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American Society for Enhanced Recovery and Perioperative Quality Initiative (POQI-4) Joint Consensus Statement on Persistent Postoperative Opioid Use: Definition, Incidence, Risk Factors, and Health Care System Initiatives.

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Abstract

Persistent postoperative opioid use (PPOU) is thought to contribute to the ongoing opioid epidemic in the United States. However, efforts to study and address the issue have been stymied by the lack of a standard definition, which has also hampered efforts to measure the incidence of and risk factors for PPOU. The objective of this systematic review is to: (1) determine a clinically relevant definition of PPOU and (2) characterize its incidence and risk factors for several common surgeries. Our approach leveraged a group of international experts from the Perioperative Quality Initiative (POQI)-4, a consensus-building conference that included representation from anesthesiology, surgery, and nursing. A search of medical literature yielded 46 manuscripts addressing PPOU in adults after arthroplasty, abdominopelvic surgery, spine surgery, thoracic surgery, mastectomy, and thoracic surgery. In opioid naive patients, the overall incidence ranged from 2–6% based on moderate-level evidence. However, patients who use opioids preoperatively had an incidence over 30%. Preoperative opioid use, depression, factors associated with the diagnosis substance use disorder, preoperative pain, and tobacco use were reported risk factors. In addition, while anxiety, sex, and psychotropic prescription are associated with PPOU, these reports are based on lower-level evidence. While limited manuscripts addressed health policy or prescriber characteristics that influence PPOU, efforts to modify prescriber behaviors and health system characteristics are likely to have success in reducing PPOU.

Introduction

In light of the opioid epidemic in the United States, anesthesiologists, are uniquely positioned to play a role in reducing opioid use for surgical patients, for whom opioids continue to be first line analgesic agents and non-opioid medications are inconsistently prescribed.^{1,2} Crucially, several studies suggest that surgery is associated with an increased risk of long-term opioid use, a phenomenon known as Persistent Postoperative Opioid Use (PPOU).^{3,4} As such, efforts to reduce the risk of PPOU can have a direct effect on opioid use at the population level. In addition, decreasing the risk of PPOU could also have indirect benefits in reducing population-level opioid use by reducing the incidence of diversion, particularly in the light of studies suggesting a substantial amount of opioid over-prescription and large amounts of unused pills among surgical patients.^{5–7}

Efforts to address PPOU have faced several limitations. First, it remains poorly defined in the literature (Table 1). Additionally, it is likely driven by a wide variety of causal factors, including patient characteristics (e.g., comorbidities), the nature of the patient's surgery, and health system characteristics (e.g, clinical pathways and health legislation).⁸ Indeed, one stated benefit of initiatives such as the Perioperative Surgical Home and Enhanced Recovery After Surgery Programs (ERPs) is the possibility that they may reduce the risk of PPOU. As a result of these limitations, to date there have been few systematic attempts to characterize the incidence of PPOU and the associated patient, surgery, and health care system

characteristics that may serve as risk factors. As part of the 4th American Society for Enhanced Recovery (ASER) Perioperative and Quality Initiative (POQI - 4) working group, we used a systematic literature review and modified Delphi GRADE consensus process to address the following questions:

- What is the definition and incidence of PPOU?
- What are patient and surgery characteristics associated with PPOU?
- What are health system characteristics associated with PPOU?

Methods

Expert Group and Process

The 4th Perioperative Quality Initiative (POQI-4) conference was convened with the goal of advancing understanding of the use of opioid throughout all perioperative phases. This report is the result of a modified Delphi analysis performed by the POQI-4 working subgroup whereby evidence pertaining to perioperative opioid use was reviewed. The Delphi method is detailed in the first paper in this series.⁹ Twenty four experts in anesthesiology, nursing, surgery, pharmacy, and pain medicine met on January 4–6, 2018 in Nashville, TN. Each workshop participant was chosen based on a record of significant clinical and/or research experience in perioperative pain medicine. We systematically reviewed the literature pertaining to the definition/incidence of and risk factors for PPOU within specific surgical subtypes. In the interest of feasibility, the workgroup focused on five commonly performed surgery subtypes affecting major body regions and tissue types including joint arthroplasty, mastectomy, spine surgery, thoracic surgery, abdominopelvic surgery. Based on the literature review described below, the working group arrived at consensus regarding (1) the definition and incidence of PPOU, (2) the patient and surgeries that are associated with PPOU, and (3) the health care system characteristics associated with PPOU. These results were presented to the POQI-4 collaborative, and the conclusions and recommendations below reflect the consensus of the collaborative.

