, Ateschrang A, Schreiner AJ, Kraus TM, Stockle U, et al. Risk factors for opioid analgesic drug use at discharge after sports traumatology procedure. Sports Orthopaedics and Traumatology. 2019;35(4):435-42.

188. Log T, Skurtveit S, Hartz I, Tverdal A, Handal M, Furu K. The effect of adolescent smoking on opioid use - A prospective population based cohort study. Pharmacoepidemiology and Drug Safety (PDS). 2009;18 (S1):S235-S6.

189. Ménard S PM, André G, Ariano-Lortie, Pathé A, Lévesque M, Houle J, Raymond M, Rochon A, Vargas-Schaffer G, Royer C, Cogan J. The Prevalence of Pain 6 Months After Cardiac Surgery and the Likelihood of Continued Opioid Requirements - Preliminary Data. . 17e congrès mondial, Pain IASP, Boston, État-Unis. 12-16 septembre 12-16 2018.

190. Nicholson AD, Kassam HF, Steele JL, Passarelli NR, Blaine TA, Kovacevic D. Development of a clinical risk calculator for prolonged opioid use after shoulder surgery. Journal of shoulder and elbow surgery. 2019;28(11):2225-31.

191. Ren M, Bryant BR, Harris AB, Skolasky RL, Kebaish KM, Riley LH, et al. 255. Preoperative opioid dosage and duration are associated with increased long-term opioid use after adult spinal deformity surgery. Spine Journal. 2019;19(9 Supplement):S125.

192. Rosenbloom BN, McCartney CJL, Canzian S, Kreder HJ, Katz J. Predictors of Prescription Opioid Use 4 Months After Traumatic Musculoskeletal Injury and Corrective Surgery: A Prospective Study. Journal of Pain. 2017;18(8):956-63.

193. Simoni AH, Nikolajsen L, Olesen AE, Christiansen CF, Pedersen AB. Opioid use after hip fracture surgery. Pharmacoepidemiology and Drug Safety. 2018;27 (Supplement 2):329.

194. Sutin AR, Stephan Y, Luchetti M, Terracciano A. The prospective association between personality traits and persistent pain and opioid medication use. Journal of psychosomatic research. 2019;123:109721.

195. Uhrbrand P, Helmig P, Nikolajsen L. Prolonged Opioid-use after planned spinal surgery: A prospective study. Acta Anaesthesiologica Scandinavica. 2019;63(8):e36.

196. Westermann RW, Anthony CA, Bedard N, Glass N, Bollier M, Hettrich CM, et al. Opioid Consumption After Rotator Cuff Repair. Arthroscopy. 2017;33(8):1467-72.

197. Yenikomshian HA, Curtis EE, Carrougher GJ, Qiu Q, Gibran NS, Mandell SP. Outpatient opioid use of burn patients: A retrospective review. Burns : journal of the International Society for Burn Injuries. 2019;45(8):1737-42.

198. Chenaf C, Kabore JL, Delorme J, Pereira B, Mulliez A, Zenut M, et al. Prescription opioid analgesic use in France: Trends and impact on morbidity-mortality. Eur J Pain. 2019;23(1):124-34.

199. Wright AK, Sikora M, Leveque J-C. Characterizing the Risk of Long-Term Opioid Utilization in Patients Undergoing Lumbar Spine Surgery. Spine. 2020;45(1):E54-E60.

200. Plott D, Miller S. Predictors for high dose chronic opioid therapy. Drug and Alcohol Dependence. 2015;156:e178.

201. Carman WJ, Cook SF, Wurzelmann JI, McAfee AT. Characteristics of users of chronic prescription analgesics. Pharmacoepidemiology and Drug Safety. 2011;1):S35.

202. Argoff C, Stanos S, Irving G, Puenpatom R, Zhao S, Gould E. Demographic characteristics of patients prescribed chronic opioid therapy for chronic noncancer pain: Data from the opioid utilization study (OPUS). Journal of Pain. 2010;1):S46.

203. Adan M, Chen LC, Knaggs R. Exploring factors linked to in-patient hospitalisation amongst non-cancer pain patients prescribed long-term strong opioids in UK primary care. Pharmacoepidemiology and Drug Safety. 2016;25 (Supplement 3):670.

204. Foy R, Leaman B, McCrorie C, Petty D, House A, Bennett M, et al. Prescribed opioids in primary care: cross-sectional and longitudinal analyses of influence of patient and practice characteristics. BMJ Open. 2016;6(5):e010276.

205. Whiteside LK, Russo J, Wang J, Ranney ML, Rivara F, Peterson R, et al. Determinants of long-term prescription opioid use after acute trauma in adolescents. Academic Emergency Medicine. 2014;1):S47-S8.

206. Krebs EE, Lurie JD, Fanciullo G, Tosteson TD, Blood EA, Carey TS, et al. Predictors of long-term opioid use among patients with painful lumbar spine conditions. Journal of Pain. 2010;11(1):44-52.

207. Grace TR, Khanna K, Choo KJ, Croci R, Feeley BT, Ma CB, et al. The influence of preoperative opioid use on inpatient opioid requirements and discharge prescriptions after primary shoulder arthroplasty. Journal of Shoulder & Elbow Surgery. 2018;27(9):1572-9.

208. Ashaye T, Hounsome N, Carnes D, Taylor SJC, Homer K, Eldridge S, et al. Opioid prescribing for chronic musculoskeletal pain in UK primary care: results from a cohort analysis of the COPERS trial. BMJ Open. 2018;8(6):e019491.

209. Bolarinwa SA, Casp AA, Cancienne JM, Werner BC, Browne JA. Narcotic use and total hip arthroplasty. Hip international : the journal of clinical and experimental research on hip pathology and therapy. 2019;29(4):379-84.

210. Young JC, Wu JM, Pate V, Funk MJ. Estimates of prolonged opioid use following surgery vary by orders of magnitude across various definitions. Pharmacoepidemiology and Drug Safety. 2019;28(Supplement 2):231.

211. Young JC, Dasgupta N, Chidgey BA, Jonsson Funk M. Postsurgical Opioid Prescriptions and Risk of Long-term Use: An Observational Cohort Study Across the United States. Annals of Surgery. 2019.

212. Young JC, Jonsson Funk M, Willis-Gray M, Pate V, Wu JM. Risk of prolonged opioid use after surgery for stress incontinence and pelvic organ prolapse. Female Pelvic Medicine and Reconstructive Surgery. 2019;25(5 Supplement 1):S55.

213. Tam C, Yan P, Raisky J, Gunaseelan V, Kim T, Leavitt D, et al. New persistent opioid use after ureteroscopy for stone treatment. European Urology, Supplements. 2019;18(1):e196-e7.

214. Nicholson AD, Kassam HF, Steele J, Passarelli N, Blaine TA, Kovacevic D. * Development and Validation of a Risk Calculator for Prolonged Opioid Use After Shoulder Surgery. Journal of Shoulder and Elbow Surgery. 2019;28(8):e288-e9.

215. Karhade AV, Ogink PT, Thio QCBS, Cha TD, Gormley WB, Hershman SH, et al. Development of machine learning algorithms for prediction of prolonged opioid prescription after surgery for lumbar disc herniation. The spine journal : official journal of the North American Spine Society. 2019;19(11):1764-71.

216. Karhade AV, Ogink PT, Thio QCBS, Broekman MLD, Cha TD, Hershman SH, et al. Machine learning for prediction of sustained opioid prescription after anterior cervical discectomy and fusion. The spine journal : official journal of the North American Spine Society. 2019;19(6):976-83.

217. Karhade AV, Chaudhary MA, Bono CM, Kang JD, Schwab JH, Schoenfeld AJ. Validating the Stopping Opioids after Surgery (SOS) score for sustained postoperative prescription opioid use in spine surgical patients. The spine journal : official journal of the North American Spine Society. 2019;19(10):1666-71.

218. Edwards NM, Varnum C, Overgaard S, Nikolajsen L, Pedersen AB. Risk factors for new and persistent chronic opioid use after hip fracture surgery: A Danish nationwide cohort study from 2005 to 2016. Pharmacoepidemiology and Drug Safety. 2019;28(Supplement 2):321-2.

219. Deyo RA, Hallvik SE, Hildebran C, Marino M, O'Kane N, Carson J, et al. Use of prescription opioids before and after an operation for chronic pain (lumbar fusion surgery). Pain. 2018;159(6):1147-54.

220. Cook DJ, Kaskovich S, Pirkle S, Ho A, Conti Mica M, Shi L, et al. Benchmarks of Duration and Magnitude of Opioid Consumption After Common Spinal Procedures: A Database Analysis of 47,823 Patients. Spine. 2019;44(23):1668-75.

221. Zamora-Legoff JA, Achenbach SJ, Crowson CS, Davis IJM, Matteson EL. Trends in the use of opiates in rheumatoid arthritis (RA) compared to non-RA: A population based study in 2003-2012. Arthritis and Rheumatology Conference: American College of Rheumatology/Association of Rheumatology Health Professionals Annual Scientific Meeting, ACR/ARHP. 2015;67(SUPPL. 10).

222. Wren A, Bensen R, Yu H, Wong J, MacIsaac D, Sellers Z, et al. Prevalence of chronic opioid use among adolescents and young adults with inflammatory bowel disease. Journal of Pediatric Gastroenterology and Nutrition. 2017;65 (Supplement 2):S34.

223. Westermann RW, Anthony C, Bedard N, Glass NA, Bollier MJ, Hettrich CM, et al. Patient factors associated with prolonged opioid use after rotator cuff repair. Journal of Shoulder and Elbow Surgery. 2017;26 (5):e151.

224. Weisner CM, Campbell CI, Ray GT, Saunders K, Merrill JO, Banta-Green C, et al. Trends in prescribed opioid therapy for non-cancer pain for individuals with prior substance use disorders. Pain. 2009;145(3):287-93.

225. Swenson CW, Seiler K, Kamdar N, Morgan D. Prevalence of new persistent opioid use among opioid naive women undergoing hysterectomy. American Journal of Obstetrics and Gynecology. 2018;218 (2 Supplement 2):S885-S6.

226. Soneji N, Clarke H, Ko DT, Yun L, Wijeysundera D. Risk factors for prolonged opioid use after major surgery: A population-based cohort study. Anesthesia and Analgesia Conference. 2013;116(SUPPL. 1).

227. Skurtveit S, Furu K, Selmer R, Handal M, Tverdal A. Nicotine dependence predicts problematic use of prescribed opioids. Prospective population based cohort study. Pharmacoepidemiology and Drug Safety (PDS). 2009;18 (S1):S246.

228. Skurtveit S, Furu K, Handal M, Borchgrevin P, Fredheim O. To which extent does a cohort of new users of weak opioids develop persistent or probable problematic opioid use? Pharmacoepidemiology and Drug Safety. 2011;1):S223.

229. Skurtveit S, Furu K, Bramness J, Selmer R, Tverdal A. Benzodiazepines predict use of opioids--a follow-up study of 17,074 men and women. Pain Medicine. 2010;11(6):805-14.

230. Silverberg MJ, Ray GT, Saunders K, Rutter CM, Campbell CI, Merrill JO, et al. Prescription long-term opioid use in HIV-infected patients. Clinical Journal of Pain. 2012;28(1):39-46.

