

Supplementary Online Content

Lawal OD, Gold J, Murthy A, et al. Rate and risk factors associated with prolonged opioid use after surgery: a systematic review and meta-analysis. *JAMA Netw Open*. 2020;3(6):e207367. doi:10.1001/jamanetworkopen.2020.7367

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This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Literature Search Strategy for MEDLINE

1. Exposure

((("codeine"[MeSH Terms] OR "codeine"[All Fields]) OR ("fentanyl"[MeSH Terms] OR "fentanyl"[All Fields]) OR ("hydrocodone"[MeSH Terms] OR "hydrocodone"[All Fields]) OR ("hydromorphone"[MeSH Terms] OR "hydromorphone"[All Fields]) OR ("levorphanol"[MeSH Terms] OR "levorphanol"[All Fields]) OR ("meperidine"[MeSH Terms] OR "meperidine"[All Fields]) OR ("morphine"[MeSH Terms] OR "morphine"[All Fields]) OR ("oxycodone"[MeSH Terms] OR "oxycodone"[All Fields]) OR ("oxymorphone"[MeSH Terms] OR "oxymorphone"[All Fields]) OR ("pentazocine"[MeSH Terms] OR "pentazocine"[All Fields]) OR ("levopropoxyphene"[MeSH Terms] OR "levopropoxyphene"[All Fields] OR "propoxyphene"[All Fields] OR "dextropropoxyphene"[MeSH Terms] OR "dextropropoxyphene"[All Fields]) AND ("sufentanil"[MeSH Terms] OR "sufentanil"[All Fields])) OR ("tramadol"[MeSH Terms] OR "tramadol"[All Fields]) OR ("tapentadol"[MeSH Terms] OR "tapentadol"[All Fields]) OR ("buprenorphine"[MeSH Terms] OR "buprenorphine"[All Fields]) OR ("analgesics, opioid"[Pharmacological Action] OR "analgesics, opioid"[MeSH Terms] OR ("analgesics"[All Fields] AND "opioid"[All Fields]) OR "opioid analgesics"[All Fields] OR "opioid"[All Fields])) AND "Analgesics, Opioid"[Mesh]

2. Population of interest

(((((("Surgical Procedures, Operative"[Mesh] OR (major[All Fields] AND ("surgical procedures, operative"[MeSH Terms] OR ("surgical"[All Fields] AND "procedures"[All Fields] AND "operative"[All Fields]) OR "operative surgical procedures"[All Fields] OR ("surgical"[All Fields] AND "procedures"[All Fields]) OR "surgical procedures"[All Fields]))) OR "Minor Surgical Procedures"[Mesh]) OR ("minor surgical procedures"[MeSH Terms] OR ("minor"[All Fields] AND "surgical"[All Fields] AND "procedures"[All Fields]) OR "minor surgical procedures"[All Fields])) OR ("General Surgery"[Mesh] AND "Surgical Procedures, Operative"[Mesh])) OR ("surgery"[Subheading] OR "surgery"[All Fields] OR "surgical procedures, operative"[MeSH Terms] OR ("surgical"[All Fields] AND "procedures"[All Fields] AND "operative"[All Fields]) OR "operative surgical procedures"[All Fields] OR "surgery"[All Fields] OR "general surgery"[MeSH Terms] OR ("general"[All Fields] AND "surgery"[All Fields]) OR "general surgery"[All Fields])) OR "Pain, Postoperative"[Mesh]

3. Outcomes

((((((((((opioid prolonged use postoperative) OR opioid prolonged use surgery) OR opioid dependence postoperative) OR opioid persistent use postoperative) OR opioid chronic use postoperative) OR opioid dependence surgery) OR opioid chronic use postoperative) OR opioid dependence surgery) OR opioid persistent use surgery) OR opioid chronic use surgery

4. Limits

(((((("humans"[MeSH Terms] OR "humans"[All Fields] OR "human"[All Fields])) NOT ("animals"[MeSH Terms:noexp] OR animal[All Fields])) NOT ("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields])) OR ("animals"[MeSH Terms:noexp] OR animal[All Fields])

Free text search for other databases

opioid chronic use surgery, opioid persistent use surgery, opioid dependence surgery, opioid chronic use postoperative, opioid persistent use postoperative, opioid dependence postoperative, opioid prolonged use surgery, and opioid prolonged use postoperative