Literature Review

Data Sources and Search—We complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines conducting a systematic search of available literature pertaining to the incidence of and risk factors for PPOU. We searched MEDLINE, Embase, and Scopus within the last ten years (1/1/2007 to 2/2/2018) restricting articles to the English language (Supplemental Material-PPOU Database Search). Due to the recent expansion of ERPs, comprehensive acute pain management programs, and recent attention to opioid over prescription, the working group chose a 10-year search strategy. As seen below, only one of 46 articles that met inclusion criteria was published before 2010. We constructed a search strategy using terms focusing on adults undergoing arthroplasty, mastectomy, spine surgery, thoracic surgery, abdominopelvic surgery (Population), postoperative opioids (Exposure), and incidence of or risk factors for PPOU (Outcome). As evidence for contributory health care system characteristics to PPOU is emerging, we decided to narratively review this topic and offer recommendations for research and policy considerations.

Inclusion Criteria and Outcome Definition—We included studies of adults within the United States and Canada undergoing total knee/hip arthroplasty, mastectomy, thoracic surgery, abdominopelvic surgery, and spine surgery. The United States and Canada were chosen due to similar opioid prescribing practices and being characterized by the highest opioid consumption in the world.^{10,11} We required that the patient's opioid use or exposure be measured during the post discharge period and include the incidence of and/or risk factors for opioid use or prescription filling after 90 days postoperatively. There was no time limit on follow up for this initial search.

From our POQI-4 working group, one reviewer (M.L.K) assessed 2540 abstracts and 2478 were excluded for not meeting content inclusion criteria. 62 titles underwent full text review by two reviewers (M.L.K and G.M.O), after which, 46 studies met inclusion criteria. The primary set of outcomes included the incidence of PPOU (as defined by the given study) in opioid naive and opioid exposed patients and patient/surgical characteristics associated with the development of PPOU across all patients. These outcomes were obtained for each of the aforementioned surgical subtypes.

Quality Assessment—Two reviewers (M.L.K. & G.M.O.) independently assessed the quality of studies. The GRADE assessment for prognostic studies set forth by Iorio et al and Hugué et al. was used to evaluate study limitations, indirectness of evidence, imprecision, and publication bias.^{12,13} Limitations were primarily assessed as risk of bias with particular attention paid to appropriate study sample and adjustment for confounding prognostic factors. Indirectness of evidence was rated on whether study data corresponded to the population of interest and at the same time using appropriate measures. Imprecision was evaluated based on variables such as appropriate sample size and observation of confidence intervals for outcomes. Studies were also evaluated based on the presence of univariate/multivariate analysis. Following GRADE evaluation of individual articles, patient characteristics associated with PPOU were reviewed to generate a list of the most common factors for each surgical subtype. Based on the aggregate quality of evidence, each patient characteristic was also evaluated and assigned a GRADE score. In the case of disagreement, a third reviewer (R.W.H) functioned as a tie-breaker.

Data Extraction and Synthesis—One of the reviewers (M.L.K), extracted pertinent study characteristics using an agreed upon extraction template. Data included study design, setting, patient population, number of patients, incidence of PPOU in opioid naive and tolerant patients per the study author's definition, and risk factors.

Results

After full text review, 46 studies met inclusion criteria across pre-specified surgical subtypes (Figure 1, Supplemental Table 1). The majority of studies were retrospective with data originating from institutional records or external databases (i.e. insurance claims, state prescription monitoring, etc.). Studies addressed patient/surgical characteristics associated with PPOU, the incidence of PPOU, or both. Of note, certain retrospective cohort studies included numerous surgical subtypes and patient/surgical characteristics associated with PPOU and such studies were analyzed in aggregate.^{14–16} In these scenarios, manuscripts

underwent GRADE assessment for each respective surgical subtype, but the lack of surgery specific analysis within such mixed surgical studies was taken into account when assessing the quality of evidence. No studies received an assessment of “High Quality” largely in part due to variability in PPOU definition, sample size, and lack of representation of the entire surgery specific population.

Definition of PPOU

There was no consistent definition of PPOU across the studies, largely due to variations in how opioid use was measured (e.g., prescriptions written, prescriptions filled, or opioid usage per patient report), the starting and ending points during which opioid use was measured (e.g., 90 days postoperatively until 1 postoperative year), and the level of opioid use required to meet the threshold for PPOU. Despite this variation, a notable proportion of papers focused on the time period from 90 postoperative days to 1 postoperative year.^{3,14–41}

Incidence of PPOU

Due to the variability in time frame used to describe PPOU and the trends noted above, the consensus group chose to initially focus on studies which characterized the incidence of PPOU from 90 days until 1 year postoperatively as patients using opioids longer than 1 year postoperatively may have had other confounding painful conditions not linked to the surgical insult for which they were using opioids.

Differences were noted among each surgical subtype and a wide range of reported incidence rates were likely due to variability between studies including sample size, definition of PPOU, and the total number of institutions represented in any given study. Unlike other patient characteristics (i.e. depression, anxiety, etc.), preoperative opioid users were often treated as a separate patient category where incidence rates were measured. Thus, our working group found it important to report the differing incidence rates between these two groups (Table 2). Even when considering the heterogeneity of sample sizes and definitions of PPOU, the incidence of PPOU was over ten times greater in preoperative opioid users when compared to opioid naive patients for arthroplasty and abdominopelvic patients and was rated as High Quality evidence. In patients undergoing spine surgery, preoperative opioid users were more than twice as likely to develop PPOU when compared to opioid naive patients (59% vs 26% incidence of PPOU) in one moderate quality study.¹⁷ While only a few studies assessed PPOU in thoracic surgery (4 studies) and mastectomy (3 studies), those studies that were considered moderate quality reported the incidence of PPOU to be greater than 10% in opioid naive patients in both surgical subclasses. No studies in thoracic surgery or mastectomy evaluated preoperative opioid users.

Patient and Surgical Characteristics Associated with PPOU

The majority of studies measuring patient characteristics drew data from large insurance claim databases where comorbid conditions were gathered via International Classification of Diseases (ICD) coding. Prescription fills were determined either through claims data, state prescription monitoring databases, or institutional prescription records. Studies that were prospective observational or institutional chart review in design measured patient characteristics such as anxiety or depressive symptoms through validated research tools (i.e.

Hospital Anxiety and Depression Scale, Zung Depression Scale).^{17,29} In these studies, opioid prescription/use was measured by patient report. Only 4 studies described surgery specific variables such as the Knee Society Score for TKA or the presence of adjuvant chemotherapy/radiation in oncologic samples.^{15,29,36,37} Summative patient characteristics associated with PPOU in all of the combined surgical groups is presented in Table 3.

Arthroplasty: 17 studies assessed patient characteristics associated with PPOU in patients undergoing TKA or THA (Supplemental Tables 2–3).^{14,26–35,37,42–46} While heterogeneously defined, all studies that measured preoperative opioid use indicated a significant relationship with PPOU. Moderate Quality evidence was given to depression, substance use, preoperative painful conditions, and smoking. Five studies measured associated factors for PPOU in both THA and TKA.^{14,27,29,32,35} Three of these five studies identified TKA as a risk for PPOU when compared to THA.^{29,32,35} Additionally, Sun et al. conducted a residual confounding analysis supporting the notion that THA and TKA were themselves risk factors for PPOU when compared to a non-surgical cohort.¹⁴

Abdominopelvic: 16 studies assessed patient characteristics associated with PPOU, however, significant heterogeneity was observed regarding the types of reported surgeries (Supplemental Tables 4–5).^{3,14–16,19–25,38,41,47–49} Moderate Level evidence was observed for depression, substance use, preoperative painful conditions, tobacco use, and use of psychotropic prescription drugs. While some studies measured both minimally invasive and open surgical technique, no formal comparative analyses were performed to determine an association between surgery type and PPOU.