231. Shah AB, Hayes CJ, Martin BC. Which pain etiologies are most likely to result in long term opioid use? results from a large nationally representative inception cohort study. Value in Health. 2017;20 (5):A212.

232. Shah AB, Hayes CJ, Lakkad M, Martin BC. Impact of medical marijuana legalization on opioid use, chronic opioid use and high-risk opioid use. Value in Health. 2018;21 (Supplement 1):S247.

233. Shah AB, Hayes C, Martin BC. Choice of first opioid prescription and the transitions from acute to long term opioid use-findings from big data. Value in Health. 2016;19 (7):A598.

234. Shah A, Hayes CJ, Martin BC. Characteristics of Initial Prescription Episodes and Likelihood of Long-Term Opioid Use - United States, 2006-2015. MMWR - Morbidity & Mortality Weekly Report. 2017;66(10):265-9.

235. Rice JB, Samuelson TM, Birnbaum HG, Katz N. Identifying predictors of chronic hydrocodone use. Pain Medicine (United States). 2012;13 (2):336.

236. Raebel MA, Newcomer SR, Bayliss EA, Boudreau D, DeBar L, Elliott TE, et al. Chronic opioid use emerging after bariatric surgery. Pharmacoepidemiology & Drug Safety. 2014;23(12):1247-57.

237. Namba RS, Inacio MCS, Pratt NL, Graves SE, Roughead EE, Paxton EW. Persistent Opioid Use Following Total Knee Arthroplasty: A Signal for Close Surveillance. Journal of Arthroplasty. 2018;33(2):331-6.

238. Mosher HJ, Richardson KK, Lund BC. The 1-year treatment course of new opioid recipients in veterans health administration. Pain Medicine (United States). 2016;17(7):1282-91.

239. Mosher HJ, Jiang L, Vaughan Sarrazin MS, Cram P, Kaboli PJ, Vander Weg MW. Prevalence and characteristics of hospitalized adults on chronic opioid therapy. Journal of Hospital Medicine (Online). 2014;9(2):82-7.

240. Mosher H, Jiang L, Sarrazin MV. Chronic opioid therapy in hospitalized patients: Common but not immutable. Journal of General Internal Medicine. 2013;1):S44.

241. Mosher H, Hofmeyer B, Lund BC. From acute to chronic: Opioid receipt following incident use compared across surgical, medical and outpatient settings. Journal of General Internal Medicine. 2017;32 (2 Supplement 1):S196.

242. Lovejoy T, Dobscha S, Turk D, Weimer M, Morasco B. Predictors of prescription opioid therapy in patients with chronic pain and a history of substance use disorder. Journal of Pain. 2015;1):S84.

243. Krebs E, Fanciullo G, Lurie J, Tosteson T, Blood E, Carey T, et al. Predictors of long-term opioid use for back pain. Journal of Pain. 2009;1):S46.

244. Kim K, Anoushiravani A, Roof M, Chen K, Vigdorchik J, Schwarzkopf R. Preoperative chronic opioid use and value-based outcomes in total hip arthroplasty. HIP International. 2018;28 (Supplement 1):42-3.

245. Hunnicutt JN, Ulbricht C, Hume A, Lapane K. Resident and facility-level correlations of long-term opioid use in United States nursing homes. Pharmacoepidemiology and Drug Safety. 2017;26 (Supplement 2):14-5.

246. Hoffman EM, Watson J, St Sauver J, Staff N, Klein C. Population-based chronic opioid therapy prevalence among polyneuropathy patients and the resultant impact on functional status and adverse outcomes. Muscle and Nerve. 2017;56 (3):547.

247. Cichowski SB, Rogers RG, Komesu Y, Murata E, Qualls C, Murata A, et al. A 10-yr Analysis of Chronic Pelvic Pain and Chronic Opioid Therapy in the Women Veteran Population. Military Medicine. 2018;183(11-12):e635-e40.

248. Chen TC, Chen LC, Knaggs R. Patient characteristics associated with persistent tramadol use for patients with chronic non-cancer pain in U.K. general practices. Pharmacoepidemiology and Drug Safety. 2016;25 (Supplement 3):293-4.

249. Campbell CI, Weisner C, Leresche L, Ray GT, Saunders K, Sullivan MD, et al. Age and gender trends in long-term opioid analgesic use for noncancer pain. American Journal of Public Health. 2010;100(12):2541-7.

250. Calcaterra SL, Scarbro S, Hull ML, Forber AD, Binswanger IA, Colborn KL. Prediction of Future Chronic Opioid Use Among Hospitalized Patients. Journal of General Internal Medicine. 2018;33(6):898-905.

251. Braden JB, Sullivan MD, Ray GT, Saunders K, Merrill J, Silverberg MJ, et al. Trends in long-term opioid therapy for noncancer pain among persons with a history of depression. General Hospital Psychiatry. 2009;31(6):564-70.

252. Birke H, Kurita GP, Sjogren P, Hojsted J, Simonsen MK, Juel K, et al. Chronic non-cancer pain and the epidemic prescription of opioids in the Danish population: trends from 2000 to 2013. Acta Anaesthesiologica Scandinavica. 2016;60(5):623-33.

253. Bedard NA, Westermann RW, Pugely AJ, DeMik DE, Duchman KR, Liu SS, et al. Opioid use following UKA-trends and risk factors for prolonged use. Journal of Orthopaedic Research Conference. 2017;35(Supplement 1).

254. Bedard NA, DeMik DE, Dowdle SB, Callaghan JJ. Trends and risk factors for prolonged opioid use after unicompartmental knee arthroplasty. Bone & Joint Journal. 2018;100-B(1 Supple A):62-7.

