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Persistent Postoperative Opioid Use

A Systematic Literature Search of Definitions and Population-based Cohort Study

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Persistent opioid use after surgery is a matter of great concern
- Defining appropriate opioid prescribing practices and policies depends critically on understanding the rate of and reasons for persistent postoperative opioid use

What This Article Tells Us That Is New

- A systematic search of the literature revealed 29 distinct definitions of persistent opioid use employed in 39 different studies
- Applying the definitions to a separate study cohort of more than 162,000 surgical patients identified persistent opioid use rates varying more than 100-fold with low sensitivity for the identification of opioid use disorder

ABSTRACT

Background: While persistent opioid use after surgery has been the subject of a large number of studies, it is unknown how much variability in the definition of persistent use impacts the reported incidence across studies. The objective was to evaluate the incidence of persistent use estimated with different definitions using a single cohort of postoperative patients, as well as the ability of each definition to identify patients with opioid-related adverse events.

Methods: The literature was reviewed to identify observational studies that evaluated persistent opioid use among opioid-naive patients requiring surgery, and any definitions of persistent opioid use were extracted. Next, the authors performed a population-based cohort study of opioid-naive adults undergoing 1 of 18 surgical procedures from 2013 to 2017 in Ontario, Canada. The primary outcome was the incidence of persistent opioid use, defined by each extracted definition of persistent opioid use. The authors also assessed the sensitivity and specificity of each definition to identify patients with an opioid-related adverse event in the year after surgery.

Results: Twenty-nine different definitions of persistent opioid use were identified from 39 studies. Applying the different definitions to a cohort of 162,830 opioid-naive surgical patients, the incidence of persistent opioid use in the year after surgery ranged from 0.01% (n = 10) to 14.7% (n = 23,442), with a median of 0.7% (n = 1,061). Opioid-related overdose or diagnosis associated with opioid use disorder in the year of follow-up occurred in 164 patients (1 per 1,000 operations). The sensitivity of each definition to identify patients with the composite measure of opioid use disorder or opioid-related toxicity ranged from 0.01 to 0.36, while specificity ranged from 0.86 to 1.00.

Conclusions: The incidence of persistent opioid use reported after surgery varies more than 100-fold depending on the definition used. Definitions varied markedly in their sensitivity for identifying adverse opioid-related event, with low sensitivity overall across measures.

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Opioids may be indicated for the management of moderate to severe pain in the immediate postoperative period, but concerns have been raised that excessive exposure to opioids may lead to long-term dependence.[1–3] In this context, the concept of "new long-term use," typically defined based on filled pharmacy claims for opioids after surgery, has emerged as an important construct in research on opioid-related outcomes after acute pain treatment.[1–3] Moreover, surgeons, and postsurgical opioid prescriptions, have become a large focus of opioid-related policy, research, and intervention.[4]

The research surrounding persistent postsurgical opioid use has important methodologic limitations, which could have notable implications for patients and policy. Most importantly, the definition of persistent postsurgical opioid use is not consistent between studies, making interpretation of estimates and comparison across studies challenging.[5] Notably, it is also unknown whether definitions of persistent postsurgical opioid use reflect the patients at risk for opioid-use disorder or opioid-related toxicity.

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The objective of the study was to evaluate whether the definition of persistent postoperative opioid use impacts the reported incidence. In order to achieve this, first, we performed a systematic search of the literature to identify definitions of persistent postoperative opioid use in the medical literature. Second, we evaluated the influence of these definitions on the estimated incidence of persistent opioid use after surgery. Specifically, we applied each definition to the same cohort of opioid-naive patients presenting for surgery to determine the variability in defined persistent use based on the definition employed. Finally, we assessed the sensitivity and specificity of each definition to identify patients with opioid-related adverse events in the year after surgery.

Materials and Methods

Systematic Literature Search for Definitions of Persistent Use

Data Sources and Search Strategy. The prespecified protocol for this systematic search, which aimed to identify definitions of persistent postoperative opioid use, was developed based on Preferred Reporting Items for Systematic reviews and Meta-analyses Protocols (PRISMA) 2015 guidelines.[6] We conducted a computerized search using the OVID versions of MEDLINE, Medline-in-Process, Medline Epubs Ahead of Print (1946–June 2018), and Embase Classic+Embase databases (1946–June 2018). We used both subject headings and textword terms for Opioids AND (surgical procedures or postoperative complications) and (cohort studies or prognosis or risk or time factors). We also searched the reference lists of included studies. The complete search strategy and further details of the systematic review methods can be found in Supplemental Digital Content 1 (http://links.lww.com/ALN/C336). Each title and abstract were screened independently and in duplicate by two authors (N.J. and J.B.). Full-text articles were obtained for any study considered potentially relevant for defining and/or estimating the incidence of persistent opioid use after surgery.

Study Selection and Outcome Definition. Two reviewers assessed the full text of each retrieved citation independently and in duplicate. We included studies of adults (18 yr or older) undergoing any surgical procedure. We required that studies have a cohort study design and measure a patient's opioid use at least 30 days after discharge from surgery and provided a definition for persistent opioid use in the postoperative period. We excluded studies that (1) were not performed in humans, (2) were not written in English, (3) were review articles, (4) were randomized controlled trials as these are likely to be highly selected (selection bias) and were unlikely to estimate the incidence of persistent postoperative opioid use, or (5) where we were unable to extract the relevant data. Our outcome of interest was the definition(s) of persistent postoperative opioid use employed by the authors.