Spine: 5 of 13 studies reported on associated patient characteristics, and a significant degree of diversity in surgery types was observed (Supplemental Tables 6–7).^{17,18,39,40,50–58} Lumbar arthrodesis was the most commonly reported surgical intervention. Preoperative opioid use and depression were assigned High Quality level of evidence for their influence on PPOU. Larger than other surgical types, the baseline presence of preoperative opioid use was noted to be >50%.^{17,55} Relative to other spine surgical subclasses, two studies observed lumbar fusion as having a higher association with PPOU while the three remaining studies identified revision and/or more invasive surgeries as risks.^{17,18,52,53,55}

Thoracic Surgery: All four studies which involved thoracic surgery were conducted on mixed surgical groups (Supplemental Table 8–9).^{15,16,25,59} Two of the four studies analyzed the same sample from a large Canadian database but utilized two different measures of postoperative opioid use.^{16,25} Given these limitations, preoperative opioid use was given a Low Quality level of evidence. Very Low Quality evidence was observed for depression, substance use, age, and use of prescription psychotropic drugs. One study, Clark et al, reported a significantly higher risk of PPOU in open thoracic surgeries versus minimally invasive approaches.¹⁶

Mastectomy—Three studies evaluated risk factors in patients undergoing mastectomy (Supplemental Table 10–11).^{15,36,44} Only one study focused solely on opioid naive patients undergoing mastectomy with immediate reconstruction instead of a mixed surgical cohort.³⁶ Given this, a Low Quality level of evidence was observed for preoperative opioid use,

anxiety, and depression. No studies conducted a comparative analysis of differing surgical types (i.e. radical mastectomy versus simple mastectomy, etc.).

Discussion

Defining Persistent postoperative opioid use (PPOU)

There are three elements in defining PPOU: how to measure opioid use, the timeframe to measure opioid use, and the magnitude of opioid use required to trigger a diagnosis of PPOU. With regards to the former, the working group noted that direct measurements of opioid consumption are labor intensive and expensive for researchers to measure and are also not readily available for most clinicians. By contrast, prescription data are easier for researchers and clinicians to obtain, and the use of prescription data as a proxy for actual drug consumption is a commonly used practice.⁶⁰ Therefore, the working group decided that any definition of PPOU should be based on prescription data.

In terms of time-frame to measure PPOU, since some opioid use immediately after surgery is expected, the working group decided that the timeframe should start at a point when acute surgical pain should have resolved, and should end at a point that (a) provides enough time to evaluate an individual's opioid use over the longer term and (b) is practical for research purposes, since patients can be lost to follow up over longer periods of time. Overall, the working group decided that PPOU should be measured during on opioid use between postoperative days 90–365 for two reasons. First, this was a common period described for the assessment of PPOU for several of the studies we examined.^{3,14} Second, this time frame corresponds to a period where acute surgical pain should have resolved.^{61,62,63}

Defining the level of opioid use during this timeframe that is required to trigger the diagnosis of PPOU was also considered. Any choice of threshold incorporates a tradeoff between sensitivity and specificity: lower thresholds make a diagnosis more likely but also run the risk of including postsurgical patients who are incidentally using opioids for nonsurgical reasons. For example, in a large retrospective analysis of health care claims, Sun et al. reported PPOU rates < 2% across numerous surgical groups using a threshold of having filled 10 or more prescriptions or more than 120 days' supply within 90 days to 1 year postoperatively.¹⁴ Conversely, Brummett et al. reported rates of PPOU of 5.9–6.5% using a less restrictive definition of opioid prescription fulfillment between 90–180 days postoperatively.³ In addition, any threshold should be based on the level of opioid use prior to surgery, as patients who use opioids preoperatively may be expected to have higher postoperative use than opioid-naïve patients. Based on the studies we reviewed, the working group suggested that in the case of opioid-naïve patients, PPOU should be defined as having filled opioid prescriptions for a at least 60 days' supply during postoperative days 90–365 (Table 4). For patients who used opioids prior to surgery, we suggest that PPOU be defined as any increase in opioid use relative to baseline (Table 4).

Incidence of Risk Factors for PPOU

Across surgeries in moderate quality studies, the incidence of PPOU ranges from 0.6%–26% for opioid-naïve patients and 35%–77% for patients with previous opioid exposure. These

ranges take into account variations in the definition and measurement of PPOU across the studies in our review. The following patient characteristics were consistently identified as risk factors for PPOU: preoperative opioid use, depression, substance use, tobacco use, gender, psychotropic drug prescription, and anxiety (Tables 3). Indeed one strength of these associations is that they were robust across a wide array of definitions for each characteristic (e.g., preoperative opioid use was not defined consistently across studies). However, few studies assessed the relative importance of these risk factors. In addition, no studies assessed whether modification of these risk factors was associated with a reduced risk of PPOU, which is a promising area for further research.

We were unable to identify any specific surgeries that were identified with an increased risk of PPOU. A few studies suggest that total knee arthroplasty, open thoracic, and lumbar fusion may be linked to higher rates of PPOU within their own subclasses (i.e. orthopedics, thoracic surgery, etc.), but large scale studies where important biopsychosocial variables are controlled for between surgical groups have not occurred.^{14,16} Of note, one study suggested that the incidence of PPOU was fairly consistent across major and minor surgeries, suggesting that surgery characteristics may play a small role in determining the risk of PPOU.³

Systems and Prescribing Characteristics Associated with PPOU

Finally, we found only one study that examined the association between PPOU and prescriber or health care system characteristics⁶⁴. In this large database of commercially insured patients, the duration of the initial opioid prescription, not the total dosage of opioids prescribed was associated with factors indicative of PPOU including opioid dependence, misuse or overdose after surgery. This finding was stable across 7 different surgical types.

This paucity of studies is concerning because PPOU likely represents the end result of numerous interactions between a patient and their health care team, such as their surgeon, anesthesiologist, and primary care provider. Moreover, there recently have been many efforts aimed at modifying prescriber behaviors and modifying health care systems with the goal of reducing PPOU, such as surgeon education^{6,65}, quality improvement initiatives^{6,66-69}, legislative initiatives to reduce opioid prescribing⁷⁰⁻⁷³, and initiatives to limit coverage for opioids.⁷² However, whether these efforts have succeeded in reducing PPOU remains unknown. Overall, characterizing the prescriber and health care system characteristics remains an important area for further study.

Study Limitations

We recognize numerous limitations regarding the incidence of and risk factors for PPOU. One limit relates to the heterogeneous definition of PPOU used in studies leading to variability in reported rates of PPOU. Additionally, risk factors for PPOU were often measured via different systems whether by ICD diagnostic codes (Depression, Substance Abuse, etc.) or symptoms related to a particular condition (i.e. Anxiety symptoms as measured by the Hospital Depression and Anxiety Scale). Future studies that utilize consistent definitions of PPOU and standardized outcomes that consider condition duration and severity will likely further specify PPOU rates and risk factors. Our review is also

limited by differing measures of opioid use or prescription. These measures were heterogeneously reported and represent different facets of PPOU. Studies where opioid use was reported often described a link to the surgical insult whereas opioid prescription filling cannot always be clearly linked to surgery. Future studies that focus on contributions of patient use versus opioid availability (i.e. prescription) will provide additional clarity and possible strategies to curb PPOU. Finally, we recognize that our focus on U.S. and Canadian health care systems introduces bias as other international sites were not included. While this decision was made based on similar opioid prescribing practices, future studies that stratify PPOU by country, region, and health care models are needed.

Conclusions

In sum, our working group arrived at the following conclusions:

For opioid naïve patients, PPOU should be defined as having filled 60 days supply of opioid during postoperative days 90–365. For patients who used opioids prior to surgery, PPOU should be defined as any increase in opioid use above baseline during this time period.

The incidence of PPOU ranges from 0.6%–26% for opioid-naïve patients and 35%–77% for patients with previous opioid exposure.

Patient characteristics associated with an increased risk of PPOU included: preoperative opioid use, depression, substance use disorder, preoperative pain conditions, and smoking. Whether specific surgeries are associated with an increased risk of PPOU remains unclear, and is the extent to which the risk of PPOU has been affected by health care system characteristics and health policy.

As a result of its analysis, the working group provides several recommendations (Table 4 and Figure 2) to the anesthesiology and medical community. Each of these recommendations is rooted in the results of the literature review described above. By implementing these recommendations, the working group believes that physicians and other healthcare givers will be better positioned to find ways of reducing the risk of PPOU among surgical patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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PRISMA 2009 Flow Diagram

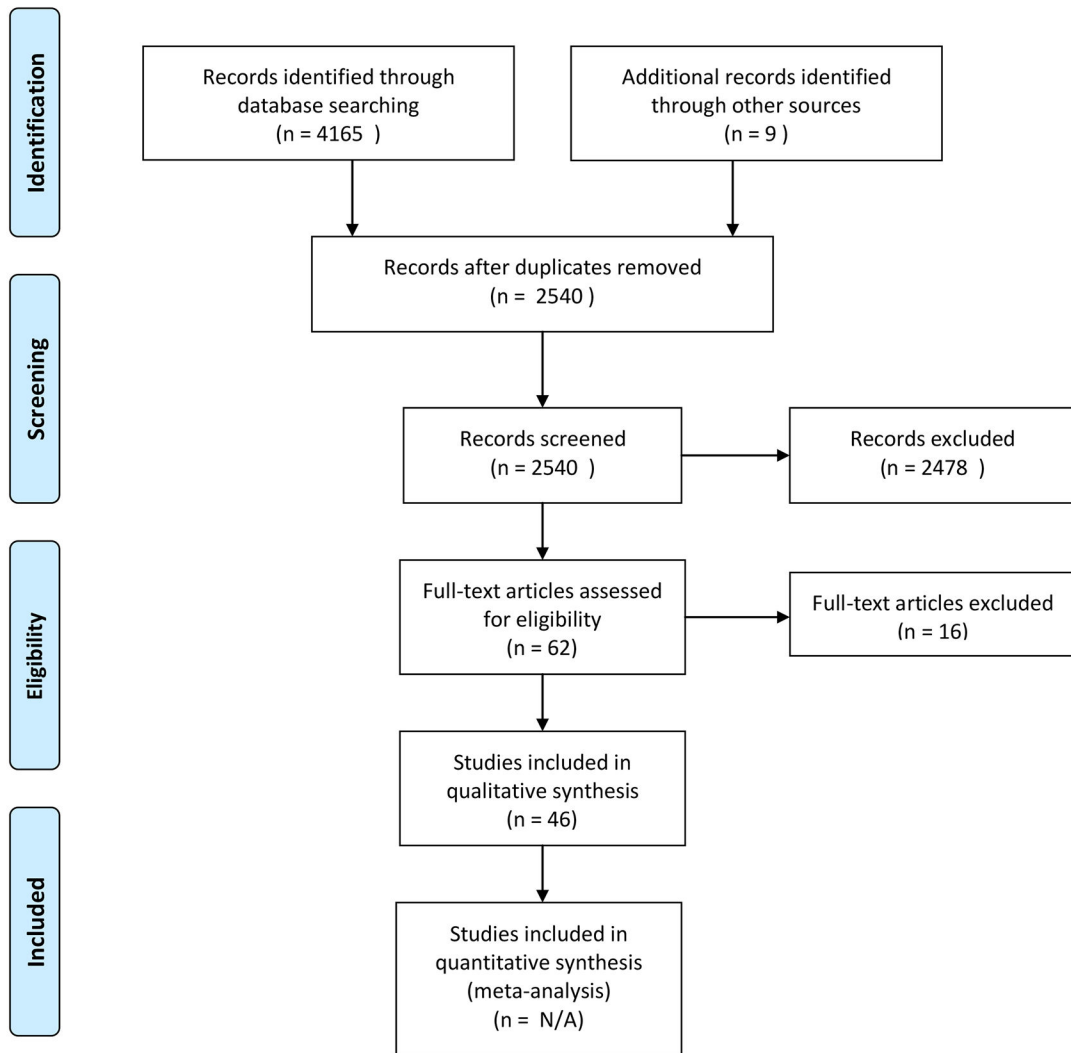


Figure 1:
PRISMA Flowchart

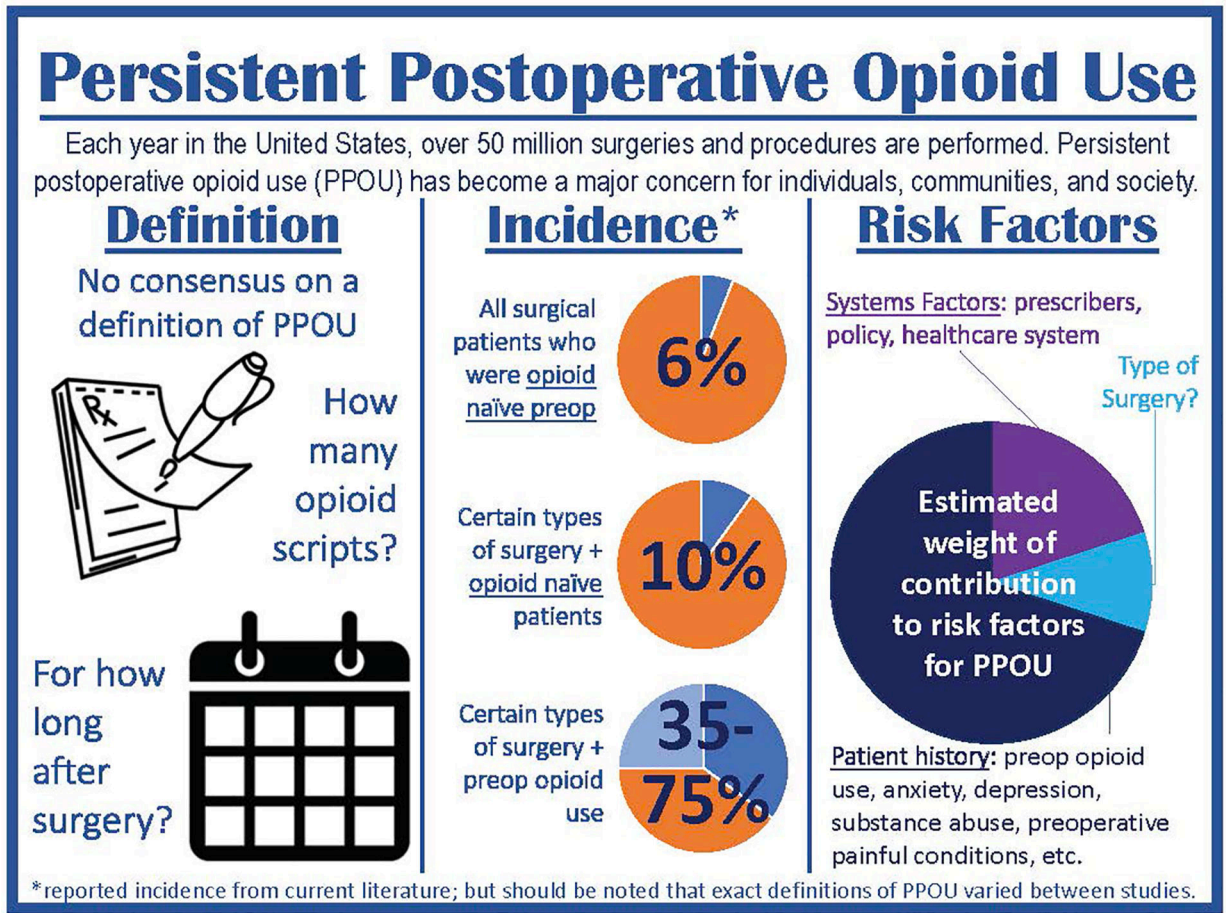


Figure 2: Summary of variables impacting the definition and incidence of PPOU. Figure reused with the permission of the Perioperative Quality Initiative (POQI). For permission requests, contact poqiusa@gmail.com.

Table 1:
Example Reported Definitions/Measures of Persistent Postoperative Opioid Use

One or more opioid prescriptions within 1 to 90 days after surgery along with one or more prescriptions for opioids within 91 to 180 days after surgery. ¹⁶
Having filled 10 or more prescriptions or more than 120 days' supply within a 1-year period. ¹⁴
Opioid prescription fulfillment between 90 and 180 days among those patients who filled opioid prescriptions peri-operatively. ³
Filling an opioid prescription within the perioperative period and continued to refill between postoperative days 90 and 120. ³⁶
Trajectory analysis of opioid filling for 12 consecutive 30 day periods postoperatively. ²⁰
Patients who filled an opioid prescription attributed to surgery, then filled at least one additional opioid prescription between 90 and 180 days after surgery. ¹⁵
Time until opioid cessation. ^{44,74}
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). ¹⁹
Number of patient using opioids 2 and 5 years postoperatively. ⁷⁵

Table 2-

Reported Incidences of PPOU Across Surgical Subgroups

Surgery	Overall Sample	Opioid Naive Sample	Preoperative Opioid Sample
<i>Arthroplasty</i>			
All Studies	5.5–32%	0.6–8%	14–68%
Moderate Level	5.5–32%	0.6%–4%	35–68%
<i>Abdominopelvic</i>			
All Studies	0.36–77%	.09–12%	8.1–77%
Moderate Level	.36–14%	.119–6%	59–77%
<i>Spine</i>			
All Studies	18–85%	.02–26%	59%
Moderate Level	18–59%	26%	59%
<i>Mastectomy</i>			
All Studies	N/A	10–11%	N/A
Moderate Level	N/A	10–11%	N/A
<i>Thoracic</i>			
All Studies	22%	<2%–14%	N/A
Moderate Level	N/A	14%	N/A

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Risk Factors for PPOU in Combined Surgical Groups:

Limitations - #1 - No Serious Limit, #2- Serious Limitation, #3-Very Serious Limitation. Quality of Evidence: + Very Low Quality, ++ Low Quality, +++ Moderate Quality, ++++ High Quality.

Table 3:

Risk Variable	Study Limitations	Indirectness	Imprecision	Inconsistency	Level of Evidence
Preoperative Opioid Use	2	2	1	1	++++
Depression	2	2	1	1	++++
Substance Abuse	2	3	1	1	+++
Preoperative Pain Condition	2	3	2	1	+++
Smoking	2	2	2	2	+++
Anxiety	2	2	2	3	++
Gender	2	2	2	3	++
Psychotropic Drug Use (Antidepressant, Benzodiazepine)	2	3	2	1	++

Table 4:

POQI-4 Consensus Statement Regarding PPOU

#1 We recommend PPOU in the opioid naive patient (no history of opioid use in the 90 days prior to surgery) ⁵⁵ be defined as having used opioids for 60 days during postoperative days 90–365.
#2 For patients who use opioids prior to surgery ⁵⁵ , we recommend PPOU be defined as any increase in opioid use during postoperative days 90–365, relative to opioid use in the 90 days prior to surgery.
#3 We suggest providers use known risk factors to identify high risk patients for PPOU.
#4 Since PPOU occurs in the setting of a patient's interaction with numerous healthcare providers and institutions, addressing system-based characteristics may be more determinative of PPOU than clinical decision making. We strongly recommend the evaluation of public health initiatives, policies, and legislation at the local, state and federal levels aimed at safe opioid prescribing with subsequent recommendation for further improvements that target all healthcare system components.

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