255. Bateman BT, Franklin JM, Bykov K, Huybrechts KF, Fischer MA, Choudhry NK. Persistent opioid use following cesarean delivery: Patterns and predictors among opioid naive women. Pharmacoepidemiology and Drug Safety. 2014;1):20.

256. Axeen S. Trends in Opioid Use and Prescribing in Medicare, 2006-2012. Health Services Research. 2018;53(5):3309-28.

257. Anderson JT, Tye E, Haas A, Ahn NU. Predictors of chronic opioid therapy after lumbar fusion surgery for degenerative disc disease in a workers' compensation setting. Spine Journal. 2016;16 (10 Supplement 1):S343.

258. Wilson B, Smith A, Murata G, Murata A, Qualis C, Cichowski S. A 10 year analysis of chronic pelvic pain and chronic narcotic use in the male veteran population. Journal of Urology. 2019;201(4 Supplement 1):e454.

259. Welk B, McClure JA, Clarke C, Vogt K, Campbell J. An Opioid Prescription for Men Undergoing Minor Urologic Surgery Is Associated with an Increased Risk of New Persistent Opioid Use. European urology. 2020;77(1):68-75.

260. Wang MC, Lozen AM, Laud PW, Nattinger AB, Krebs EE. Factors associated with chronic opioid use after cervical spine surgery for degenerative conditions. Journal of Neurosurgery: Spine. 2020;32(1):1-8.

261. Overton S NM, MacPherson R, Costa D. . Developing a Screening Tool to Identify Patients at Risk of Transitioning from Acute to Chronic Postsurgical Pain, as Well as Those at Risk of Continuing Opioid Use in the Postsurgical Period. IASP World Congress On Pain Boston September 2018.

262. Moskowitz D, Amin K, Lucioni A, Kobashi K, Lee U. Opioid Prescription and Use in Sacral Neuromodulation, Mid Urethral Sling and Pelvic Organ Prolapse Surgery: An Educational Intervention to Avoid Over Prescribing. The Journal of urology. 2019;201(5):979-86.

263. Iverson N, Najafi N, Abe-Jones Y, Fang M, Kangelaris K, Prasad PA, et al. A fluid discharge: Liquid opioids and other risk factors that contribute to excessive opioid prescriptions from a hospital medicine service. Journal of General Internal Medicine. 2019;34(2 Supplement):S109.

264. Hill CJ, Winters JR, Frasier SD, Braxton J, Schlocker CM. Post-operative narcotic usage after tonsillectomy. Otolaryngology - Head and Neck Surgery. 2019;161(2 Supplement):P61-P2.

265. Harris AB, Neuman BJ, Soroceanu A, Hostin RA, Protopsaltis TS, Passias PG, et al. 253. Factors associated with chronic opioid use in preoperative opioid nonusers following adult spinal deformity surgery. Spine Journal. 2019;19(9 Supplement):S123-S4.

266. Cotta B, Bechis S. Risk factors for prolonged opiate use in patients with acute nephrolithiasis. Journal of Urology. 2019;201(4 Supplement 1):e843-e4.

267. Chaitoff A, Taksler GB, Misra-Hebert AD, Udeh B, Rothberg MB. Opioid prescribing patterns for chronic non-cancer pain in a primary care population. Journal of General Internal Medicine. 2019;34(2 Supplement):S298-S9.

268. Berger I, Strother M, Talwar R, Ziemba J, Wirtalla C, Xia L, et al. National Variation in Opioid Prescription Fills and Long-Term Use in Opioid Naive Patients after Urological Surgery. The Journal of urology. 2019;202(5):1036-43.

269. Young JC, Funk MJ, Dasgupta N. Indications for long-term extended-release opioid therapy in commercially-insured adults in the US, 2006-2014. Pharmacoepidemiology and Drug Safety. 2017;26 (Supplement 2):628.

270. Yang S, Werner BC. Risk Factors for Prolonged Postoperative Opioid Use After Spinal Fusion for Adolescent Idiopathic Scoliosis. Journal of Pediatric Orthopaedics. 2018;19.

271. Wren A, Bensen R, Sceats L, Yu H, Wong J, Sellers Z, et al. Persistent opioid use and healthcare utilization among adolescents and young adults with inflammatory bowel disease in the United States. Gastroenterology. 2018;154 (1 Supplement 1):S46.

272. Svendsen K, Borchgrevink P, Fredheim OM, Skurtveit S. How are opioids used in Norway? Persistent use, utilization of depot formulation and age profile in non-palliation patients. Scandinavian Journal of Pain. 2010;1 (3):171.

273. Sullivan MD, Richardson L, Edlund M, Martin B, Russo J, De Vries A. Initiation of opioid treatment among adolescents with chronic pain. Pain Medicine. 2011;12 (3):481.

274. Smith ME, Bonham A, Ghaferi A. New persistent opioid use and outcomes following bariatric surgery. Surgical Endoscopy and Other Interventional Techniques. 2018;32 (1 Supplement 1):S43.

275. Rogers K, Kemp A, McLaughlan A, Blyth F. Patterns of prescription opioid use for non-cancer pain in the 45 and up study cohort. Anaesthesia and Intensive Care. 2012;40 (3):549.

276. Mohanty S, Lee JS, Ross RA, Stricklen A, Carlin AM, Ghaferi AA. New persistent opioid use after bariatric surgery. Journal of the American College of Surgeons. 2017;225 (4 Supplement 1):S123.

277. Miceli L, Bednarova R, M DIC, Santori E, Spizzichino M, L DIM, et al. Outpatient therapeutic chronic opioid consumption in Italy: a one-year survey. Minerva Anestesiologica. 2017;83(1):33-40.

278. Mattson AE, Scherber K, Dierkhising R, Rudis M. Prevalence and risk factors for episodic and long-term opioid use after initial prescribing in the emergency department. Annals of Emergency Medicine. 2016;68 (4 Supplement 1):S91.