Data Extraction. Two reviewers extracted data independently and in duplicate using a standard form (N.J., F.R., J.B.). Information extracted included patient characteristics, study design, setting, surgical procedures, the definition of persistent postoperative opioid use employed, and the type of opioids measured.

Population-based Cohort Study

After approval by Sunnybrook Health Sciences Center Research Ethics Board (Toronto, Canada), we then used a population-based sample of opioid-naive patients undergoing surgery to assess the estimate of persistent opioid use with each definition. We used health administrative data from the province of Ontario, Canada. All residents of Ontario, which has a population of approximately 14 million individuals, obtain their healthcare services from a single payer and provider (the Government of Ontario). Each individual is assigned a unique, encoded identifier that permits linkage deterministically across provincial and national administrative databases and analysis at ICES. For details of the databases, see Supplemental Digital Content 2 (http://links.lww.com/ALN/C337). These databases have high levels of completeness and have been validated for many outcomes, exposures, and comorbidities.[7,8]

Our population of interest was all patients who were 18 yr or older between July 1, 2013, and March 30, 2017. Our exposure of interest was 1 of 18 surgical procedures, using Canadian Classification of Health Intervention codes (to identify procedures) and associated International Statistical Classification of Diseases and Related Health Problems, Tenth Revision codes (to identify diagnoses; Supplemental Digital Content 3, http://links.lww.com/ALN/C338). This enrollment window was selected to provide a minimum 1-yr look-back period and 1-yr follow-up period for all patients. The index date was defined as the date of admission (inpatient surgery) or date of surgery (outpatient surgery). The specific procedures included those listed in Supplemental Digital Content 3 (http://links.lww.com/ALN/C338). These surgical procedures were chosen as they are common,[9] and have been previously used to evaluate postoperative opioid consumption.[10] The validity and reliability of codes to identify surgical procedures have been confirmed through reabstraction studies.[11]

We excluded patients if they (1) did not have valid provincial health insurance; (2) had a surgical procedure in the year before their index surgical procedure; (3) sought palliative care services, as subsequent opioid use was likely for end-of-life care[12]; and (4) had a prolonged hospitalization defined as a length of stay greater than 7 days. Finally, we excluded patients who filled one or more opioid prescription(s) in the year before surgery, omitting the first 30 days preoperatively (*e.g.*, –365 days to –31 days, preoperatively). This definition was chosen as it represented the most inclusive definition of opioid-naive in our literature review and facilitated the operationalization of the greatest number of persistent postoperative opioid use outcome definitions.

Outcomes. The primary outcome was persistent postoperative opioid use. We operationalized each definition of persistent postoperative opioid use obtained from our systematic literature review (table 1). If persistent opioid use was defined

