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## Rate and Risk Factors Associated With Prolonged Opioid Use After Surgery

A Systematic Review and Meta-analysis

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## Key Points

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### Question

What are the rate and risk factors associated with prolonged use of opioid medications after surgery?

### Findings

In this systematic review and meta-analysis of 33 observational studies including more than 1.9 million patients, 7% of patients continued to fill opioid prescriptions more than 3 months after surgery. Preoperative use of opioids, illicit cocaine use, and pain conditions before surgery had the strongest associations with prolonged opioid use after surgery.

### Meaning

The findings suggest that an evaluation of opioid use among patients before surgery and modification of patient-level risk factors when possible may be included as part of a comprehensive strategy to reduce the risk of prolonged opioid use after surgery.

## Abstract

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### Importance

Prolonged opioid use after surgery may be associated with opioid dependency and increased health care use. However, published studies have reported varying estimates of the magnitude of prolonged opioid use and risk factors associated with the transition of patients to long-term opioid use.

### Objectives

To evaluate the rate and characteristics of patient-level risk factors associated with increased risk of prolonged use of opioids after surgery.

### Data Sources

For this systematic review and meta-analysis, a search of MEDLINE, Embase, and Google Scholar from inception to August 30, 2017, was performed, with an updated search performed on June 30, 2019. Key words may include *opioid analgesics*, *general surgery*, *surgical procedures*, *persistent opioid use*, and *postoperative pain*.

### Study Selection

Of 7534 articles reviewed, 33 studies were included. Studies were included if they involved participants 18 years or older, evaluated opioid use 3 or more months after surgery, and reported the rate and adjusted risk factors associated with prolonged opioid use after surgery.

## Data Extraction and Synthesis

The Meta-analysis of Observational Studies in Epidemiology (MOOSE) and Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines were followed. Two reviewers independently assessed and extracted the relevant data.

## Main Outcomes and Measures

The weighted pooled rate and odds ratios (ORs) of risk factors were calculated using the random-effects model.

## Results

The 33 studies included 1 922 743 individuals, with 1 854 006 (96.4%) from the US. In studies with available sex and age information, participants were mostly female (1 031 399; 82.7%) and had a mean (SD) age of 59.3 (12.8) years. The pooled rate of prolonged opioid use after surgery was 6.7% (95% CI, 4.5%-9.8%) but decreased to 1.2% (95% CI, 0.4%-3.9%) in restricted analyses involving only opioid-naïve participants at baseline. The risk factors with the strongest associations with prolonged opioid use included preoperative use of opioids (OR, 5.32; 95% CI, 2.94-9.64) or illicit cocaine (OR, 4.34; 95% CI, 1.50-12.58) and a preoperative diagnosis of back pain (OR, 2.05; 95% CI, 1.63-2.58). No significant differences were observed with various study-level factors, including a comparison of major vs minor surgical procedures (pooled rate: 7.0%; 95% CI, 4.9%-9.9% vs 11.1%; 95% CI, 6.0%-19.4%;  $P = .20$ ). Across all of our analyses, there was substantial variability because of heterogeneity instead of sampling error.

## Conclusions and Relevance

The findings suggest that prolonged opioid use after surgery may be a substantial burden to public health. It appears that strategies, such as proactively screening for at-risk individuals, should be prioritized.

## Introduction

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The misuse, overdose, and abuse of prescription opioids constitute sources of substantial morbidity and mortality in the US and globally.<sup>1,2,3,4,5</sup> Approximately 130 individuals in the US die each day of opioid overdose, with one of the largest proportion of preventable deaths in the US being attributable to opioid-related deaths.<sup>3</sup> In addition to the substantial mortality burden, prescription opioid misuse, abuse, dependence, and overdose were reported to cost the US health care system an estimated \$78.5 billion in 2013.<sup>6</sup> Increases in prescription opioid use and incidence of opioid-related deaths have also been reported globally, including in European countries and Canada.<sup>4,5,7,8,9</sup>