279. Lo Casale RJ, Kern DM, Zhou S, Chavoshi S, Tunceli O, Sostek M. Profiling chronic opioid use for non-cancer pain in the United States. Pharmacoepidemiology and Drug Safety. 2013;1):481.

280. Lee YC, Kremer J, Guan H, Greenberg JD, Solomon DH. Trends and predictors of chronic opioid use in individuals with RA. Arthritis and Rheumatology Conference: American College of Rheumatology/Association of Rheumatology Health Professionals Annual Scientific Meeting, ACR/ARHP. 2017;69(Supplement 10).

281. Kang CL, Shu X, Herrell SD, Miller N, Hsi R. Predictors of persistent opiate use after ureteroscopy. Journal of Urology. 2018;199 (4 Supplement 1):e916.

282. Jeffery MM, Bellolio MF, Shah ND, Henk HJ, McLeod S, Borgundvaag B, et al. Opioid prescribing for acute pain in the emergency department. Academic Emergency Medicine. 2017;24 (Supplement 1):S31.

283. Hoppe JA, Kim HS, Heard SM, Heard K. Long-term opioid use after emergency department discharge. Academic Emergency Medicine. 2014;1):S116.

284. Heard K, Hoppe J, Kim H. Long-term opioid use among patients taking opioids and treated for a minor painful condition in the ED. Academic Emergency Medicine. 2015;1):S407.

285. Hah J, Zocca J, Sharifzadeh Y, Mackey S. Risk factors for long-term prescription opioid therapy for chronic non-cancer pain. Journal of Pain. 2016;1):S10-S1.

286. Crocker J, Yu H, Tuskey A, Conaway M, Behm B. Functional GI disorders are associated with high rates of chronic narcotic use and misuse in patients with crohn's disease. Inflammatory Bowel Diseases. 2013;1):S61-S2.

287. Cancienne JM, Gwathmey FW, Werner BC. Risk factors for prolonged narcotic use following arthroscopic rotator cuff repair. Orthopaedic Journal of Sports Medicine Conference. 2017;5(7 Supplement 6).

288. Bennett KG, Harbaugh CM, Hu HM, Vercler CJ, Buchman SR, Brummett CM, et al. Persistent Opioid Use Among Children, Adolescents, and Young Adults After Common Cleft Operations. Journal of Craniofacial Surgery. 2018;29(7):1697-701.

289. Bateman BT, Franklin JM, Bykov K, Avorn J, Shrank WH, Brennan TA, et al. Persistent opioid use following cesarean delivery: patterns and predictors among opioid-naive women. American Journal of Obstetrics & Gynecology. 2016;215(3):353.e1-.e18.

290. Anoushiravani A, Kim K, Roof M, Chen K, Vigdorchik J, Schwarzkopf R. Risk factors associated with persistent chronic opioid use following tha. HIP International. 2018;28 (Supplement 1):88.

291. Boudreau D, Von Korff M, Rutter CM, Saunders K, Ray GT, Sullivan MD, et al. Trends in long-term opioid therapy for chronic non-cancer pain. Pharmacoepidemiology & Drug Safety. 2009;18(12):1166-75.

292. Deyo RA, Smith DH, Johnson ES, Donovan M, Tillotson CJ, Yang X, et al. Opioids for back pain patients: primary care prescribing patterns and use of services. Journal of the American Board of Family Medicine: JABFM. 2011;24(6):717-27.

293. Skurtveit S, Furu K, Borchgrevink P, Handal M, Fredheim O. To what extent does a cohort of new users of weak opioids develop persistent or probable problematic opioid use? Pain. 2011;152(7):1555-61.

294. Alam A, Gomes T, Zheng H, Mamdani MM, Juurlink DN, Bell CM. Long-term analgesic use after low-risk surgery: a retrospective cohort study. Archives of Internal Medicine. 2012;172(5):425-30.

295. Richardson LP, Russo JE, Katon W, McCarty CA, DeVries A, Edlund MJ, et al. Mental health disorders and long-term opioid use among adolescents and young adults with chronic pain. Journal of Adolescent Health. 2012;50(6):553-8.

296. Dobscha SK, Morasco BJ, Duckart JP, Macey T, Deyo RA. Correlates of prescription opioid initiation and long-term opioid use in veterans with persistent pain. Clinical Journal of Pain. 2013;29(2):102-8.

297. Chevalier P, Smulders M, Chavoshi S, Sostek M, LoCasale R. A description of clinical characteristics and treatment patterns observed within prescribed opioid users in Germany and the UK. Pain Management. 2014;4(4):267-76.

298. Fredheim OM, Mahic M, Skurtveit S, Dale O, Romundstad P, Borchgrevink PC. Chronic pain and use of opioids: a population-based pharmacoepidemiological study from the Norwegian prescription database and the Nord-Trondelag health study. Pain. 2014;155(7):1213-21.

299. Kulshrestha S, Barrantes F, Samaniego M, Luan FL. Chronic opioid analgesic usage post-kidney transplantation and clinical outcomes. Clinical Transplantation. 2014;28(9):1041-6.

300. Morden NE, Munson JC, Colla CH, Skinner JS, Bynum JP, Zhou W, et al. Prescription opioid use among disabled Medicare beneficiaries: intensity, trends, and regional variation. Medical Care. 2014;52(9):852-9.

301. Anderson JT, Haas AR, Percy R, Woods ST, Ahn UM, Ahn NU. Chronic Opioid Therapy After Lumbar Fusion Surgery for Degenerative Disc Disease in a Workers' Compensation Setting. Spine. 2015;40(22):1775-84.