Table 1. Definitions of Persistent Postoperative Opioid Use

Definition	Source
Prescriptions filled, or opioid consumed at a distinct time point	
Filled more than 30 days postoperatively	
Opioid prescription beyond 30 days after date of surgery*	Stafford *et al.*[17]
Opioid consumed 6 weeks postoperatively (patient-reported)†	Grace *et al.*[18]
	Hernandez *et al.*[19]
Filled 90–180 days postoperatively	
Filled at least one opioid prescription between 90 and 180 days after surgery	Cancienne *et al.*[20]
	Qureshi *et al.*[21]
	Ladha *et al.*[22]
Continuation of prescription opiates greater than 12 weeks postoperatively‡	Holman *et al.*[23,24]
(1) Filled prescription within 1 to 90 days after discharge; and (2) filled at least one additional opioid prescription between 91 and 180 days after surgery	Clarke *et al.*[25]
(1) Filled prescription within 30 days before surgery and 14 days after discharge; (2) filled at least one additional opioid prescription between 90 and 180 days after surgery	Johnson *et al.*[26]
	Lee *et al.*[27]
	Brummett *et al.*[10]
Filled at least one opioid prescription overlapping 90 or 180 days	Lindestrand *et al.*[28]
Opioid consumption at time of interview (180 days postoperatively)§	Goesling *et al.*[29]
	Kim *et al.*[30]
Filled 90–120 days postoperatively	
Opioid use, based on questionnaire, between 90 and 120 days after surgery‖	Stark *et al.*[31]
(1) Filled prescription within 30 days before surgery and 30 days after discharge; (2) filled at least one additional opioid prescription between 90 and 120 days after surgery	Marcusa *et al.*[32]
Filled 90–365 days postoperatively	
Filled at least one opioid prescription between 90 and 365 days after surgery	Mueller *et al.*[33]
Filled more than 1 opioid prescription more than 90 days after surgery	Pang *et al.*[34]
Filled within 60 days of the 1-yr anniversary date (*e.g.*, 305–425 days after the index date)	Alam *et al.*[35]
Opioid use at 12 months (365 days) postoperatively#	Pugely *et al.*[36]
Filled more than 3 yr postoperatively	
Filled at 795 days postoperatively	Yang *et al.*[37]
Multiple days of opioid prescribing or patient reported opioid consumption	
Opioids filled at multiple time points	
Filled at three distinct time points: (1) 28–56 days, (2) 90–180 days, and (3) 300–365 days after surgery (or first two time intervals if the patient had an event [death and/or graft loss] between 3 and 12 months)	Kulshrestha *et al.*[38]
60 days of noncontinuous use	
60 days of noncontinuous prescriptions filled (within 275 days, excluding the first 90 days)**	Kent *et al.*[5]
90 days of continuous use or 120 days of noncontinuous use	
90 days of continuous use or at least 120 days of noncontinuous use (within 275 days, excluding the first 90 days)	Hansen *et al.*[39]
	Inacio *et al.*[40]
150–180 days of continuous use	
Prescribed opioids for more than 6 contiguous months after surgery (followed for 24 months postoperatively)††	Politzer *et al.*[41]
Patient reported continuous consumption of opioid (with no gaps greater than 5 days) in the 150 days after discharge‡‡	Carroll *et al.*[42]
Opioids prescribed uninterrupted for greater than 3 months after surgery	Rozet *et al.*[43]
365 days of continuous or noncontinuous use	
365 days of filled opioid prescriptions (within 24 months after surgery)	Connolly *et al.*[44]
Continuously filled prescriptions (with no gaps greater than 14 days) in the 12 months after discharge	Hadlandsmyth *et al.*[45]
Time to discontinuation	
Authors used "Time to Discontinuation." Sustained opioid use was defined as a consistently filled prescription beginning within 30 days of hospital discharge and continuing with no more than 30 days elapsing between prescription refills until 6 months postoperatively.	Schoenfeld *et al.*[46]
Combination of days supplied and number of prescriptions	
(1) 10 or more prescriptions; or (2) more than 120 days' supply within the first year of surgery (excluding the first 90 postoperative days)	Sun *et al.*[47,48]
	O'Connell *et al.*[49]
(1) 10 or greater opioid prescriptions (over 90 or more days); or (2) 120 or more total days' supply dispensed (within 330 days, excluding the first 30 days)	Raebel *et al.*[50,51]
(1) Filled prescription within 15 to 90 days after discharge and filled at least one additional opioid prescription between 91 and 180 days after surgery; and, (2) either (A) 1,150 oral morphine equivalents total dose OR (B) 39 days supplied and two filled prescriptions	Swenson *et al.*[52]
Model derivation approaches	
Based on trajectory of opioid use in 12 months after surgery: defined the group of patients with the highest probability of filling over time as persistent users	Bateman *et al.*[53]
Having any use of opioid prescriptions in each of the 12 months continuously based on a group-based trajectory modeling	Kim *et al.*[54]

*Operationalized as one prescription filled between 30 and 365 days postoperatively. †Operationalized as one prescription filled that overlaps, defined as the date prescription filled plus days supplied, 42 days from the date of discharge. ‡Operationalized as at least one opioid prescription filled between 90 and 180 days after surgery. §Operationalized as one prescription filled that overlaps, defined as the date prescription filled plus days supplied, 180 days from the date of discharge. ‖Operationalized as a prescription dispensed between 90 and 120 days after discharge. #Operationalized as a prescription dispensed that overlaps, defined as the date prescription filled plus days supplied, 365 days from the date of discharge. **Consensus Definition proposed by the Enhanced Recovery and Perioperative Quality Initiative-4. ††To operationalize this definition, we divided the 365 days after surgery into 12 months and classified persistence opioid use as a patient who filled a prescription in *each* of the first 12 months. ‡‡To operationalize this, we attributed each postoperative prescription and associated days supplied to a calendar date from the date of discharge to day 150 postoperatively. If a patient had opioid supply for all 150 calendar days, with no gaps greater than 5 days, then they were classified as a persistent opioid user.

as a prescription filled beyond 1 yr postoperatively, these definitions were not assessed. However, for opioid consumption definitions that used patient-reported measures (in-person, survey, or telephone), we interpreted these definitions to be operationalized using prescription information available in the administrative data. Finally, a recent consensus statement proposed a new definition of persistent opioid use.[5] As this definition has not yet been evaluated in a surgical population, we included this definition *post hoc* in our analysis.

Opioids included were the most commonly prescribed outpatient opioids, and captured the greatest number of opioids used in our review: morphine, hydromorphone, fentanyl, codeine, oxycodone, tramadol, and meperidine.[13] Oral formulations, buccal strips, and transdermal patches were the only formulations included. Opioids primarily used as cough suppressants in Ontario such as hydrocodone and normethadone were not included. Opioid prescriptions were identified using Drug Identification Numbers in the Narcotic Monitoring System. Since July 1, 2012, pharmacist data entry into the Narcotic Monitoring System is mandatory for any opioid dispensed in Ontario irrespective of age or insurance coverage.[14]

As a secondary analysis, we evaluated whether each definition of persistent opioid use reflected the patients at risk for opioid-related events, defined as development of opioid-use disorder or opioid-related toxicity. Opioid-use disorder was defined as either (1) presentation to an emergency department, an acute care facility or mental health institution in the year after discharge with a diagnosis of opioid use disorder, using International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Canadian Modification (ICD-10-CA) diagnosis code F11.XX, or (2) filling a new prescription of buprenorphine or methadone in the year after surgery as identified using Drug Identification Numbers in the Narcotic Monitoring System. Opioid-related toxicity was defined using ICD-10-CA diagnosis codes T40.0, T40.1, T40.2, T40.3, T40.4, and T40.6.[15] All available data were used for each analysis, and as such, formal sample size calculations were not performed.

Statistical Analysis. We described the baseline characteristics of opioid-naive patients presenting for surgery; see Supplemental Digital Content 2 (http://links.lww.com/ALN/C337) for details of variables. Normally distributed patient characteristics are described using means and SDs, while nonnormally distributed characteristics are described using a median and interquartile range. While 0.5% of patients had missing data for Neighborhood Income Quintile, they were not excluded from the cohort, and all patients were included in each analysis.

We then computed the incidence of persistent postoperative opioid use based on each outcome listed in table 1. Each definition provided a binary outcome (persistent postoperative opioid use or no persistent postoperative use). The incidence was calculated as the total number of patients classified as persistent users using each definition divided by the total number of patients in the cohort.

Next, to measure the degree to which commonly used definitions identified the same individuals as persistent postoperative opioid users, we did pairwise comparisons of the five most commonly applied definitions in the literature. We computed the level of agreement between each pair of definitions using Cohen's κ coefficient, where greater than 0.61 was defined as substantial agreement.[16] Akin to inter-rater reliability used in qualitative research,[16] this enabled us to calculate the "interdefinition" reliability between each pair of definitions. Cohen's κ was calculated based on methods described previously.[16]

Finally, we calculated the sensitivity and specificity of each definition of persistent postoperative opioid use to identify patients with opioid-related events. Sensitivities and specificities were calculated based on 2×2 tables that were constructed for each definition of persistent opioid use. True positive represented an individual classified with persistent postoperative opioid use based on the definition used and had an opioid-related adverse event in the year after surgery. Conversely, true negative represented an individual who was classified without persistent postoperative opioid use and did not have an opioid-related adverse event in the following year. All analyses were conducted using SAS software (Enterprise Edition, Version 9.4, SAS Institute Inc., USA).

Sensitivity Analysis. As patients who filled a prescription for opioids in the 30 days before surgery were not excluded from our study, it is possible that these individuals had preexisting pain and, as a result, were more likely to meet definitions of persistent postoperative opioid use. Therefore, in a secondary analysis, we excluded all patients with an opioid prescription in the year before index date and calculated the proportion of patients who met each definition of persistent postoperative opioid use.

Results

Definitions of Persistent Postoperative Opioid Use

After removal of duplicate studies, the search retrieved 9,431 articles, and 39 articles were eligible for inclusion (fig. 1).[5,17–54] Postoperative opioid use was evaluated by measuring filled or written opioid prescriptions (32 studies) or patient-reported opioid consumption (seven studies; table 1). The majority of studies (22 studies) classified persistent opioid use as a patient who filled one or more prescriptions, or reported consuming opioids, at a distinct time point. Second most frequent was the classification of persistent use based on the duration of filled or written opioid prescriptions (15 studies). Finally, studies classified persistent opioid use based on the number of prescriptions written or filled, or their associated duration or dose (six studies). The majority of studies (24 studies) did not define which type or formulation of opioids were used in the classification of persistent opioid use. Of the remaining studies (15 studies), three studies excluded opioids primarily used for the

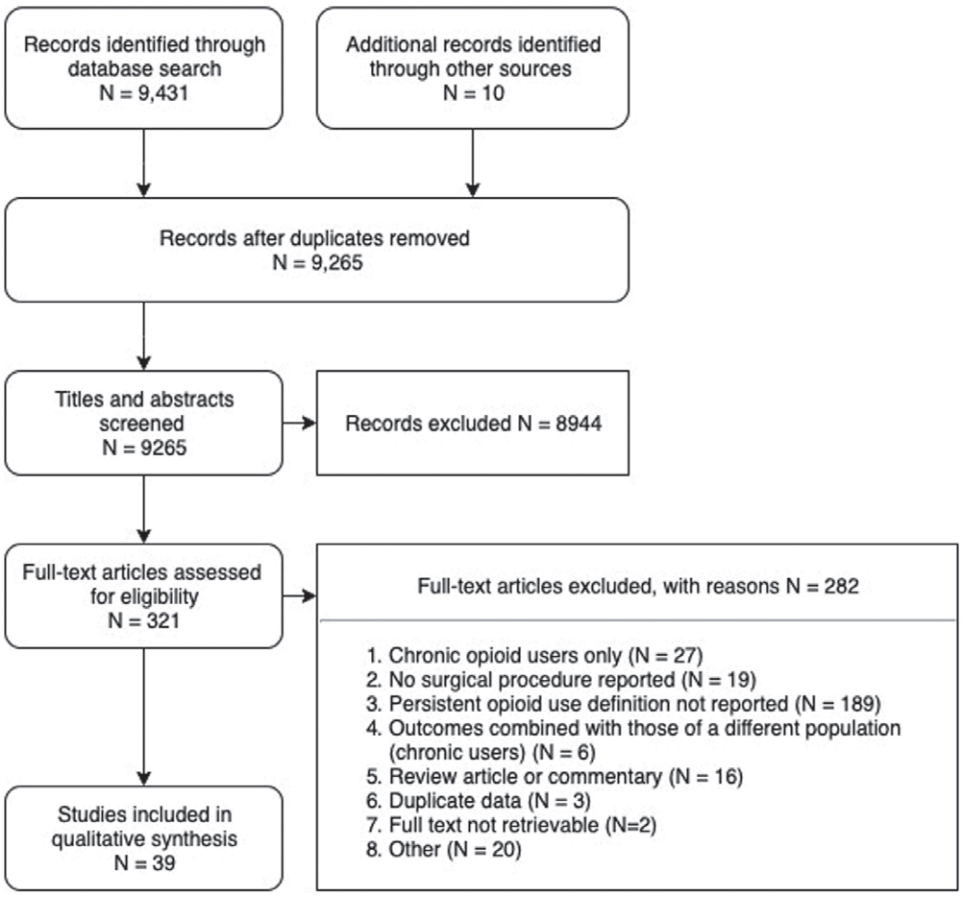

Fig. 1. Diagram of the study selection process for the systematic review.

management of cough, three studies did not include tramadol, and all studies included methadone (see Summary of Definitions, Supplemental Digital Content 4, http://links.lww.com/ALN/C339).

Estimated Rates of Persistent Opioid Use

After exclusions (see Supplemental Digital Content 5 for flow diagram, http://links.lww.com/ALN/C340), a total of 162,830 (mean age ± SD, 50.1 ± 15.7; 67.9% women) opioid-naive patients underwent one of the chosen surgical procedures during the study period (table 2), and 66% (n = 107,496) of patients filled an opioid prescription within the first 7 days of discharge. Estimates of persistent opioid use in the year after surgery ranged from 0.01% (n = 10) to 14.7% (n = 23,442) of patients, depending on the definition of persistent use employed (fig. 2). In a sensitivity analysis excluding individuals who filled an opioid prescription in the 30 days before surgery, the incidence of persistent opioid use after surgery remained qualitatively unchanged (Supplemental Digital Content 6, http://links.lww.com/ALN/C341).

Agreement between Definitions of Persistent Opioid Use

The five most common definitions found in our literature search were further examined to evaluate whether they identified the same patients, namely their level of agreement (see Supplemental Digital Content 7 for full results, http://links.lww.com/ALN/C342). While most definitions had relatively low levels of agreement (Cohen's $\kappa <$ 0.50), more stringent definitions of opioid use in the year after surgery such as 90 days of continuous prescribing or 120 nonconsecutive filled prescriptions in 90 to 365 days postoperatively, or 10 more prescriptions or 120 nonconsecutive days of filled prescription in the 90 to 365 days postoperatively, had high levels of agreement (Cohen's κ = 0.84; 95% CI, 0.82 to 0.87).

Identification of Patients with Opioid-related Events

In the cohort of 162,830 patients, 0.1% (n = 164) had an opioid-related adverse event. Specifically, the proportion of patients who had an opioid-related overdose in the year of follow up was 0.01% (n = 20). Furthermore, 146 patients (0.1%) were classified as patients with opioid use disorder

Table 2. Characteristics of Surgical Cohort

	Surgical Patients N = 162,830
Surgical procedure, n (%)	
Varicose vein	4,692 (2.9)
Open cholecystectomy	611 (0.4)
Laparoscopic cholecystectomy	42,392 (26.0)
Laparoscopic appendectomy	14,713 (15.2)
Open appendectomy	2,411 (1.5)
Hemorrhoidectomy	15,565 (9.6)
Thyroidectomy	6,106 (3.8)
Carpal tunnel release	16,476 (10.1)
Hysterectomy	31,604 (19.4)
Laparoscopic colectomy	1,588 (1.0)
Open colectomy	1,752 (1.1)
Laparoscopic ventral hernia	944 (0.6)
Open ventral hernia	3,291 (2.0)
Open gastric bypass	21 (0.0)
Laparoscopic gastric bypass	5,092 (3.1)
Transurethral resection of the prostate	3,927 (2.4)
Parathyroid	1,432 (0.9)
Reflux surgery	186 (0.1)
Age, yr, mean ± SD	50.1 ± 15.7
Female, n (%)	110,585 (67.9)
Charlson Category, n (%)*	
No hospitalization	132,633 (81.5)
0	23,019 (14.2)
1	3,374 (2.1)
≥ 2	3,777 (2.3)
Comorbidities, n (%)	
Rheumatoid arthritis	1,896 (1.2)
Asthma	13,696 (8.4)
Cancer diagnosis	12,476 (7.7)
Congestive heart failure	2,156 (1.3)
COPD	12,841 (7.9)
Dementia	939 (0.6)
Diabetes	22,340 (13.7)
Hypertension	49,651 (30.5)
Previous myocardial infarct	1,425 (0.9)
Psychiatric diagnosis	25,791 (15.8)
Physician visits, median (IQR)†	33 (17–53)
Household income (quintiles), n (%)	
Missing income	734 (0.5)
1 (lowest)	28,058 (17.2)
2	31,416 (19.3)
3	33,079 (20.3)
4	36,371 (22.3)
5 (highest)	33,145 (20.4)
Rural residence, n (%)	17,190 (14.6)
Preoperative drug use, n (%)‡	
Barbiturate	98 (0.1)
Benzodiazepine	14,383 (8.8)
Preoperative diagnosis, n (%)§	
Opioid overdose	< 6 (0.0)
Nonopioid overdose	65 (0.1)
Opioid use disorder	< 6 (0.0)
Filled opioid prescriptions, n (%)‖	
7 days	107,496 (66.0)
30 days	108,895 (66.9)
Morphine equivalents dispensed within 7 days postoperatively (MME), n (%)#	
0	55,308 (34.0)
1–100	21,879 (13.4)
101–150	47,023 (28.9)
151–200	9,332 (5.7)
> 200	29,261 (18.0)
Duration of first postoperative prescription, median days (IQR)	3 (3–5)