Many of the efforts to curb the opioid crisis in the US have focused on regulatory changes regarding opioid use for chronic, noncancer pain, with the guidance for postoperative opioid analgesia use being less clear.<sup>10,11,12</sup> The medical literature<sup>12,13</sup> purports that inappropriate opioid prescribing for peri- and postoperative analgesia in the form of inadequate or excessive dispensing may contribute to the ongoing epidemic. Of note, opioids remain the standard of care for treatment of acute and routine postoperative pain,<sup>14,15</sup> and surgical procedures remain the primary reason for exposure to these medications.<sup>12,16</sup> There is also substantial variation in opioid prescribing among clinicians, particularly in the quantities and dosages of opioids after common general surgical procedures.<sup>17,18</sup> This variation is further complicated with the potential for misuse and diversion, with 67% to 92% of all opioids prescribed for postoperative pain remaining unused.<sup>19</sup>

The association between opioid prescribing after surgery and the opioid crisis is complex. Inadequate postoperative pain management, including using opioids, has been reported to be associated with increased

risk for chronic pain, thus warranting the need for long-term opioid use.<sup>20,21,22,23,24,25</sup> Conversely, the receipt of prescription opioids after surgery is suggested to be associated with increased risk for chronic opioid use. In a retrospective analysis of population-based claims data from Canada,<sup>26</sup> individuals prescribed opioids within 7 days of a low-risk surgical procedure were 44% more likely to become prolonged opioid users within 1 year after surgery compared with individuals who did not receive these medications. Lastly, undergoing a surgical procedure has been hypothesized as an independent risk factor for prolonged opioid use after surgery.<sup>11,12,27,28,29</sup>

Although several studies have sought to quantify the rate of and characterize risk factors for prolonged opioid use after surgery, the extent and strength of association have been inconsistent. Despite using similar definitions of prolonged opioid use and eligibility criteria, studies<sup>30,31,32</sup> enrolling opioid-naïve patients undergoing major surgical procedures in the US reported incidence rates ranging from 0.5% to 13.0%. Incidence rates as high as 44% for 1 year after surgery have also been reported.<sup>33,34</sup> To address these conflicting results and to account for potential bias related to differences in study-level factors and low sample sizes, we performed a meta-analysis of published literature to systematically characterize and aggregate the magnitude and patient-level risk factors associated with increased risk of prolonged opioid use after surgery.

## Methods

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This systematic review and meta-analysis was conducted according to the Meta-analysis of Observational Studies in Epidemiology ([MOOSE](#)) and Preferred Reporting Items for Systematic Reviews and Meta-analyses ([PRISMA](#)) reporting guidelines.<sup>35,36</sup> The study protocol is available in the PROSPERO database ([CRD42019129239](#)).

### Literature Search

Relevant studies were identified through an initial literature search of MEDLINE, Embase, and Google Scholar from inception of these databases to August 30, 2017, with an updated search performed on June 30, 2019. Eligible studies were identified from electronic databases using search terms and keywords such as *opioid analgesics*, *general surgery*, *surgical procedures*, *persistent opioid use*, and *postoperative pain*. The full search strategy is available in the eAppendix in the [Supplement](#). We also searched bibliographies of relevant articles to identify additional eligible publications.

### Study Selection

Two of us (J.G. and A.M.) independently assessed all titles and abstracts of studies to determine studies eligible for full-text review. Eligible studies were restricted to published observational studies evaluating opioid use after surgery. Studies were included if they (1) were published in the English language; (2) enrolled participants 18 years or older; (3) included a minimum of 50 patients; (4) involved a noninjectable opioid prescription fill at least 3 months after the index surgical procedure; and (5) reported the rate and adjusted outcome estimates for patient-level risk factors associated with prolonged opioid use after surgery. Given differences with opioid use in cancer vs noncancer pain management, we excluded studies evaluating cancer pain. In addition, eligible studies needed to have accounted for opioids dispensed in the perioperative period or to have incorporated a lag period for at least 1 month after the index surgical procedure. This criterion was included to account for opioids prescribed as part of routine management of postoperative pain before assessing prolonged opioid use after surgery.