302. Buckley JP, Cook SF, Allen JK, Kappelman MD. Prevalence of chronic narcotic use among children with inflammatory bowel disease. Clinical Gastroenterology & Hepatology. 2015;13(2):310-5.e2.

303. Halbert B, Chiodi SN, Davis RB, Wee CC. Opioid use with mental health disorders: Are we over-prescribing? Journal of General Internal Medicine. 2015;2):S216-S7.

304. Al Dabbagh Z, Jansson KA, Stiller CO, Montgomery S, Weiss RJ. Long-term pattern of opioid prescriptions after femoral shaft fractures. Acta Anaesthesiologica Scandinavica. 2016;60(5):634-41.

305. Bedson J, Chen Y, Hayward RA, Ashworth J, Walters K, Dunn KM, et al. Trends in long-term opioid prescribing in primary care patients with musculoskeletal conditions: an observational database study. Pain. 2016;157(7):1525-31.

306. Heins SE, Feldman DR, Bodycombe D, Wegener ST, Castillo RC. Early opioid prescription and risk of long-term opioid use among US workers with back and shoulder injuries: a retrospective cohort study. Injury Prevention. 2016;22(3):211-5.

307. Inacio MC, Hansen C, Pratt NL, Graves SE, Roughead EE. Risk factors for persistent and new chronic opioid use in patients undergoing total hip arthroplasty: a retrospective cohort study. BMJ Open. 2016;6(4):e010664.

308. Kim KY, Anoushiravani AA, Chen KK, Roof M, Long WJ, Schwarzkopf R. Preoperative Chronic Opioid Users in Total Knee Arthroplasty-Which Patients Persistently Abuse Opiates Following Surgery? Journal of Arthroplasty. 2018;33(1):107-12.

309. Lovejoy TI, Dobscha SK, Turk DC, Weimer MB, Morasco BJ. Correlates of prescription opioid therapy in Veterans with chronic pain and history of substance use disorder. Journal of Rehabilitation Research & Development. 2016;53(1):25-36.

310. Mudumbai SC, Oliva EM, Lewis ET, Trafton J, Posner D, Mariano ER, et al. Time-to-Cessation of Postoperative Opioids: A Population-Level Analysis of the Veterans Affairs Health Care System. Pain Medicine. 2016;17(9):1732-43.

311. Sani AR, Zin CS, Noor ZM, Mohamed AH, Nissen LM. Differential patterns of persistent opioid use in patients with cancer and non-cancer pain. Value in Health. 2016;19 (7):A814.

312. Smolina K, Gladstone EJ, Rutherford K, Morgan SG. Patterns and trends in long-term opioid use for non-cancer pain in British Columbia, 2005-2012. Canadian Journal of Public Health Revue Canadienne de Sante Publique. 2016;107(4-5):e404-e9.

313. Alghnam S, Castillo R. Traumatic injuries and persistent opioid use in the USA: findings from a nationally representative survey. Injury Prevention. 2017;23(2):87-92.

314. Anthony CA, Westermann RW, Bedard N, Glass N, Bollier M, Hettrich CM, et al. Opioid Demand Before and After Anterior Cruciate Ligament Reconstruction. American Journal of Sports Medicine. 2017;45(13):3098-103.

315. Birke H, Ekholm O, Sjogren P, Kurita GP, Hojsted J. Long-term opioid therapy in Denmark: A disappointing journey. European Journal of Pain. 2017;21(9):1516-27.

316. Callinan CE, Neuman MD, Lacy KE, Gabison C, Ashburn MA. The Initiation of Chronic Opioids: A Survey of Chronic Pain Patients. Journal of Pain. 2017;18(4):360-5.

317. Chen S, Feldman CH, Brill G, Lee YC, Desai RJ, Kim SC. Use of prescription opioids among patients with systemic inflammatory diseases (SID) versus patients with hypertension but no SID. Arthritis and Rheumatology Conference: American College of Rheumatology/Association of Rheumatology Health Professionals Annual Scientific Meeting, ACR/ARHP. 2017;69(Supplement 10).

318. Cichowski S, Rogers R, Murata A, Murata E, Murata G. A 10 year analysis of chronic pelvic pain (CPP) and chronic narcotic use (CNU) in the female veteran population. Obstetrics and Gynecology. 2017;129 (Supplement 1):83S-4S.

319. Connolly J, 3rd, Javed Z, Raji MA, Chan W, Kuo YF, Baillargeon J. Predictors of Long-term Opioid Use Following Lumbar Fusion Surgery. Spine. 2017;42(18):1405-11.

320. Deyo RA, Hallvik SE, Hildebran C, Marino M, Dexter E, Irvine JM, et al. Association Between Initial Opioid Prescribing Patterns and Subsequent Long-Term Use Among Opioid-Naive Patients: A Statewide Retrospective Cohort Study. Journal of General Internal Medicine. 2017;32(1):21-7.

321. Shah A, Hayes CJ, Martin BC. Factors Influencing Long-Term Opioid Use Among Opioid Naive Patients: An Examination of Initial Prescription Characteristics and Pain Etiologies. Journal of Pain. 2017;18(11):1374-83.

322. Stark N, Kerr S, Stevens J. Prevalence and predictors of persistent post-surgical opioid use: a prospective observational cohort study. Anaesthesia & Intensive Care. 2017;45(6):700-6.

323. Thielke SM, Shortreed SM, Saunders K, Turner JA, LeResche L, Von Korff M. A Prospective Study of Predictors of Long-term Opioid Use Among Patients With Chronic Noncancer Pain. Clinical Journal of Pain. 2017;33(3):198-204.

324. Adogwa O, Davison MA, Vuong VD, Desai SA, Lilly DT, Moreno J, et al. Regional Variation in Opioid Use After Lumbar Spine Surgery. World Neurosurgery. 2018.

325. Anciano Granadillo V, Cancienne JM, Gwathmey FW, Werner BC. Perioperative Opioid Analgesics and Hip Arthroscopy: Trends, Risk Factors for Prolonged Use, and Complications. Arthroscopy. 2018;34(8):2359-67.

326. Bertenthal D, Yaffe K, Barnes DE, Byers AL, Gibson CJ, Seal KH, et al. Do postconcussive symptoms from traumatic brain injury in combat veterans predict risk for receiving opioid therapy for chronic pain? Brain Injury. 2018;32(10):1188-96.

327. Bolarinwa S, Casp AA, Cancienne JM, Werner BC, Browne JA. Narcotic use and total hip arthroplasty. HIP International. 2018.

328. Cancienne JM, Patel KJ, Browne JA, Werner BC. Narcotic Use and Total Knee Arthroplasty. Journal of Arthroplasty. 2018;33(1):113-8.

329. Chui PW, Bastian LA, DeRycke E, Brandt CA, Becker WC, Goulet JL. Dual Use of Department of Veterans Affairs and Medicare Benefits on High-Risk Opioid Prescriptions in Veterans Aged 65 Years and Older: Insights from the VA Musculoskeletal Disorders Cohort. Health Services Research. 2018;53 Suppl 3:5402-18.

330. Fritz JM, King JB, McAdams-Marx C. Associations Between Early Care Decisions and the Risk for Long-term Opioid Use for Patients With Low Back Pain With a New Physician Consultation and Initiation of Opioid Therapy. Clinical Journal of Pain. 2018;34(6):552-8.

331. Hernandez NM, Parry JA, Mabry TM, Taunton MJ. Patients at Risk: Preoperative Opioid Use Affects Opioid Prescribing, Refills, and Outcomes After Total Knee Arthroplasty. Journal of Arthroplasty. 2018;33(7S):S142-S6.

332. Hunnicutt JN, Chrysanthopoulou SA, Ulbricht CM, Hume AL, Tjia J, Lapane KL. Prevalence of Long-Term Opioid Use in Long-Stay Nursing Home Residents. Journal of the American Geriatrics Society. 2018;66(1):48-55.

333. Lalic S, Gisev N, Bell JS, Korhonen MJ, Ilomaki J. Predictors of persistent prescription opioid analgesic use among people without cancer in Australia. British Journal of Clinical Pharmacology. 2018;84(6):1267-78.

334. Politzer CS, Kildow BJ, Goltz DE, Green CL, Bolognesi MP, Seyler TM. Trends in Opioid Utilization Before and After Total Knee Arthroplasty. Journal of Arthroplasty. 2018;33(7S):S147-S53.e1.

335. Steiner SRH, Cancienne JM, Werner BC. Narcotics and Knee Arthroscopy: Trends in Use and Factors Associated With Prolonged Use and Postoperative Complications. Arthroscopy. 2018;34(6):1931-9.

336. Taqi A, Otete H, Knaggs R. Opioid prescription patterns in UK primary care patients with knee osteoarthritis: A population-based study. Pharmacoepidemiology and Drug Safety. 2018;27 (Supplement 2):324-5.

337. Thornton JD, Dwibedi N, Scott V, Ponte CD, Ziedonis D, Sambamoorthi N, et al. Predictors of Transitioning to Incident Chronic Opioid Therapy Among Working-Age Adults in the United States. American Health & Drug Benefits. 2018;11(1):12-21.

338. Barham DW, McMann LP, Musser JE, Schisler JQ, Speir RW, Olcese SP, et al. Routine Prescription of Opioids for Post-Vasectomy Pain Control Associated with Persistent Use. The Journal of urology. 2019;202(4):806-10.

339. Barnett ML, Zhao X, Fine MJ, Thorpe CT, Sileanu FE, Cashy JP, et al. Emergency Physician Opioid Prescribing and Risk of Long-term Use in the Veterans Health Administration: an Observational Analysis. Journal of general internal medicine. 2019;34(8):1522-9.

340. Basilico M, Bhashyam AR, Harris MB, Heng M. Prescription Opioid Type and the Likelihood of Prolonged Opioid Use After Orthopaedic Surgery. The Journal of the American Academy of Orthopaedic Surgeons. 2019;27(9):e423-e9.

341. Beliveau A, Castilloux AM, Tanenbaum C, Vincent P, De Moura CS, Bernatsky S, et al. Incidence of chronic opioid use in seniors. Pharmacoepidemiology and Drug Safety. 2019;28(Supplement 2):329.

342. Bennett KG, Kelley BP, Vick AD, Lee JS, Gunaseelan V, Brummett CM, et al. Persistent Opioid Use and High-Risk Prescribing in Body Contouring Patients. Plastic and reconstructive surgery. 2019;143(1):87-96.

343. Birke H, Ekholm O, Sjogren P, Fredheim O, Clausen T, Skurtveit S. Tramadol use in Norway: A register-based population study. Pharmacoepidemiology and drug safety. 2019;28(1):54-61.

344. Desai RJ, Jin Y, Franklin PD, Lee YC, Bateman BT, Lii J, et al. Association of Geography and Access to Health Care Providers With Long-Term Prescription Opioid Use in Medicare Patients With Severe Osteoarthritis: A Cohort Study. Arthritis & rheumatology (Hoboken, NJ). 2019;71(5):712-21.

345. Gibson CJ, Li Y, Huang AJ, Rife T, Seal KH. Menopausal Symptoms and Higher Risk Opioid Prescribing in a National Sample of Women Veterans with Chronic Pain. Journal of general internal medicine. 2019;34(10):2159-66.

346. Goplen CM, Randall JR, Kang SH, Vakilian F, Jones CA, Voaklander DC, et al. The Influence of Allowable Refill Gaps on Detecting Long-Term Opioid Therapy: An Analysis of Population-Based Administrative Dispensing Data Among Patients with Knee Arthritis Awaiting Total Knee Arthroplasty. Journal of managed care & specialty pharmacy. 2019;25(10):1064-72.

347. Harris RA, Kranzler HR, Chang K-M, Doubeni CA, Gross R. Long-term use of hydrocodone vs. oxycodone in primary care. Drug and alcohol dependence. 2019;205:107524.

348. Hedenmalm K, Slattery J, Skibicka-Stepien I, Kurz X, Morales D. Prescribing patterns of tramadol in adults in IMS primary care databases in France and Germany between 1 January 2006 and 30 June 2016. European journal of clinical pharmacology. 2019;75(5):707-16.

349. Hirji SA, Landino S, Cote C, Lee J, Orhurhu V, Shah RM, et al. Chronic opioid use after coronary bypass surgery. Journal of cardiac surgery. 2019;34(2):67-73.

350. Lee YC, Kremer J, Guan H, Greenberg J, Solomon DH. Chronic Opioid Use in Rheumatoid Arthritis: Prevalence and Predictors. Arthritis & rheumatology (Hoboken, NJ). 2019;71(5):670-7.

351. Musich S, Wang SS, Slindee L, Kraemer S, Yeh CS. Characteristics associated with transition from opioid initiation to chronic opioid use among opioid-naive older adults. Geriatric nursing (New York, NY). 2019;40(2):190-6.

352. Rogero R, Fuchs D, Nicholson K, Shakked RJ, Winters BS, Pedowitz DI, et al. Postoperative Opioid Consumption in Opioid-Naive Patients Undergoing Hallux Valgus Correction. Foot & ankle international. 2019;40(11):1267-72.

353. Agarwalla A, Liu JN, Gowd AK, Amin NH, Werner BC. Differential Use of Narcotics in Total Hip Arthroplasty: A Comparative Matched Analysis Between Osteoarthritis and Femoral Neck Fracture. The Journal of arthroplasty. 2020;35(2):471-6.

354. Young JC, Wu JM, Willis-Gray M, Pate V, Jonsson Funk M. Persistent Opioid Use After Hysterectomy in the United States, 2005-2015. Obstetrics and gynecology. 2020;135(1):123-32.

Iris PUJADE

Incidence et facteurs associés à la prescription à long terme d'opioïdes dans la population non atteinte de cancer : revue systématique et méta-analyse

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Lieu et date de soutenance : Le 02 Octobre 2020 à la faculté Bordeaux Segalen, site Victoire

Résumé en français :

Contexte et justification : La prescription à long terme d'opioïdes dans la population non cancéreuse est très controversée avec un rapport bénéfices risques complexe. L'identification des facteurs associés à la prescription à long terme peut être utile comme outil de décision pour les cliniciens lorsqu'ils initient ou poursuivent un traitement par opioïdes. **Objectif** : Estimer l'incidence de la progression vers la prescription d'opioïdes à long terme chez les patients non cancéreux qui initient un traitement et identifier les facteurs associés. **Schéma** : Revue systématique et méta-analyse. **Recherche** : Medline et Embase ont été consultées du 1er janvier 2009 au 15 janvier 2020. Des sources supplémentaires ont été investiguées par des recherches pragmatiques. **Sélection** : Les études observationnelles sur la prescription à long terme d'opioïdes dans la population non cancéreuse de tous âges et présentant une définition de prescription à long terme, des estimations de l'incidence et/ou des facteurs associés étaient admissibles. Deux auteurs ont sélectionné indépendamment les titres et les résumés, les conflits étant résolus par un troisième auteur. **Extraction et analyse statistique** : Les données ont été extraites par un auteur et validées par un deuxième auteur. La qualité méthodologique des études individuelles a été évaluée à l'aide des outils JBI. Pour les facteurs de risque potentiels étudiés dans au moins deux études, une méta-analyse des mesures de risque ajustées a été réalisée en utilisant un modèle à effet aléatoire, et exprimée sous la forme d'OR avec un IC à 95%. L'hétérogénéité statistique des estimations a été évaluée à l'aide des statistiques I2. **Résultats** : Un total de 64 études d'observation comprenant de 96 à 1 353 902 patients non cancéreux ont été incluses dans la revue systématique. Parmi les utilisateurs d'opioïdes, l'incidence de la progression vers la prescription à long terme variait de 0,2 à 703,4 pour 10 000 personnes années (médiane : 41,6), l'incidence la plus élevée étant observée dans le contexte post-chirurgical. Les facteurs associés à la consommation à long terme étaient : l'obésité (RC 1,32, 95 % IC 1,23-1,42), le tabagisme (1,60, 1,42-1,80), l'anxiété (1,36, 1,14-1,61) et la prescription pour "toute douleur" (1,64, 1,39-1,95), sans aucune preuve d'hétérogénéité statistique entre les études. Dans les analyses en sous-groupes basées sur les caractéristiques sociodémographiques, la définition et la qualité des études, le sexe masculin, les troubles psychiatriques, les antécédents de dépendance et l'indication pour des douleurs dorsales étaient également des facteurs associés. **Conclusion :** Cette étude a démontré que la prescription d'opioïdes à long terme est fréquente, en particulier en contexte post-chirurgical. Des facteurs associés ont été identifiés, dont certains pourraient être intégrés à la pratique médicale.

Titre en anglais : Incidence and factors associated with long-term prescription opioid use in the non-cancer population: a systematic review and meta-analysis of observational studies.

Discipline administrative : Pharmacie, spécialisée Innovation Pharmaceutique et Recherche (IPR)

Mots-clés : Opioïdes, prescription à long-terme, douleur, revue-systématique, méta-analyse