*Deyo Method, a 5-yr lookback period from the index date, was used to calculate the Charlson score. †Defined as the number of visits where a physician billing code was used in the year before index date. ‡Defined as one or more prescription(s) filled in the year before index date. §A 1-yr lookback period was used to identify overdoses. ‖Defined as the number of individuals who filled an opioid prescription within 7 or 30 days of discharge from surgery. #Of those who filled an opioid prescription within 7 days. Defined as the total morphine equivalent dose of the first prescription filled within 7 days (day 0–6) of discharge from surgery. Methods described in Ladha et al.[55]

COPD, chronic obstructive pulmonary disease; IQR, interquartile range; MME, morphine milligram equivalent.

in the same time period. We assessed the sensitivity and specificity of each operationalized definition to identify patients with the composite measure of opioid-use disorder or opioid-related toxicity (table 3). The sensitivity of each operationalized definition ranged from 0.01 to 0.36, while specificity ranged from 0.86 to 1.00.

Discussion

In our systematic search of the literature, we identified 29 unique definitions of persistent postoperative opioid use employed in 39 studies. Using a standardized population of opioid-naive adults who had surgery, the incidence of estimated persistent opioid use varied more than 100-fold, depending on the definition used. There was similar variability in the sensitivity of these definitions for detection of opioid-related events, which was low in absolute terms across all measures used.

The high variability in definitions of persistent use, and subsequent estimates using these definitions, have important implications for patients, prescribers, researchers, and policy makers.

First is the concern of misinterpretation of results. A definition that requires a prescription for opioids filled 90 to 180 days after surgery has been described by the mainstream media as a patient who is "still taking opioids three to six months later"[56] or who "continues to take drugs for three to six months after surgery."[57] However, one prescription filled during this time frame may not represent continued opioid use, albeit being interpreted as such. For example, while 4.7% of patients filled one prescription of opioids in the 90 to 180 days after surgery, less than 0.3% filled prescriptions that represent 90 days of continuous use or at least 120 days of noncontinuous use in the year after surgery. As persistent opioid use often implies and is interpreted as continuous use, we suggest that definitions with

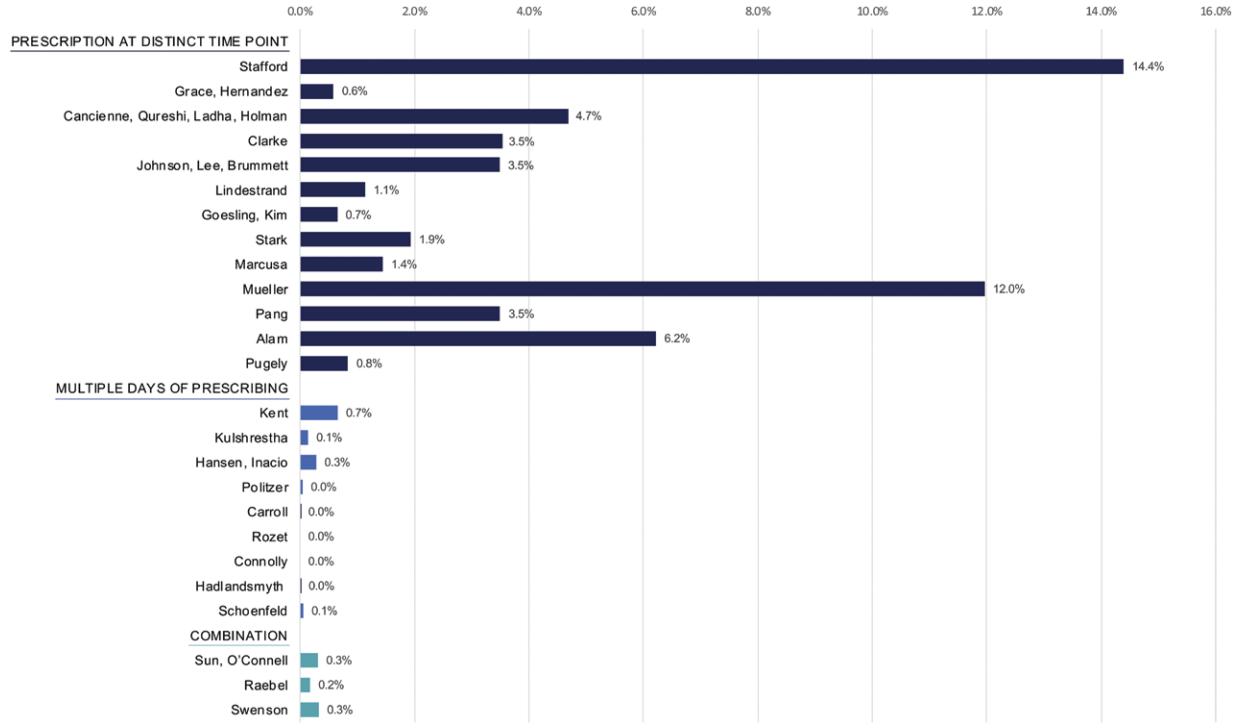

Fig. 2. Rates of persistent postoperative opioid use based on definitions obtained from systematic literature review applied to a single cohort of patients age greater than 18 yr who had 1 of 18 surgical procedures (N = 162,803).

one filled prescription are likely inadequate to represent persistent use and may overestimate the risk associated with surgery. Moreover, as nearly 14% of Ontario residents fill a prescription for opioids in a given year,[58] it is possible that some definitions of persistent use approximate the baseline rate of use in the general population.

When the reported rate of persistent opioid use is high, this can create anxiety in patients, who may refuse opioids in the treatment of acute pain for fear of developing opioid use disorder.[59] Moreover, policy efforts to curb opioid use have focused on the supply of opioids, such as opioid prescribing guidelines, dose-limit laws, and law enforcement.[60] These efforts alongside the high reported rates of persistent use, while successfully preventing excess opioid prescribing, may also contribute to a fear of opioid prescribing in physicians. Importantly, inadequate postoperative pain control can be associated with worse outcome for patients such as increased length-of-stay, reduced likelihood of mobilization, and sleep disturbance.[61] Conversely, when the reported rate of persistent opioid use is low, physicians and patients may underestimate the risk associated with a single, short, initial prescription. Finally, research that aims to evaluate the effect of interventions on opioid use over the long term will benefit from standardization of definitions.

We have demonstrated that defining the time frame and degree of opioid prescribing that adequately characterizes persistent opioid use is a challenge of balancing sensitivity and specificity, while maintaining face validity. When persistent use was defined as at least one opioid prescription filled between 90 and 365 days after surgery, we identified patients at risk for opioid use disorder or toxicity more often. However, this definition likely identified patients who obtained opioids for reasons other than surgery. Similarly, classification of persistent use required 10 or more opioid prescriptions or greater than 120 days' supply within 90 to 365 days postoperatively represented patients with significant opioid use but missed patients at risk for opioid-related overdose or use disorder. In our assessment of agreement among the most frequently used definitions, the highest agreement was noted with definitions that required some duration of prescriptions rather than relying on prescriptions filled within a certain time period. Our work demonstrates that, akin to concurrent criterion validity, definitions that represented patients with more severe opioid use in the year after surgery such as 120 days of noncontinuous prescribing or 10 or more filled prescriptions had high levels of agreement. Definitions with requirements of continuous opioid use are likely to reflect the patients with true persistent use. Moreover, prolonged opioid therapy may be associated with respiratory depression, addiction, and accidental death.[62] Thus, more stringent definitions of persistent use likely reflect patterns of use that place the patient at risk for harm.

Table 3. Sensitivity and Specificity of Each Definition to Identify the 164 Patients with Opioid-related Adverse Events in the Year after Surgery

	Sensitivity (95% CI)	Specificity (95% CI)
Prescriptions at distinct timepoint		
Opioid prescription beyond 30 days after date of surgery[17]	0.36 (0.21–0.53)	0.86 (0.85–0.86)
Opioid consumed 6 weeks postoperatively (patient reported)[18,19]	0.05 (0.01–0.17)	0.99 (0.99–0.99)
Filled at least one opioid prescription between 90 and 180 days after surgery[20–24]	0.12 (0.08–0.34)	0.95 (0.95–0.95)
(1) Filled prescription within 1 to 90 days after discharge; and (2) filled at least one additional opioid prescription between 91 and 180 days after surgery[25]	0.13 (0.04–0.27)	0.96 (0.96–0.97)
(1) Filled prescription within 30 days before surgery and 14 days after discharge; (2) filled at least one additional opioid prescription between 90 and 180 days after surgery[10,26,27]	0.13 (0.04–0.27)	0.97 (0.96–0.97)
Filled at least one opioid prescription overlapping 90 or 180 days[28]	0.15 (0.06–0.31)	0.99 (0.99–0.99)
Opioid consumption at time of interview (180 days postoperatively)[29,30]	0.10 (0.03–0.24)	0.99 (0.99–0.99)
Opioid use, based on questionnaire, between 90 and 120 days after surgery[31]	0.08 (0.02–0.21)	0.98 (0.98–0.98)
(1) Filled prescription within 30 days before surgery and 30 days after discharge; (2) filled at least one additional opioid prescription between 90 and 120 days after surgery[32]	0.05 (0.01–0.17)	0.99 (0.98–0.99)
Filled at least one opioid prescription between 90 and 365 days after surgery[33]	0.31 (0.17–0.48)	0.88 (0.88–0.88)
Filled more than one opioid prescription more than 90 days after surgery[34]	0.21 (0.09–0.36)	0.97 (0.96–0.97)
Filled within 60 days of the 1-yr anniversary date (*e.g.*, 305–425 days after the index date)[35]	0.15 (0.06–0.31)	0.94 (0.94–0.94)
Opioid use at 12 months (365 days) postoperatively[36]	0.05 (0.01–0.17)	0.99 (0.99–0.99)
Multiple days of prescribing		
Filled at three distinct time points: (1) 28–56 days, (2) 90–180 days, and (3) 300–365 days after surgery (or first two time intervals if the patient had an event (death and/or graft loss) between 3 and 12 months)[38]	0.03 (0.00–0.13)	1.00 (1.00–1.00)
60 days of noncontinuous prescriptions filled (within 275 days, excluding the first 90 days)[5]	0.08 (0.02–0.21)	0.99 (0.99–0.99)
90 days of continuous use or at least 120 days of noncontinuous use (within 275 days, excluding the first 90 days)[39,40]	0.05 (0.01–0.17)	1.00 (1.00–1.00)
Prescribed opioids for more than 6 contiguous months after surgery (followed for 24 months postoperatively)[41]	0.00 (0.00–0.00)	1.00 (1.00–1.00)
Patient reported continuous consumption of opioid (with no gaps greater than 5 days) in the 150 days after discharge[42]	0.00 (0.00–0.00)	1.00 (1.00–1.00)
Opioids prescribed uninterrupted for greater than 3 months after surgery[43]	—	—
Continuously filled prescriptions (with no gaps greater than 14 days) in the 12 months after discharge[45]	0.00 (0.00–0.00)	1.00 (1.00–1.00)
Sustained opioid use was defined as a consistently filled prescription beginning within 30 days of hospital discharge and continuing with no more than 30 days elapsing between prescription refills until 6 months postoperatively.[46]	0.05 (0.01–0.17)	1.00 (1.00–1.00)
Combination		
(1) 10 or more prescriptions; or (2) greater than 120 days' supply within the first year of surgery (excluding the first 90 postoperative days)[47–49]	0.08 (0.02–0.21)	1.00 (1.00–1.00)
(1) 10 or more opioid prescriptions (over 90 days or more); or (2) 120 or more total days' supply dispensed (within 330 days, excluding the first 30 days)[50,51]	0.05 (0.01–0.17)	1.00 (1.00–1.00)
(1) Filled prescription within 15 to 90 days after discharge and filled at least one additional opioid prescription between 91 and 180 days after surgery; and, (2) either (A) 1,150 oral morphine equivalents total dose OR (B) 39 days supplied and two filled prescriptions[52]	0.05 (0.01–0.17)	1.00 (1.00–1.00)

Our study has a number of strengths. First, we performed a rigorous, systematic search of the literature to identify the full range of definitions of persistent opioid use after surgery. While the incidence of persistent opioid use after surgery has been extensively addressed in the literature, many of these studies highlight that comparing estimates across studies is not possible due to differing definitions of persistent use or surgical procedures. This study addresses both of these issues, and identifies the significant influence outcome classification has on estimates of persistent use. The majority of research evaluating persistent opioid use is limited to specific populations, such as veterans, those who are insured by specific insurance plans, or specific age groups. This study included population-level data of all residents of Ontario presenting for one of our chosen procedures, irrespective of age.

The results of this study need to be interpreted in the context of its limitations. First, we used prescription claims data that cannot capture actual opioid consumption or, more importantly, the reason for the opioid fills. We note that in most studies reviewed, authors attribute longer-term opioid prescriptions to the surgery. However, it is unclear whether persistent opioid use in some individuals is the result of a subsequent unrelated pain complaint. Additionally, these data only captured outpatient prescriptions. As a result, we were unable to evaluate whether the surgical patients were exposed to opioids as inpatients. Second, while we attempted to accurately operationalize each definition of persistent opioid use, for definitions that required in-person follow-up, we may have over- or underestimated rates. Third, in order to evaluate each definition quantitatively, we calculated the sensitivity and specificity of each definition to identify patients with opioid use disorder or toxicity. This definition was defined based on ICD-10-CA codes and therefore only identifies patients with severe opioid use disorder who present to an acute care center for diagnosis. In this context, it is likely that we underestimated the

incidence of opioid use disorder in the population and, as a result, the sensitivity of each definition of persistent opioid use. Similarly, as opioid-related adverse events were rare, the reported sensitivity and specificity estimates had broad CIs, making interpretation of the specific performance of each definition difficult. Furthermore, our follow-up period may be inadequate to capture opioid use disorder that emerges as a consequence of opioid exposure after surgery. Finally, many studies of surgical patients involve different types of surgeries. While our study isolated the impact of the definition used for the outcome of persistent opioid use, other sources of variability exist, such as the individual procedure performed or the system of care, that were not addressed in this study.

Conclusions

This systematic literature search and population-based cohort study demonstrated the variability of definitions of persistent opioid use employed in the current medical literature. More importantly, this study highlights that among a population of opioid-naive patients, the estimated incidence of persistent opioid use is highly dependent on the definition employed. The development of a clinically meaningful definition of persistent opioid use will require consensus from patients, providers, and policy makers. Widespread adoption of a single definition is important not only for comparability of studies but also to ensure accurate communication of risk.

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Competing Interests

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