Currently, there is not an accepted definition of prolonged opioid use in the medical literature. Therefore, all studies that met the inclusion criteria were considered regardless of variations in the operational definition of prolonged opioid use within and among studies. However, because opioids are often

prescribed preemptively to manage peri- or postoperative pain during the few days or months, in some instances, after surgery, we set a 3-month threshold after the index surgical procedure before assessing prolonged opioid use. As such, prolonged opioid use in this study refers to any opioid use pattern reported by the included studies occurring at least 3 months after surgery. An exception is use of the term *chronic opioid use*. Based on previous literature,<sup>2,11,37,38,39,40</sup> we defined *chronic opioid use* as the receipt of at least 10 opioid prescription fills, at least 90 consecutive days' supply of opioids, or 120 cumulative days in the first year after surgery, excluding the initial 90 postoperative days. Because we expected substantial between-study variation in prolonged opioid use definitions, in sensitivity analyses, we repeated our primary analysis to assess the pooled rate of prolonged opioid use by aggregating evidence across studies involving comparable definitions for opioid use after surgery (eTable 1 in the [Supplement](#)).

## Data Extraction

Data extraction was performed by the same 2 reviewers (J.G. and A.M.) from the literature search using structured forms. A third reviewer (O.D.L.) assessed the data extraction forms for completeness and accuracy. Extracted information from eligible studies included the study design, sample size, length of follow-up, types of surgical procedure, proportions of opioid-naive and opioid-experienced individuals at baseline, and the definitions of prolonged opioid use after surgery. In addition, rates and adjusted estimates associated with the longest follow-up time were extracted. We did not contact authors for information missing from published texts.

## Quality Assessment

The quality of included studies was assessed by 2 independent reviewers (O.D.L. and J.G.) using the Newcastle-Ottawa Scale,<sup>41</sup> and disagreements were resolved by discussion. Studies with a Newcastle-Ottawa Scale score greater than 7 were considered to be high in quality.

## Statistical Analysis

The primary outcomes of interest were the pooled rate and magnitude for individual risk factors of prolonged opioid use after surgery. No restrictions were made in the type of effect estimates extracted; therefore, studies reporting odds ratios (ORs), risk ratios, or hazard ratios were eligible for inclusion. Based on the overall low prevalence of the risk factors in the individual studies (ie, <10%), we regarded risk ratios and ORs as equivalent risk measures. However, we pooled studies reporting hazard ratios in a separate analysis. We calculated the pooled rate of prolonged opioid use after surgery weighted by the sample size of each eligible study. When 2 or more studies reported adjusted estimates for the same risk factor, a pooled OR and the corresponding 95% CI were estimated using the inverse variance method with a random-effects model.<sup>42</sup> Based on an a priori assumption of substantial between-study variation, we prespecified to use the random-effects model for all meta-analyses. Between-study heterogeneity was tested using the Cochran Q statistic<sup>43</sup> and quantified by the  $I^2$  value.<sup>44</sup> We considered heterogeneity to be significant at  $P < .10$  and  $I^2 > 50\%$  to indicate substantial between-study variation that was beyond chance.<sup>45</sup> Heterogeneity was further assessed in sensitivity analyses. Small-study effect, commonly referred to as publication bias, was examined using a funnel plot and the Egger regression test. Except for heterogeneity, statistical significance was set at  $P < .05$ ; all tests were 2-sided. Statistical analyses were conducted using Comprehensive Meta-Analysis Software, version 3.0 (Biostat).

We performed additional analyses to evaluate the potential sources of heterogeneity and robustness of the primary findings. First, we restricted our analyses to studies enrolling only opioid-naive patients before surgery. We accepted definitions of opioid naive from each eligible study. The definitions of opioid naivety in studies enrolling only opioid-naive participants are presented in eTable 2 in the [Supplement](#). Second, we examined whether the rate of prolonged opioid use after surgery differed by source population or insurance

plan, follow-up period ( $\leq 6$  months vs  $> 6$  months), type of surgery (major vs minor surgery and orthopedic vs nonorthopedic surgery), and studies conducted in the US vs non-US countries to assess whether our main finding was moderated by potential differences in prescribing patterns across countries. Classification of major or minor surgery was based on previously published reports<sup>11,12,46</sup> and expert opinion (E.B.) (eTable 3 in the [Supplement](#)). We then aggregated evidence across studies involving comparable definitions for chronic or prolonged opioid use after surgery. Lastly, for each risk factor reported by at least 3 studies, we recalculated the pooled effect by omitting 1 study at a time. This leave-one-out analysis was performed to determine the influence of an individual study on the pooled effects.

## Results

### Study Selection

The search of electronic databases yielded 7534 citations. After removal of duplicates and full-text reviews, a total of 33 studies involving 1 922 743 individuals, with 1 854 006 (96.4%) from the US<sup>11,12,16,27,29,30,31,32,33,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69</sup> The PRISMA diagram is shown in [Figure 1](#).

### Study Characteristics

Characteristics of the eligible studies are presented in [Table 1](#). Sample sizes of included studies ranged from 109 to 675 527 participants. The included studies were conducted in Australia, Canada, Denmark, France, the US, and the UK, with 26 (78.8%) from the US. Of the 1 247 216 individuals enrolled in 32 studies with sex information,<sup>11,12,16,27,29-33,46,48-69</sup> 1 031 399 (82.7%) were females. Information on age was available in 22 studies<sup>11,12,27,29,30,33,48,50,53,54,58-60,62-69</sup>; the mean (SD) age of participants was 59.3 (12.8) years. The minimum age of participants was 39.0 years and the maximum age was 80.0 years. Of the 33 studies, 14 (42.4%) involved data from commercial insurance plans, 12 (36.4%) used hospital institution data, 5 (15.2%) involved military or veterans' insurance plans, and the remaining 2 (6.1%) were based on data from national, publicly funded health care systems. Eight studies (24.2%) enrolled only opioid-naive participants,<sup>11,12,16,30,31,32,46,50</sup> 18 (54.5%) enrolled both opioid-naive and opioid-experienced participants,<sup>27,29,33,48,49,51,52,55,56,57,58,59,60,61,66,70</sup> and the remaining 7 studies lacked sufficient information to categorize participants.<sup>47,53,54,62,63,64,65</sup> The definitions of *long-term*, *persistent*, and *prolonged opioid use* and *opioid naivety* varied across studies ([Table 1](#), and eTables 1-2 in the [Supplement](#)). Subgroup analysis based on quality was not performed because the individual summed score from the Newcastle-Ottawa-Scale varied between 7 and 9, suggesting that all included studies were high quality.

### Primary Outcomes

Across the 33 eligible studies based on random-effects analysis, the pooled rate of prolonged opioid use after surgery was 6.7% (95% CI, 4.5%-9.8%) ([Figure 2](#)), with substantial between-study heterogeneity ( $P < .001$ ;  $I^2 = 99.96\%$ ).

With the exception of anxiety, we were unable to find comparable risk factors across the 2 studies<sup>50,55</sup> that used hazard ratios. Therefore, our analyses on risk factors for prolonged opioid use were derived from studies reporting risk ratios or ORs.

Significantly increased risks were observed among females compared with males (OR, 1.16; 95% CI, 1.08-1.25) and among individuals with a high school degree vs a college degree or higher (OR, 1.20; 95% CI, 1.04-1.37) ([Table 2](#)).

Increased risk of prolonged opioid use was associated with use of antidepressants, opioids,

benzodiazepines, alcohol, cocaine, or tobacco before surgery ([Table 2](#)). Preoperative use of opioids (OR, 5.32; 95% CI, 2.94-9.64), tobacco (OR, 1.55; 95% CI, 1.23-1.96), or cocaine (OR, 4.34; 95% CI, 1.50-12.58) were identified as having the strongest associations with prolonged use of opioids after surgery.

Medical comorbidities were differentiated into 3 specific categories: psychological, pain-associated conditions, and a broader category composed of disorders such as diabetes, pulmonary disease, and obesity ([Table 2](#)). When evaluating the association between psychological disorders before surgery and prolonged opioid use after surgery, increased risks were observed among participants with diagnoses of anxiety (OR, 1.14; 95% CI, 1.06-1.23), depression (OR, 1.54; 95% CI, 1.25-1.91), and mood disorders (OR, 1.85; 95% CI, 1.11-3.07). In contrast, patients with a diagnosis of bipolar disorder before surgery had significantly lower risks for prolonged opioid use after surgery (OR, 0.88; 95% CI, 0.79-0.98). Among pain conditions aggregated across all studies, prolonged opioid use after surgery was most strongly associated with a history of back pain (OR, 2.05; 95% CI, 1.63-2.58) and fibromyalgia (OR, 1.43; 95% CI, 1.15-1.79) ([Table 2](#)).

### Sensitivity and Additional Analyses

Our primary findings remained largely unchanged in leave-one-out analyses (eTable 4 in the [Supplement](#)). No evidence of publication bias was found with the Egger regression-based test (intercept, -20.99; 95% CI, -46.04% to 4.07%; SE, 12.28;  $P = .10$ ) (eFigure in the [Supplement](#)). Studies involving only opioid-naive participants before surgery had lower pooled rates of prolonged opioid use after surgery (1.2%; 95% CI, 0.4%-3.9%). In the restricted analysis assessing chronic opioid use,<sup>11,50,57,67,68,69,71</sup> we observed a pooled rate of 2.3% (95% CI, 0.5%-10.6%). Similarly, in the 10 studies<sup>12,30,31,33,46,53,55,58,59,61</sup> defining prolonged opioid use as the filling of at least 1 opioid prescription within the first 90 days after surgery and the filling of at least 1 additional opioid prescription from 91 to 180 days after surgery, the pooled rate was 13.8% (95% CI, 7.9%-23.0%). No significant difference was observed in a comparison of major vs minor surgical procedures (pooled rate, 7.0%; 95% CI, 4.9%-9.9% vs 11.1%; 95% CI, 6.0%-19.4%; ( $P = .20$ ). Results from meta-analyses of other study-level factors are presented in [Table 3](#).

### Discussion

This systematic review and meta-analysis of observational studies<sup>11,12,16,27,29,30,31,32,33,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69</sup> extend the results of a previous meta-analysis<sup>73</sup> reporting prolonged opioid use among approximately 1 in 10 individuals undergoing a major or minor surgical procedure. Our analyses indicated that approximately 7% of patients filled opioid prescriptions at 3 months and more than 1 year after surgery, a time beyond the normal postoperative recovery period.<sup>74</sup> A higher rate was observed when prolonged opioid use was defined as the filling of at least 1 prescription for opioids within 91 to 180 days after surgery. However, our primary pooled rate was attenuated when we restricted our analyses to patients considered as opioid naive before surgery or to studies involving a more conservative definition of prolonged use that is commonly used in the medical literature to characterize chronic opioid use. Although these rates may appear to be relatively low, the negative consequences that prolonged opioid use may impose on public health is perhaps better elucidated when indexed to the number of surgical procedures performed annually in the US. In 2010, approximately 51.4 million inpatient and 48.3 million ambulatory surgical procedures were estimated to have been performed in the US.<sup>75,76</sup> Based on previous studies<sup>77</sup> reporting that 4 of 5 patients undergoing surgery receive opioids, our pooled rate of 6.9%, when extrapolated to the total number of surgical procedures, implies that up to 5.7 million Americans may potentially become persistent opioid users annually after surgery. Of note, individuals with prolonged opioid use after surgery constitute a group with potentially significant risk of chronic use. Therefore, prioritizing strategies that mitigate the transition of patients undergoing surgery to persistent opioid use while still optimizing the management of

postoperative pain is of importance.

A possible approach to reducing the burden of prolonged opioid use is to characterize the underlying mechanisms, including patient-level risk factors, that may be associated with prolonged and/or chronic use of opioids after surgery. This approach, in part, rests on the assumption that patient-level risk factors associated with prolonged opioid use may be modifiable and can be used in screening for at-risk individuals.<sup>74</sup> Our results indicate that preoperative exposure to medications, such as opioids, antidepressants, benzodiazepines, or cocaine; demographic factors, such as sex; and presence of medical comorbidities, including chronic pain, back pain, substance abuse, mood disorders, or depression before surgery, had some of the strongest associations with prolonged opioid use after surgery. Congruent with previous reviews,<sup>73,78</sup> the strongest association in the current study was observed with preoperative opioid use, wherein individuals who had filled at least 1 opioid prescription in the year before surgery had a 5.3-fold risk of prolonged opioid use after surgery (pooled OR, 5.32; 95% CI, 2.94-9.64). These findings of increased risk of preoperative opioid use and prolonged use after surgery was further corroborated when we restricted our analyses to studies enrolling opioid-naïve participants at baseline; the pooled rate of prolonged opioid use after surgery decreased more than 5-fold. Appropriate prescribing of the dose and quantity of opioids after surgery, the evaluation of opioid use in patients before surgery, and attempts to modify patient-level risk factors when possible or to treat underlying medical conditions before surgery may be included as part of a comprehensive strategy to reduce prolonged opioid use after surgery. Multimodal analgesia, psychobehavioral management of pain, and regional and neuraxial anesthesia have also been listed in the literature<sup>78,79,80</sup> as strategies associated with reducing the transition to prolonged opioid use after surgery.

Although our analyses suggest that surgery may be associated with long-term opioid use, it is possible that the observed association was enhanced by confounding from an underlying chronic pain condition, the developing of persistent postsurgical pain, or surgical procedures exacerbating preexisting conditions and thus warranting long-term opioid management. Persistent postsurgical pain is a recognized complication of surgery and has been reported after common surgical procedures, including cesarean delivery or hip replacement.<sup>38,81</sup> Several studies<sup>38,81,82,83,84</sup> suggest that between 20% and 60% of individuals who undergo surgical procedures may transition from acute to persistent or chronic postsurgical pain. Because opioids were considered the standard of care for chronic noncancer pain management for studies included in this meta-analysis,<sup>2,10</sup> the findings suggest that a high rate of prolonged opioid use after surgery may reflect the expected opioid use patterns among individuals with persistent postsurgical pain or underlying chronic pain. Because of a lack of information in the included studies, we were unable to assess the association between these confounding factors and opioid use after surgery in our analyses.

Of note, other mechanisms not associated with surgical pain before or after undergoing the procedure could have explained the findings of increased prolonged opioid use with surgery. Because major surgical procedures are likely to be associated with higher frequencies or intensities of postoperative pain and perhaps with a longer recovery time compared with minor surgical procedures, we expected significant differences in the pooled rate of prolonged opioid use in major vs minor surgical procedures. However, we found no such evidence in our subgroup analysis. Although a similar finding was recently reported in a large retrospective study of US adults undergoing minor or major surgical procedures,<sup>12</sup> a meta-analysis by Mohamadi et al<sup>72</sup> reported significant differences in prolonged opioid use between these categories of procedures. Therefore, further research should aim to delineate the causal mechanisms of continuous use of opioids in the postoperative period, particularly in the context of surgical pain.

## Limitations

This study has limitations. Because the studies included in our analyses were observational by design, our



findings may be prone to several forms of systematic bias, including selection bias and measurement errors. Of importance, our findings may have been subject to confounding by the underlying indication and inadequate bias adjustment. Second, although we performed several sensitivity analyses to explore the sources of heterogeneity, we were unable to explain the substantial heterogeneity present in most of our analyses. We used a random-effects model for our analyses, with the a priori assumption that the included studies would be heterogenous in their design, sample size, definitions of prolonged opioid use and risk factors, and adjustment of covariates. Third, because of a paucity of eligible studies and suboptimal reporting, we were unable to exclude studies involving participants with chronic opioid use at baseline, participants with preexisting pain disorders, or participants with a diagnosis of cancer before surgery—conditions that are frequently managed with opioids. Of note, the inclusion of these individuals may have led to an overestimation in the magnitude of prolonged opioid use after surgery.<sup>85</sup> In addition, although less likely to be substantial, it is unknown the extent to which some of the eligibility criteria (eg, requiring studies to have reported the rate and risk factors for prolonged use) or not contacting authors may have affected the magnitude of observed association.

Despite these limitations, confidence in our findings is perhaps reinforced because of the absence of small-study bias and consistent results from study-level factors that might have moderated our observed association. Nevertheless, further research is needed to quantify the effect of these various sources of bias on our study findings.