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

Operational definitions for opioid utilization after surgery	Author and Year
Two definitions: (a) using a trajectory model with 5 groups of subjects based on probability of filling an opioid during each of 12 consecutive 30-day period of follow-up; (b) filling an opioid in ≥ 4 , 6, or 8 months of follow-up	Bateman et al 2016 ¹
Chronic opioid use: defined as ≥ 10 opioid fills, ≥ 90 consecutive days or ≥ 120 total days' supply in the one year following surgery after accounting for the first 90 postoperative days	Raebal et al, ² 2014 Sun et al, ³ 2016 Politzer et al, ⁴ 2018 Schoenfeld et al, ⁵ 2017 Hansen et al, ⁶ 2017 Inacio et al, ⁷ 2016 Hadlandsmyth et al, ⁸ 2018
Postoperative opioid assessed as the filling of opioid prescriptions within the first 90 days after surgery and one or more prescriptions of opioids 91 – 180 days after surgery	Clarke et al, ⁹ 2014 Brummett et al, ¹⁰ 2017 Johnson et al, ¹¹ 2016 Rosenbloom et al, ¹² 2017 Bennett et al, ¹³ 2019 Lindestrand et al, ¹⁴ 2015 Carroll et al, ¹⁵ 2012 Namba et al, ¹⁶ 2018 Goesling et al, ¹⁷ 2016 Rao et al, ¹⁸ 2018
Prolonged opioid use assessed on the basis of the presence of ICD-9 diagnosis codes indicative for opioid dependence in medical records	Shah et al, ¹⁹ 2017
Prolonged opioid use defined as filling ≥ 365 days of opioid prescriptions in the 24 months following surgery	Connolly et al, ²⁰ 2017
Prolonged use assessed by monthly trend of filling of opioids for up to 1 year after surgery	Bedard et al, ²¹ 2017 Kim et al, ²² 2017 Pugely et al, ²³ 2018 Westermann et al, ²⁴ 2017 Westermann et al, ²⁵ 2019 Fuzier et al, ²⁶ 2018
Prolonged opioid use defined by filling of opioid prescriptions 3 months after surgery	Mulligan et al, ²⁷ 2016 Rozet et al, ²⁸ 2014
Prolonged opioid use defined as ≥ 2 opioid prescriptions within 6 months of index surgery with ≥ 1 fill every 3 months and either total oral morphine equivalent or equal to 1150 or ≥ 39 days opioid supply	Swenson et al, ²⁹ 2018
Prolonged opioid use was assessed by questionnaire administered 2 and 5 years after index surgery	Singh and Lewallen, ³⁰ 2012 Singh and Lewallen, ³¹ 2014 Singh and Lewallen, ³² 2010
Postoperative opioid use was assessed by questionnaire administered about 1.3 years after index surgery	Valdes et al, ³³ 2015

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

Definition of opioid-naivety	Author name
No fill of an opioid prescription in the 12 months preceding the index surgery	Sun et al, ³ 2016 Bateman et al 2016 ¹ Clarke et al, ⁹ 2014
No receipt of prescription opioid within the 6 months preceding the index surgery	Schoenfeld et al, ⁵ 2017
No opioid prescriptions during the 11 months prior to surgery	Brummett et al, ¹⁰ 2017
No opioid fills from 243 days to 31 days prior to index surgery	Swenson et al, ²⁹ 2018
No filling of an opioid prescription in the 11 months to 31 days prior to index surgery	Bennett et al, ¹³ 2019 Johnson et al, ¹¹ 2016

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

Source	Type of surgery	Surgery classification
Bateman et al 2016 ¹	Cesarean delivery	Major
Raebal et al, ² 2014	Bariatric surgery	Major
Clarke et al, ⁹ 2014	Coronary artery bypass graft surgery through sternotomy, open (thoracotomy) lung resection surgery, lung resection using video assisted thoroscopic surgery, open colon resection surgery, minimally invasive (laparoscopic) colon resection surgery, open radical prostatectomy, minimally invasive (laparoscopic or robot assisted) radical prostatectomy, open total or radical hysterectomy, and minimally invasive (laparoscopic or robot assisted) total or radical hysterectomy.	Major
Shah et al, ¹⁹ 2017	Urological surgery	Major
Sun et al, ³ 2016	Total knee arthroplasty, total hip arthroplasty, laparoscopic cholecystectomy, open cholecystectomy, laparoscopic appendectomy, open appendectomy, cesarean delivery, functional endoscopic sinus surgery [fess], cataract surgery, transurethral prostate resection, and simple mastectomy	Both
Connolly et al, ²⁰ 2017	Lumbar spinal fusion surgery	Major
Bedard et al, ²¹ 2017	Total knee arthroplasty	Major
Johnson et al, ¹¹ 2016	Hand surgery	Major
Schoenfeld et al, ