Long-term opioid therapy definitions and predictors: A systematic review

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Abstract

Purpose: This review sought to (a) describe definitions of long-term opioid therapy (LTOT) outcome measures, and (b) identify the predictors associated with the transition from short-term opioid use to LTOT for opioid-naïve individuals.

Methods: We conducted a systematic review of the peer-reviewed literature (January 2007 to July 2018). We included studies examining opioid use for more than 30 days. We classified operationalization of LTOT based on criteria used in the definitions. We extracted LTOT predictors from multivariate models in studies of opioid-naïve individuals.

Results: The search retrieved 5,221 studies, and 34 studies were included. We extracted 41 unique variations of LTOT definitions. About 36% of definitions required a cumulative duration of opioid use of 3 months. Only 17% of definitions considered consecutive observation periods, 27% used days' supply, and no definitions considered dose.

We extracted 76 unique predictors of LTOT from seven studies of opioid-naïve patients. Common predictors included pre-existing comorbidities (21.1%), non-opioid prescription medication use (13.2%), substance use disorders (10.5%), and mental health disorders (10.5%).

Conclusions: Most LTOT definitions aligned with the chronic pain definition (pain more than 3 months), and used cumulative duration of opioid use as a criterion, although most did not account for consistent use. Definitions were varied and rarely accounted for prescription characteristics, such as days' supply. Predictors of LTOT were similar to known risk factors of opioid abuse, misuse, and overdose. As LTOT becomes a central component of quality improvement efforts,

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researchers should incorporate criteria to identify consistent opioid use to build the evidence for safe and appropriate use of prescription opioids.

1 | INTRODUCTION

For the nearly 20% of Americans and Canadians suffering from chronic non-cancer pain (CNCP), pain that lasts more than 3 months, prescription opioids are commonly used to relieve pain.[1–3] Although prescription opioids may be appropriate for short-term pain relief, long-term opioid therapy (LTOT) is not associated with improvements in pain or function.[4,5] LTOT can lead to tolerance and escalating doses, and is associated with greater risk of opioid-related overdose and mortality.[6] Across populations and health care settings, the rising prevalence of LTOT has paralleled increases with opioid-related overdose and mortality rates.[7–13] Previous studies, which defined LTOT as opioid use of more than 90 days, found that the prevalence of LTOT was 5.4% in the United States and 17% in Canada. [11,14]

Defining LTOT is critical to understanding the risk factors that lead to LTOT and the evaluation of clinical practices and policies aimed at reducing risky opioid use that may occur with LTOT (eg, high doses, concurrent benzodiazepine prescriptions, or other forms of opioid use that are associated with behaviors related to abuse, misuse, and addiction).[15] The concept of LTOT has become a central component to assess quality of care. In 2018, the National Committee for Quality Assurance added "Risk of Continued Opioid Use" as a quality of care measure.[16] The Centers for Disease Control and Prevention's (CDC) guide to monitor quality of the implementation of the 2016 Guideline for Prescribing Opioids for Chronic Pain defines nine measures corresponding to different types of risky LTOT.[17,18]

Adapted from the 2008 seminal observational study by Von Korff and colleagues on LTOT, clinical guidelines define LTOT as "use of opioids on most days for more than 3 months."[18–21] Yet, in research and clinical practice, the criteria used to define LTOT vary. Similar to other measures of medication use (eg, adherence, persistence, and compliance), researchers seeking to define LTOT need to select cutoffs for the duration of medication use, length of time for follow-up, frequency of fills, quantity, and days' supply to define LTOT. [22–24] Previous systematic reviews of pain medication use (covering studies published before 2014) for CNCP, examined constructs relating to adherence such as overuse, underuse, and misuse of opioid and non-opioid medications, but did not specifically examine LTOT.[25,26] Reviews also examined predictors of opioid misuse and abuse, and overdose, but predictors may differ for LTOT.[27–32]

Little is known about the criteria used to define LTOT for research purposes, and there has been no synthesis of the risk factors associated with transition from short-term opioid therapy to LTOT. Without an understanding of the criteria or the predictors of LTOT, it is difficult to understand the strengths and limitations regarding the evidence on the risk of LTOT, distinguish between episodic and long-term opioid use, and monitor the prevalence and incidence of LTOT. The purpose of this systematic review is to (a) document the varied definitions of LTOT used as an outcome in observational research and (b) identify the risk factors associated with transition from short-term opioid therapy to LTOT.

2 | METHODS

2.1 | Database and search strategy

We systematically reviewed the peer-reviewed literature to identify empirical studies investigating LTOT as an outcome following an indication for pain or initiation of prescription opioid therapy. We searched Pubmed, Medline, and Scopus databases for peer-reviewed articles published from January 2007 to July 2018. We chose this time period because the Food and Drug Administration received additional authority for post-approval monitoring in 2007, and there was specific attention to LTOT as demonstrated by the publication of clinical guidelines and recognition that LTOT was an important clinical outcome of prescribed opioid use for patients with CNCP during this time period.[20,21,33] We worked with a research librarian to develop a search strategy based on synonyms for three concepts: opioids, long-term opioid therapy, and risk factors (Appendix 1).

2.2 | Study selection

We considered LTOT definitions that examined prescription opioid therapy over 30 days or more of calendar time follow-up. We did not require specific study designs but required studies to measure LTOT as an outcome to understand the methodology used to define LTOT. To extract the predictors of LTOT, the study had to compare LTOT with short-term opioid therapy either by including a comparison group or examining opioid therapy over time to capture the shift from short-term to LTOT and have LTOT as an outcome. Articles were excluded if they were not written in English or were not original research. We also excluded studies not conducted in the United States or Canada to focus on countries with similar population characteristics and trends in opioid use.[13,34] We excluded studies where the outcome was chronic pain but not LTOT. Studies with pediatric or cancer patients were excluded because guidelines for LTOT may differ for these populations compared with patients with CNCP.[18,19] Within included studies, we identified a subset of studies with a new user study design to examine transitions to LTOT from an opioid-naïve state, defined using a washout period, or the period of time before the index date without any opioid use.[35] Two authors screened each study based on the title, abstract, and full text. We had group discussions to resolve conflicts and reach consensus for inclusion.

2.3 | Data extraction

For each included study, we extracted information about the sample (size and characteristics), data source, comparison group, and LTOT prevalence. We indicated whether studies applied a new user study design. If studies did not use a new user study design, we examined how opioid use was assessed during the lookback period or time period before the index date.

We identified distinct definitions of LTOT used in each study and deconstructed the components of each definition, which may capture the following:

- type of event used to identify the index date for assessing LTOT;

- follow-up time: calendar time observed after the index date;

- start of the measurement of LTOT: time points after the index date to collect information for LTOT definition;

- cumulative duration of opioid use: total amount of calendar time used to define LTOT;

- use of multiple, distinct observation periods;

- use of consecutive observation periods;

- number of prescriptions;

- days' supply: total number of days covered by a prescription;

- gaps or overlaps between prescriptions.

The CDC guideline indicates that the risk of opioid use increases with dose.[18] Therefore, we examine whether LTOT definitions use dose, reported in morphine milligrams equivalent (MME). We also examined whether definitions identified specific opioid types (eg, oxycodone, hydrocodone, long-acting, etc.). Both dose and opioid type may be used to distinguish between high- and low-risk LTOT.

Two authors independently identified study and definition characteristics and conflicts were resolved by group discussion. Since many studies had more than one definition, we present the percentage of definitions with each criterion.

Among the subset of studies with a new user study design, we identify the predictors associated with the transition from short-term opioid therapy to LTOT from multivariate models. We classified predictors according to the conceptual framework developed by Hooten and colleagues to understand the gaps in evidence on the predictors of LTOT.[36] Predictors were grouped into three domains: patient characteristics, practice characteristics, and prescriber characteristics.[36] Within each domain, we grouped similar predictors into categories. We describe the number of times a predictor was used across the models, whether the odds ratio for each predictor was less than 1, more than 1, not significant, or not reported.

3 | RESULTS

The search retrieved 5221 studies (Figure 1). After removing duplicates, we reviewed 3555 studies and selected 183 studies for full text review. Thirty-four studies were included for data extraction (Table 1).

Over 75% (n = 27) of the studies examined LTOT among patients who underwent surgery, and 25% (n = 7) examined LTOT among patients with CNCP. Seven studies had a new user study design. Data sources included administrative claims data (N = 20), medical records (N = 13), and survey data (N = 3).

3.1 | Characteristics of LTOT definitions

We extracted 41 unique variations of definitions of LTOT outcome measures (Table 2). Common definitions of the index date included the surgery date (71% of definitions), the

first opioid prescription (10%), and the first visit (10%). Follow-up times for studies varied from 3.5 months to 3 years, and the most common follow-up time was 1 year (44%). Most definitions had at least one measurement on the index date (51%), and 37% of definitions had at least one measurement at 3 months after the index date. Cumulative duration of opioid use to define LTOT varied from 6 weeks to 1 year, and most definitions used 3 months (46%).

Almost 30% of the definitions required more than one distinct observation period during study follow-up. For example, one definition used two observation periods: between 30 days before surgery and 2 weeks after the surgery and 3 to 6 months after surgery.[37] Only 17% of definitions explicitly specified consecutive observation periods. For example, one definition required a prescription fill for four consecutive 90-day time periods in the follow-up year.[38]

The number of prescriptions required for LTOT varied from one or more (61%) to 12 or more (2%). Days' supply was used for 27% of the definitions, and 90 days' supply was the most common cutoff (12%). No definitions considered dose and 68% of definitions considered product type. Only 7% of definitions accounted for the possibility of overlapping prescriptions. For 10% of the definitions, LTOT was self-reported from patient surveys.

About 64% of the definitions specified opioid use in the lookback period. The length of time used for the lookback period varied from 3 months (17%) to 1 year (22%), and most definitions had a 1-year lookback period.

Only 24% of definitions specified a washout period for opioid use, or time without opioid use before the index date. The amount of time for the washout period varied from 3 months (7%) to 3 years (5%), and most definitions had a 3-month washout period (7%).

3.2 | Prevalence of LTOT

Estimates of LTOT prevalence varied across studies by the population studied and LTOT definition used (Table 1). For studies involving opioid-naïve patients with surgery (n = 3), the prevalence of LTOT during study follow-up ranged from 5.3% to 13%.[37,39] The prevalence of LTOT among studies of opioid-naïve patients (n = 4) with CNCP ranged from 1.3% to 25%.[40,41] Two studies did not provide enough information to calculate the LTOT prevalence.[42,43]

3.3 | Predictors of LTOT

For the seven studies with opioid-naïve individuals, we identified 76 unique possible predictors of LTOT across eight analytic models that examined LTOT as an outcome (Table 3). According to the domains of the conceptual framework by Hooten and colleagues for LTOT, all predictors were classified as patient characteristics and none of the predictors captured the practice environment or prescriber characteristics.[36] Within the patient characteristics domains, 44.7% of predictors were classified as medical and mental health conditions, 19.7% were sociodemographic factors, and 11.8% were pain etiology. There were no predictors that assessed individual responses to pain and opioids. Although not included in the conceptual framework, 23% of the predictors referred to prior or baseline health service and medication use.[36]

The most common predictors included age (eight models), sex (eight models), opioid dose at baseline (four models), arthritis (four models), black race (four models), and presence of chronic pain (four models). Arthritis, chronic pain, tobacco use, drug disorders, and mental health disorders were consistently associated with greater risk of LTOT.

4 | DISCUSSION

This systematic review identified 41 unique variations of definitions of LTOT across 34 studies. The definition of LTOT differed by the follow-up time, cumulative duration of opioid use for LTOT, the time points used to define LTOT, and consistency of opioid use. All studies included follow-up time of at least 3 months, but half of the definitions had follow-up times that were less than 1 year. Shorter follow-up times make it difficult to observe LTOT, which is defined as longer than 3 months. For example, LTOT that begins near the end of a follow-up period would be misclassified as short-term opioid therapy. Longer follow-up times would improve LTOT identification and distinguish LTOT from episodic opioid therapy.

Most definitions used more than 3 months as the cumulative duration of opioid use for LTOT, which aligns with guideline definitions of chronic pain.[3,18,19] However, the length of time required for LTOT does not always account for consistent opioid therapy during follow-up. The definitions of opioid therapy during the time windows within the follow-up time were not strict and many definitions only required one opioid prescription during a predefined time period for LTOT.[40,43–54] For example, one study defined LTOT as at least one prescription 305 to 425 days after a hospital discharge.[44]

By only requiring one prescription during a specified window of time after the index date, these definitions fail to identify consistent use. Studies often used EHR data or claims data which contain rich information about prescriptions, but LTOT definitions rarely incorporated prescription characteristics such as the frequency of fills, fill dates, and days' supply. These characteristics capture consistent opioid use and overlapping prescriptions which exemplify differing levels of risky LTOT.[18] Eleven definitions used days' supply, and only three definitions used daily use to identify LTOT, a stark contrast to traditional measures of adherence which often require days' supply in the definition.[23] Only three definitions described methods used to account for gaps between prescriptions and overlapping prescriptions.[39,41] Identifying consistent use is important because it more closely reflects actual opioid therapy characteristics, compared with fills at various time points during follow-up.

While length of time of opioid therapy is the only necessary criterion to define LTOT, context about the nature of LTOT is important to identify patients who are at the highest risk for adverse outcomes. According to clinical guidelines, dose and opioid type are associated with greater risk of adverse events.[18] None of the included studies used dose, and 68% of definitions distinguished opioid type in the definition of LTOT. Patients with LTOT may become tolerant or increase doses over time.[18] Similarly, patients may also switch between long and short acting opioids during opioid use. Although technically reflective of LTOT, measures that do not account for these characteristics may not identify high-risk populations.

[27] For example, identifying patients with doses above recommended thresholds (more than 90 MME) during LTOT allows providers to identify patients who could benefit from tapering opioid doses.[18]

Assessing clinical appropriateness of LTOT is challenging because definitions lacked clinical information (eg, pain scores or functional status). Clinical information may not be available or easily accessible in claims or EHR data. Both claims and EHR data provide "as-prescribed" information, but they do not include patient behaviors (whether and how medications are consumed, disposed of, or diverted). For example, claims data only has data on prescriptions reimbursed by insurers, and does not have data on medications that were prescribed and never filled, or prescriptions that were paid for out-of-pocket or by other insurers. EHRs may not contain information about all medications dispensed. Without data on clinical indicators and all opioid prescriptions, clinically appropriate LTOT is difficult to distinguish from risky LTOT.

Very few LTOT definitions were described and implemented in exactly the same way. The definition of LTOT by Von Korff and colleagues was cited by several included studies.[20] LTOT was defined as "more than 90 days and more than 10 opioid prescriptions or more than 120 days' supply" during a 6-month follow-up time.[20] The definition also incorporated average daily doses by delineating between high-doses (more than 20 MME) and low doses (less than 20 MME).[20] The application of these definitions in the included studies was not always clear. Interestingly, one study took a data-driven approach for LTOT definitions by using group-based trajectory modeling, which identifies types of opioid use depending on changes in opioid use over time.[55–57] Data-driven approaches may improve the classification of LTOT, but studies have not compared the performance of data-driven approaches to a simple, binary measures defined at prespecified time points. These definitions have not been validated with patient self-reports or monitoring with urine drug screens.

Only a handful of included studies used prescription characteristics to define LTOT, potentially reflecting a lack of guidance on using prescription characteristics, limited analytic resources, or belief that prescriptions characteristics do not improve the sensitivity of the measure. Existing guidance for researchers and health systems contains conflicting definitions for LTOT.[16–18,58,59] As illustrated in one study using prescription registry data to create different LTOT definitions based on the dose, number of prescriptions, consistency of use, population characteristics vary depending on the criteria used.[60] Inconsistent definitions of LTOT inhibit our understanding of the utility of LTOT as an indicator of high-risk opioid use. We found that application of the various definitions has led to highly variable estimates of the prevalence of LTOT and inconclusive evidence on the risk factors of LTOT.

Across the studies of opioid-naïve individuals, the evidence regarding the predictors associated with LTOT is limited to patient characteristics, reflecting the data elements available in administrative data. The lack of evidence about individual responses to pain and opioid use as well as the patient's preferences, knowledge, beliefs, and psychosocial stressors indicates limited self-reported data available from opioid-naïve patients who develop LTOT. There was no evidence about prescriber characteristics (eg, pain management training, beliefs about opioid prescriptions, and professionalism) and the practice

environment (eg, health care team composition, capacity to deliver care, incentives, guideline adoption, prescribing laws, and prescription drug monitoring use) in the included studies. Further research is needed to understand how patient characteristics, prescriber characteristics, and practice environment characteristics interact with one another to influence LTOT.

The most common predictors used in studies include age, sex, opioid dose at baseline, and race, but the direction of the association varied depending on the model. However, in these studies, arthritis, chronic pain, tobacco use, drug disorders, and mental health disorders were consistently identified as risk factors for LTOT, many of which are similar to the risk factors associated with misuse, abuse, and overdose.[27–32] Finally, only three predictors examined prior opioid prescriptions, suggesting limited evidence on how initial prescribing may lead to LTOT. In a study not included in this review because it included pediatric patients, the number of fills and total dose during the first month of opioid use were associated with greater risk of LTOT.[61]

This review has several limitations. Our focus on the transition from short-term to LTOT means we did not examine studies of the time to opioid discontinuation. We also excluded studies where LTOT definitions were used solely to identify populations to target for interventions or where LTOT was a predictor. A meta-analysis of the predictors of LTOT was not feasible because of heterogeneity in study design and populations across the studies. Comparing findings for predictors across studies may be difficult because of the variation in the LTOT definition. Finally, we excluded studies that were published prior to 2007, which may have resulted in the exclusion of additional definitions of LTOT. The evidence from this review is limited to only the definitions of LTOT and does not assess how these definitions may impact the estimates for the risk of adverse events associated with LTOT. The above limitations are unlikely to alter our overall findings that the heterogeneity in study designs, populations, and LTOT definitions prevent the meta-analysis and comparison of predictors of LTOT across studies.

The implications of measurement error and misclassification, particularly for opioid research using large administrative datasets, are not unique to defining LTOT, and have been discussed in reviews of other measures such as opioid abuse and nonmedical prescription opioid use.[30,62,63] This study does not identify a common length of time for LTOT, nor did it aim to address the appropriate cutoff for the length of time used to define LTOT. At a minimum, researchers should include criteria that reflect consistent opioid use over time. Validation of LTOT definitions can better support efforts to predict and prevent LTOT. Researchers should consider incorporating clinical information available from data sources, such as patient-reported outcome measures (eg, pain and functioning) or EHR data, to better distinguish between clinically appropriate and inappropriate LTOT as well as low-risk and high-risk LTOT. Incorporating opioid dose exposure into LTOT definitions can distinguish the risks associated with LTOT. Patient reported measures and opioid dose can create risk-stratified definitions of LTOT to inform the selection of interventions for LTOT based on risk. Diverse data sources, including primary collection, could identify multilevel risk factors that influence LTOT. Researchers should perform sensitivity analyses around their selected definition of LTOT to evaluate the robustness of their measure. Applying these

recommendations will reduce bias and improve the internal validity of studies that examine LTOT as an outcome.[63]

5 | CONCLUSION

LTOT is quickly becoming a component used to assess quality of care for CNCP patients. We found that across studies of CNCP patients from the last decade, definitions of LTOT have been inconsistent, often lacking key prescription characteristics, such as opioid product type (eg, long acting vs short acting), frequency of fills, dose, and days' supply, that could distinguish between low- and high-risk LTOT. Use of unstandardized LTOT definitions has led to inconsistent estimates of the prevalence of LTOT and weak evidence on the risk factors of LTOT. Without addressing the potential bias resulting from misclassification and measurement error of LTOT measures, translating findings into policies and clinical practices to prevent adverse events that stem from LTOT will be difficult.

Appendix

APPENDIX 1:

SEARCH TERMS

Key Term	Search Words
Opioids	Analgesics, Opioid[MeSH] OR opiate, opiates, opioid, opioids, addnok, belbuca, buprenex, buprenophine, buprenorfina, buprenorphine, buprenorphinum, buprigesic, butrans, morgesic, norphin, norspan, probuphine, subutex, temgesic, tidigesic, butorphanol, codeine, methylmorphine, "morphine monomethyl ether", codhydrine, cohydrin, dehacodin, didrate, dihidrocodeina, dihydrin, dihydrocodeine, dihydrocodeinum, dihydrocodeinum, dihydrokodein, dihydrokodein, dihydroneopine, diidrocodeina, drocode, hydrocodeine, hydrocodin, nadeine, novicodin, novicondin, paracodin, paracodine, parzone, rapacodin, "alpha-hydrocodol", dihydromorfin, dihydromorphine, hydromorphine, paramorfan, paramorphan, difenossilato, difenoxilato, diphenoxalate, diphenoxylate, diphenoxylatum, abstral, duragesic, durogesic, durotep, fentanest, fentanil, fentanila, fentanyl, fentanylum, fentora, lazanda, matrifen, pecfent, phentanyl, recuvyra, sentonil, sublimase, subsys, codinovo, dicodid, dihydrocodeinone, hycodan, hycon, hydrocodeinonebitartrate, hydrocodon, hydrocodone, hydrocon, robidone, dihydromorfinon, dihydromorphinone, dilaudid, dimorphone, exalgo, hidromorfona, hydromorfona, hydromorph, hydromorphone, hydromorphonum, idromorfone, jurnista, palladone, aromarone, levorfanol, levorfanolo, levorphan, levorphanol, levorphanolum, demerol, dolantin, dolcontral, dolosal, dolsin,

Key Term	Search Words
	isonipecaine, lydol, meperidine, mialgin, pethidin, pethidine, pethidinum, petidin, petidina, petydyna, sauteralgyl, spasmedal, spasmodolin, adanon, algovetin, althose, amidon, amidone, dextromethadone, diaminon, dolophin, dolophine, fenadone, heptadone, heptanon, ketalgin, levometadona, levomethadonum, levothyl, metadona, metadone, metasedin, methadon, methadona, methadonum, methaquaione, phenadone, polamidone, polamivet, sedo-rapide, tussol, westadone, methadone, ambenyl, avinza, bromanyl, chembl70, codrix, depodur, dimetane, infumorph, kadian, morphine, mybanil, triacin, nalbuphine, nubain, opium, codeinone, combunox, dihydrohydroxycodeinone, dihydrohydroxycondeinone, dihydrone, dihydroxycodeinone, dinarkon, diphydrone, endine, endone, eubine, eucodal, eucodalum, hydroxycodeinon, ossicodone, oxanest, oxicodona, oxicon, oxicone, oxiconum, oxyir, oxycodeinon, oxycodeinone, oxycodon, oxycodonum, oxycone, oxycontin, oxyfast, oxynorm, pancodine, pancodone, percobarb, percodan, percolone, remoxy, roxicet, roxicodone, supendol, tekodin, theocodin, oxycodone, oxymorphone, pentazocine, talacen, talwin, biomadol, contramid, labesfal, ralivia, tradonal, tramadis, tramadol, tramadolum, tramadon, tramaliv, trapidol, ultram, zytram, darvon, dextropropoxyphene, propoxyphene, Nucynta, tapentadol
Long-term opioid therapy	long term persistent, episodic, prolonged, chronic
Risk factors	risk factor, risk factors, predictive, predict, predicts, prediction, population at risk, populations at risk, at risk population, at risk populations

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Key Points

- Despite no gold standard definitions for long-term opioid therapy (LTOT), it is increasingly used as a component of quality improvement efforts to identify populations at risk for opioid-related adverse events and inform interventions to promote appropriate opioid therapy.

- LTOT definitions often lacked information about dose and consistency of use, despite availability of these elements in secondary data sources.

- Inconsistent definitions of LTOT have led to differences in estimates of the prevalence of LTOT and inconclusive evidence of the risk factors for LTOT.

- Researchers should consider incorporating criteria that indicate consistency of opioid use when defining LTOT and perform sensitivity analyses to evaluate the robustness of LTOT measures.

- A consensus about LTOT definitions is needed to identify patients with LTOT, understand the risk factors that lead to LTOT, and evaluate clinical practices and policies aimed at reducing risky LTOT.
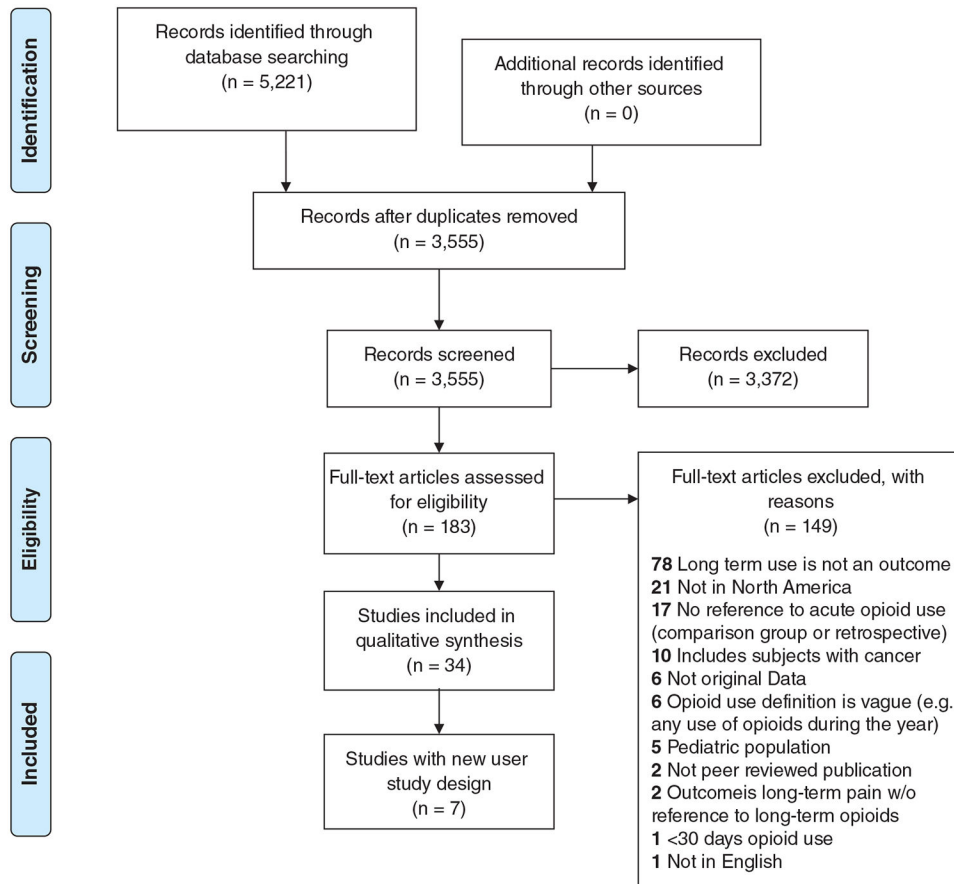
FIGURE 1.
Prisma flow diagram

TABLE 1

Characteristics of included studies

Article	Study Sample Description (N)	Source of Data for Long-Term Use Measure	Definition Summary	Comparison Group	Percent Long-Term Users
Alghnam[64]	Adults (18+) (N = 36 824)	Survey data (Medical Expenditure Panel Survey)	Self-reported opioid use in two of the final three rounds of the Medical Expenditure Panel Survey (totaling 8 mo of time)	Patients without long-term use	15.60%
Anderson[65]	Workers' compensation recipients in Ohio who had lumbar fusion from 1993 to 2013 (N = 1002)	Administrative claims database (Ohio Bureau of Workers' Compensation)	Post-operative long-term use: starting 6 wk after the surgery, more than 365 days' opioid supply in the 3-y follow-up period. Pre-operative long-term use: 120 days' opioid supply in the year before surgery.	Less than 365 days' supply of opioids in the year following a 6-wk post-operative period.	575/1002 = 57%
Bartels[53]	Patients with surgery during October 2011 and September 2013 (N = 6003)	Electronic health record (University of Colorado Hospital)	At least one opioid prescription fill 31 to 180 d after surgery	Patients without long-term prescription	43.6%
Brumett[66]	Opioid-naïve, US adults age 19 to 64 with a surgical procedure between 2013 and 2014 (N = 36 177)	Administrative claims data (Clinformatics Data Mart)	At least one opioid prescription fill in each of two time periods: 30 d before through 14 d after surgery and 90–180 d after surgery	Patients without surgery, anesthesia, or an opioid prescription in a 12-mo period	Minor surgery group: 5.9% Major surgery group: 6.5% Nonoperative control group: 0.4%
Cancienne[49]	Patients who underwent primary total knee arthroplasty from 2007 to the first quarter of 2016 (N = 113 337)	Administrative claims data (Pearldiver patient records)	At least one opioid prescription fill 3 to 6 mo after surgery.	Patients without long-term use	35 770/113 337 = 32%
Connolly[67]	US adults with lumbar spinal fusion surgery during 2009 to 2012 (N = 8377)	Administrative claims data (Clinformatics Data Mart)	At least 365 days' supply in the 2-y follow-up period after surgery.	Patients without long-term opioid use	29.34%
Crocker[68]	Patients with Crohn disease and functional gastrointestinal disorder diagnosis from 2006 to 2011 (N = 931)	Electronic medical record (University of Virginia Digestive Health Center) and the prescription monitoring program database (Virginia and West Virginia)	One opioid prescription fill per month for 3 consecutive months in a 12-mo follow-up period or more than two prescription opioid fills in any 6-mo period of the 12-mo follow-up period.	Two groups- Crohn disease with and without functional gastrointestinal disorders	192/931 = 21%
Deyo[69]	Patients with lumbar fusion from October 2012 to September 2013 (N = 2491)	Administrative data (Oregon prescription drug monitoring program)	Pre-operative long-term use was at least four opioid prescription fills in the 7 mo before the index date where three fills occur within 180 d before the index date. Post-operative long-term use was at least four opioid prescription fills in 7 mo after the index date with at least three prescriptions 30 d after the hospitalization	Patients without postoperative long-term opioid use	12.8%
Daoust[44]	Canadian adults, age 65+, with a trauma admission from April 2004 to March 2014 (N = 84 241)	Administrative database (Medical Consultations and Medication database in Quebec)	At least one opioid prescription fill 305 to 425 d after hospital discharge	Patients without opioid prescription 1 y after injury.	4337/39 833 = 10.9%

Article	Study Sample Description (N)	Source of Data for Long-Term Use Measure	Definition Summary	Comparison Group	Percent Long-Term Users
Dunn[70]	Patients who received elective spinal fusion from March 2011 to February 2016 (N = 1477)	Electronic health record (University of Virginia)	Documented opioid use at each of the following postoperative time periods: 1–3 d, 1 mo, 6 mo, and 12 mo	Patients without opioid use at 12 mo	(67 + 498)/1477 = 38%
Franklin[38]	Workers with acute back injury at risk for long-term disability from 2002 to 2004 (N = 1296)	Administrative pharmacy claims data (Washington workers' compensation medical billing database)	At least one opioid prescription fill in each of four consecutive calendar quarters	Patients with opioid use during fewer than three quarters	111/1843 = 6.02%
Goesling[43]	Patients with total knee arthroplasty and total hip arthroplasty from March 2010 to May 2013 (N = 574)	Medical records and confirmation with patients during follow-up (telephone surveys and validated questionnaires)	No explicit definition. Self-reported opioid use was assessed at 30 d, 90 d, and 180 d after surgery.	Patients without opioid use at 6 mo	Not information to calculate rate
Fritz[71]	Opioid-naïve patients with low back pain from 2012 to 2014 (N = 707)	Administrative data (University of Utah Health Plan)	More than 120 d supply or more than 10 opioid prescription fills with more than 90 d supply during 1-y follow-up.	Patients without long-term use	24.3%
Granadillo[48]	Patients with hip arthroscopy from 2007 to 2015 (N = 1708)	Administrative claims data (Pearldiver patient records)	At least one opioid prescription fill 3 to 6 mo after surgery.	Patients without long-term use	468/1708 = 27.4%
Holman[45]	Patients with orthopedic trauma from June 2005 to June 2007 (N = 748)	Administrative data (Utah Controlled Substance Database)	No explicit definition. Presence of at least one opioid prescription fill was assessed during three time periods in the 6-mo follow-up period after surgery: 0 to 6 wk, 6 to 12 wk, and more than 12 wk.	Patients without continued use of opioids 6 wk after surgery	LTOT prevalence for more than 12 wk: 19.7%
Jain[72]	Patients with primary cervical fusion for degenerative pathology from 2007 to the third quarter of 2015 (N = 29,101)	Administrative claims data (Pearldiver Humana database)	Preoperative long-term use is at least one prescription during the following preoperative time periods: 0 to two weeks, 2 wk to 1 mo, 1–3 mo, 3–6 mo, and 6 mo. Postoperative long-term use is at least one prescription during the following postoperative time periods: 0–6 wk, 6 wk to 3 mo, 3–6 mo, 6–9 mo, and 9–12 mo.	Patients without preoperative long-term use Patients without postoperative long-term use	49.2%
Jiang[46]	Adults who received surgical care from 2010 to 2011 (N = 79,123)	Electronic medical record (University of Pennsylvania Health system)	At least 90 d of opioid use between the first and last recorded outpatient visit occurring within a 2-y observation period	Patients without chronic opioid use	9.2%
Johnson[37]	Adults with elective and trauma related hand surgery procedures from 2010 to 2012 (N = 77,573)	Administrative data (Truven Market-Scan Commercial Claims Research Database)	At least one opioid prescription fill in each of two time periods: 30 d before through 14 d after surgery and 90–180 d after surgery	Patients without long-term opioid use	Of the opioid naïve patients with a perioperative opioid prescription (N = 59 735), 13%
Kim[55]	Patients with hip or knee arthroplasty from 2004 to 2013 (N = 57 545)	Administrative data (United Healthcare/Optum Clinformatics Data Mart Database)	Monthly opioid use for 12 consecutive months	Patients without long-term opioid use	4394/57 545 = 7.6%
Koeppe 2011[73]	Opioid naïve, US Adults with HIV from 11 clinics from 1998 to 2008 (N = 931)	Medical Records (data from the HIV Outpatient Study)	Measured prolonged analgesic use, defined as 90 or more consecutive days of opioid or nonopioid analgesic medication use.	Patients without long-term opioid use	931/4180 = 22%

Article	Study Sample Description (N)	Source of Data for Long-Term Use Measure	Definition Summary	Comparison Group	Percent Long-Term Users
Kulshrestha[74]	Adults who have kidney transplant from 2004 to 2008 (N = 1045)	Electronic medical record (single center study, name not reported)	1. Opioid use reported during three time periods after surgery: 1–2 mo, 3–6 mo, and 10–12 mo. 2. Opioid use reported during the 1–2-mo and 3–6-mo follow-up period only if patient had a graft loss or died during the 3–12 mo follow-up period	Patients without long-term opioid use	119/(119 + 926) = 11%
Mosher[39]	Patients with an outpatient opioid prescription during FY 2011 that was preceded by a 1-y opioid-free period (N = 43 027)	Administrative data (Veterans Health Administration)	More than 90 days of continuous opioid use (determined by the days' supply), with the initiation of the episode beginning within the first 30 d of the first prescription.	Patients without long-term use	Medicine: 15.2% Surgery: 5.3% Total sample: 9.10%
Mueller[50]	Patients with total shoulder arthroplasty and shoulder hemiarthroplasty during 2002 to 2012 (N = 6988)	Administrative claims data (Marketscan)	Preoperative long-term use was more than 10 opioid prescription fills or 120 d opioid supply during the year before surgery. Postoperative long-term use was at least one prescription during the follow-up	Patients with and without nerve block	50.1% of patients without nerve block; 49.5% among patients with nerve block
Mulligan[75]	Patients with ankle or hindfoot reconstruction (N = 132)	Electronic medical record (study site not reported)	Opioid prescription from 90 d to 2 y after surgery	Patients without continued use 90 d after surgery	35%
Namba[76]	Patients with unilateral primary total knee arthroplasty from 2008 to 2011 (N = 23 726)	Electronic medical record (Kaiser Permanente Northern California, Southern California, and Hawaii)	No explicit definition. Assessed presence of opioid prescription during each quarter of the follow-up year after surgery.	Patients without an opioid prescription in that quarter (separate models for each quarter)	Days 1–90: 92.7% Days 91–180: 42.1% Days 181–270: 32.2% Days 271–360: 30.4%
Pugley[51]	Patients with cervical spinal arthrodesis from 2007 to 2014 (N = 17 391)	Administrative data (Humana Inc via PearlDiver)	One or more opioid prescription fill at 1 y after surgery.	Patients without opioid use in the 3 mo before surgery	LTOT at 12 mo: 27.6%
Qureshi[52]	Patients with discectomy from 2007 to 2015 (N = 1321)	Administrative data (PearlDiver)	Opioid prescription fill 3–6 mo after surgery	Patients without long-term prescription	(621/621 + 700) = 47%
Raebel[77]	Adults (21+) with bariatric surgery without chronic opioid use before surgery from nine health systems from 2005 to 2009 (N = 10 643)	Electronic medical record (outpatient pharmacy dispensing data) (nine health systems participating in the Scalable Partnering Network (SPAN))	Ten or more opioid prescription fills over more than 90 d, or more than 120 d opioid supply during 1 y of follow-up More than 120 d supply during the 1-y follow-up.	Patients without chronic opioid use the year after surgery	4%
Ray 2017[41]	Opioid naïve patients (÷19) with at least 1 opioid prescription 2011 (N = 2 480 030)	Electronic medical record (Kaiser Permanente Northern California)	At least 3 mo of opioid use with either more than 120 d opioid supply or 10 or more opioid prescription fills during the 3-y follow-up period.	Cohort of patients without opioid fill in 2011	112 089/455 693 = 25%
Rosenbloom[47]	Adults with musculoskeletal surgery (n = 122)	Patient reported survey (2 large level I trauma centers (Sunnybrook Health Sciences Centre [SHSC] and St. Michael's Hospital [SMH]), in Toronto, Canada)	Self-reported opioid use in the past week at 4 mo after injury	Patients without opioid prescription at 4 mo after surgery	35%
Rozet[54]	US veterans 18 to 50 with elective ambulatory knee arthroscopic surgery from 2007 to October 2010 (N = 145)	Electronic medical record (Veterans Affairs' Tertiary Medical Center (Seattle Division, VA PSHCS))	At least 3 mo of "uninterrupted" opioid use after surgery.	Patients with and without post-traumatic stress disorder	30%

Article	Study Sample Description (N)	Source of Data for Long-Term Use Measure	Definition Summary	Comparison Group	Percent Long-Term Users
Rao[78]	Patients with shoulder arthroplasty registry from 2008 to 2014 (N = 4243)	Shoulder Arthroplasty Registry which includes data collected from electronic intraoperative forms, electronic health records, administrative claims, membership data, and mortality records (Kaiser Permanente Hawaii, Northern California, and Southern California	No explicit definition. Assessed presence of opioid prescription during each quarter of the follow-up year after surgery.	Patients without an opioid prescription in that quarter (separate models for each quarter)	Opioid use in the rehabilitation period ranged from 38% to 42% though specific percentages are not reported.
Sun[42]	Patients with total knee arthroplasty from 2002 to 2012 (N = 120 080)	Administrative claims data (Marketscan)	More than 10 opioid prescription fills or 120 d opioid supply 91–365 d post-surgery	Patients without long-term use	Unable to calculate LTOT
Thornton[40]	Patients with an opioid prescription from 2007 to May 2015 (N = 491 442)	Administrative Claims Data (IMS Health/Quintiles, IQVIA)	More than 90 d supply during the 4 mo follow up period	Patients without long-term use	1.30%

TABLE 2

Characteristics of definitions of long-term opioid use (n = 41)

Index event for Follow-up		
Surgery	**29**	**71%**
First visit	4	10%
First prescription	4	10%
Hospital discharge	2	5%
Acute injury	1	2%
14 days after hospitalization	1	2%
Unclear	2	5%
Study follow-up time		
3.5 mo	1	2%
4 mo	2	5%
6 mo	10	24%
7 mo	1	2%
1 y	18	44%
14 mo	1	2%
2 y	3	7%
3 y	3	7%
Unclear	2	5%
Time points of measurement: time points used to collect information for LTOT definition.		
1 month before index date	1	2%
Index date	21	51%
First visit with first prescription	1	2%
14 days after index date	1	2%
1 mo after index date	6	15%
6 wk after index date	3	7%
3 mo after index date	15	37%
4 mo after index date	2	5%
6 mo after index date	5	12%
8 mo after index date	1	2%
9 mo after index date	3	7%
10 mo after index date	1	2%
305 d after index date	1	2%
12 mo after index date	4	10%
16 mo after index date	1	2%
Cumulative duration of opioid use: total amount of calendar time used to define LTOT		
6 wk	1	2%
3 mo	19	46%
4 mo	5	12%
5 mo	1	2%
6 mo	3	7%

Index event for Follow-up		
Surgery	**29**	**71%**
7 mo	2	5%
8 mo	1	2%
9 mo	2	5%
1 y	7	17%
Unclear	2	5%
Use of multiple, distinct observation periods (required more than 1, not including pre/post op)		
Yes	12	29%
No	29	71%
Consecutive time periods (explicitly states consecutive)		
Yes	7	17%
Daily	3	7%
Monthly	2	5%
Quarterly	1	2%
Other	1	2%
No/not explicitly stated in the definition	34	83%
Number of prescriptions		
At least 1	25	61%
At least 2	6	15%
At least 3	2	5%
At least 4	3	7%
At least 5	1	2%
At least 10	4	10%
At least 12	1	2%
Used days' supply		
Yes	11	27%
90 d supply	5	12%
120 d supply	4	10%
365 d supply	2	5%
No	30	73%
Accounts for overlapping prescription		
Yes	3	7%
No	38	93%
Used dose		
Yes	0	0%
No	41	100%
Identified opioid product type		
Yes	28	68%
No	13	32%
Long-term use is self-reported (from patient surveys)		
Yes	4	10%
No	37	90%

Index event for Follow-up		
Surgery	**29**	**71%**
Type of data used		
Administrative data	39	95%
Survey data	4	10%
Washout period (and length of time required without opioid use)		
Yes	10	24%
3 mo before the index	3	7%
11 mo preceding the month before surgery	2	5%
12 mo before index	2	5%
3 y before index	2	5%
Unclear	1	2%
No	31	76%
Opioid use in look back period (and length of time required for look back period to detect opioid use)		
Yes	26	63%
3 mo	7	17%
4 mo	3	7%
6 mo	1	2%
>250 d	1	2%
1 y	9	22%
unclear time period	5	12%
No	15	37%

TABLE 3

Predictors of long-term opioid therapy

Category	Variable	Interpretation	Number of Time Odds Reported Greater Than 1	Number of Time Odds Reported Less Than 1	Number of Time Odds Reported Equal to 1	Number of Models	References
Demographics	Age	Older age; lower risk (measured as categorical variable)	5	4	4	8	[37, 39–41, 64, 66, 71]
Demographics	Sex	Females have greater risk	2	3	3	8	[37, 39–41, 64, 66, 71]
Opioid use	Opioid dose	greater dose, greater risk	1	3	2	4	[39, 40, 66]
Pain diagnosis	Arthritis	Presence of arthritis, greater risk	4	0	0	4	[40, 41, 66]
Demographics	Race	Compared to White, Black have a greater risk	0	1	4	4	[39, 41, 64, 66]
Pain chronicity	Chronic pain	Presence of chronic pain have greater risk	4	0	0	4	[39–41]
Medication use	Benzodiazepine use	Presence of benzodiazepine prescription vs none	2	1	0	3	[39, 40]
Mental illness	Anxiety disorder	Presence of anxiety disorder, greater risk	2	0	1	3	[39, 66, 71]
Substance use issue	Tobacco	Tobacco or Smoking increases risk	3	0	0	3	[40, 66, 71]
Substance use issue	Alcohol or substance use disorder	Presence of alcohol or substance use disorder, greater risk	2	0	1	3	[39, 66, 71]
Mental illness	Depression	Presence of depression increases risk	1	0	2	3	[39, 64, 71]
Demographics	Race	Compared to white, Other/multiracial have a greater risk	0	2	3	3	[39, 41, 64]
Opioid use[1]	Opioid type	N/A			3	3	[39, 40]
Comorbidities	Charleson comorbidities	Higher score, greater risk	1	0	1	2	[66, 71]
Demographics	Race	Compared to white, Asian have a greater risk	0	1	2	2	[41, 66]
Demographics	Race	Compared to white, Hispanic have a greater risk	0	1	1	2	[41, 66]
Mental illness	Mood disorder	Presence of mood disorder, greater risk	1	0	1	2	[66, 71]
Insurance	Type of insurance plan	compared to PPO, HMO coverage has greater risk	0	0	2	2	[37, 40]
Substance use issue	Drug disorder	Presence of drug disorder has greater risk	2	0	0	2	[40]
Substance use issue	Alcohol dependence/abuse	Presence of alcohol dependence/abuse, greater risk	0	0	2	2	[37, 40]
Medication use	Non opioid analgesic	Presence of non-opioid analgesic, greater risk	1	0	1	2	[39, 40]
Surgery[2]	Surgery	N/A	1			2	[37, 66]

Category	Variable	Interpretation	Number of Time Odds Reported Greater Than 1	Number of Time Odds Reported Less Than 1	Number of Time Odds Reported Equal to 1	Number of Models	References
Insurance	Type of insurance plan	compared to PPO, other coverage has greater risk	0	1	1	2	[37, 40]
Mental illness	Mental health disorder (schizophrenia, mood disorders, neurotic disorders, and depression)	Presence of mental health disorder, greater risk	2	0	0	2	[37, 40]
Utilization	Primary care visit (within 30 days)	Presence of primary care visit (within 30 days) has greater risk	1	1	0	2	[41, 71]
Comorbidities	Asthma	Presence of asthma, greater risk	0	1	1	2	[40, 41]
Pain diagnosis	Osteoporosis	Presence of osteoporosis, greater risk	1	0	1	2	[40, 41]

Note. This table only includes predictor variables that were in more than one model. Studies with opioid-naïve sample[37,39–41,64,66,71] Results from Koeppe 2011 are not included because the definition of opioid-naïve sample differed from the other studies.[73]

[a] Excludes variables that referenced opioid type, but models examined long-acting, tramadol, codeine, oxycodone, hydrocodone, hydrocodeine.

[b] Excludes surgery related variables, but models examined varicose vein removal, laparoscopic cholecystectomy, laparoscopic appendectomy, hemorrhoidectomy, thyroidectomy, transurethral prostate surgery, parathyroidectomy carpal tunnel, ventral incisional hernia repair, colectomy reflux surgery, bariatric surgery, hysterectomy, nonoperative comparisons, carpal tunnel release, carpometacarpal arthroplasty/arthrodesis, cubital tunnel release, trigger finger release, flexor tendon repair, metacarpal fracture fixation, closed distal radial fracture fixation, flexor tendon repair, metacarpal fracture fixation, phalangeal fracture fixation.