## Conclusions

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In this study, preoperative use of opioids and cocaine and the presence of comorbid pain conditions before surgery had the strongest associations with prolonged opioid use after surgery. These largely modifiable patient-level risk factors may be included as part of a comprehensive strategy to screen for at-risk individuals requiring transition to nonopioid interventions after surgery while ensuring appropriate short-term opioid use to manage postoperative pain. Research is needed to further investigate the association between surgical pain and prolonged opioid use after surgery.

## Notes

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### Supplement.

**eAppendix.** Literature Search Strategy for MEDLINE

**eTable 1.** Included Studies Categorized by Definitions for Assessing Opioid Utilization After Surgery

**eTable 2.** Operational Definition of Opioid Naivety in Studies Enrolling Only Opioid-Naive Individuals Before Surgery

**eTable 3.** Classification of Surgeries into Minor, Major, or Major and Minor Surgeries

**eTable 4.** Risk Factors for Prolonged Opioid Use After Surgery (Pooled Estimates After Leave-1-Out Analyses)

**eFigure 1.** Funnel Plot Assessing Publication Bias/Small-Study Effects

**eReferences.**

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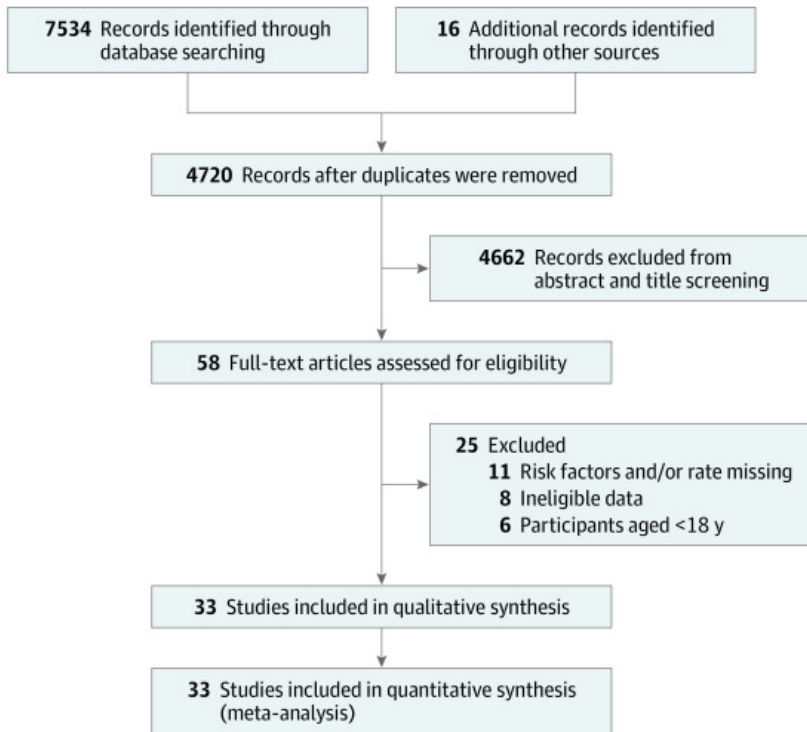
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## Figures and Tables

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**Figure 1.**



**PRISMA Flow Diagram of Included Studies**

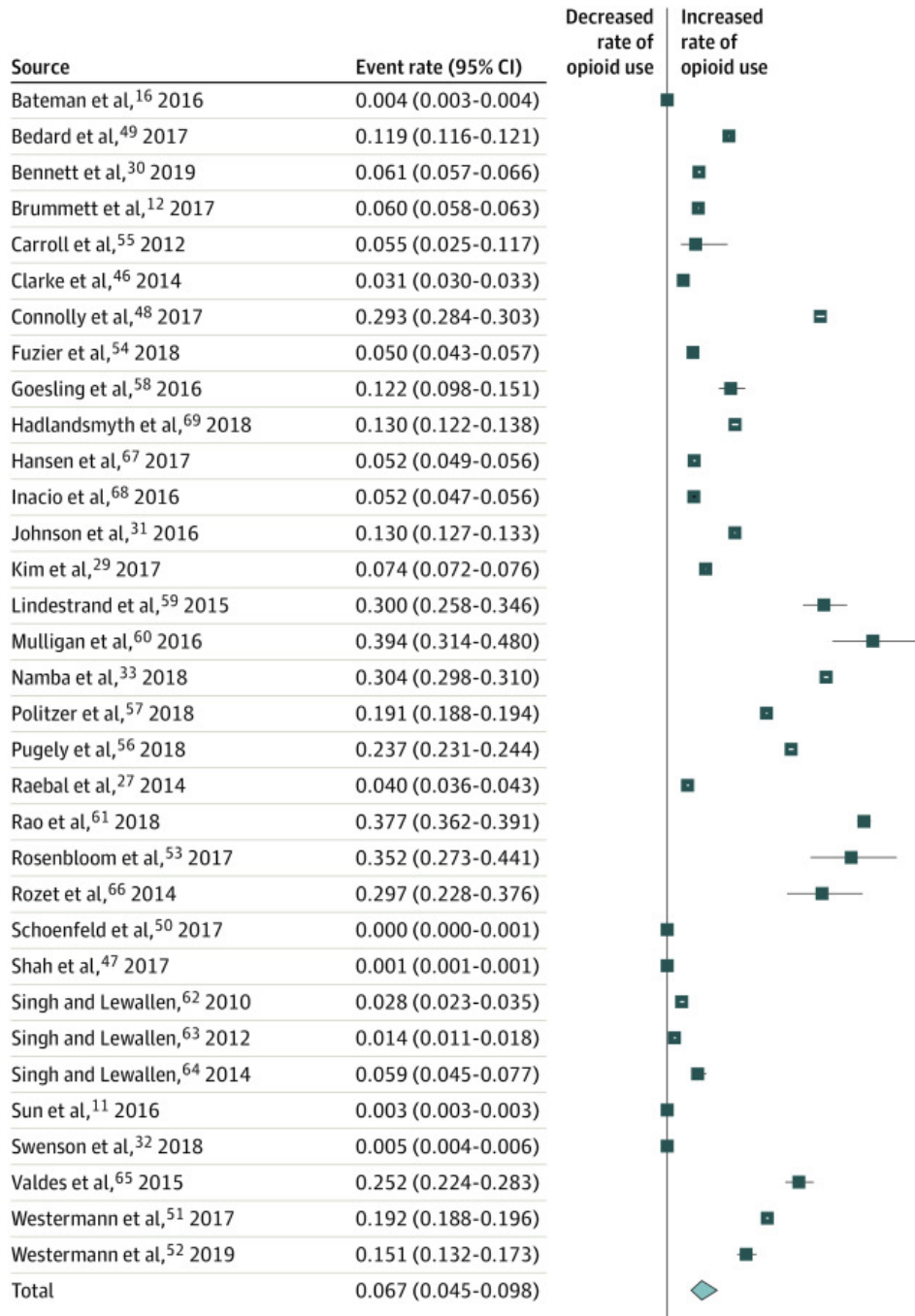
**Table 1.**

**Characteristics of Included Studies**

[Open in a separate window](#)

Abbreviations: *ICD*, *International Classification of Diseases*; *NOW*, *Newcastle-Ottawa Scale*; *NR*, not reported.

**Figure 2.**



**Forest Plot of Studies Assessing Prolonged Opioid Use After Surgery**

Squares indicate event rates, with horizontal lines representing 95% CIs. The diamond represents the pooled total, with the points of the diamond representing 95% CIs. The data show substantial between-study heterogeneity ( $P < .001$ ;  $I^2 = 99.96\%$ ).

**Table 2.**

**Baseline Characteristics Associated With Prolonged Opioid Use After Surgery**

[Open in a separate window](#)

Abbreviations: NA, not applicable; OR, odds ratio.

<sup>a</sup>Calculated as weight in kilograms divided by height in meters squared.

**Table 3.**

**Random-Effects Pooled Rates From Additional Analyses**

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Abbreviation: NA, not applicable.

<sup>a</sup>Included studies defining opioid use after surgery as the receipt of opioids for 10 opioid fills or more, 90 or more consecutive days' supply of opioids, or 120 cumulative days in the first year after surgery after excluding the first 90 postoperative days.

<sup>b</sup>Included studies defining prolonged opioid use as 1 opioid fill or more within 91 to 180 days after surgery.













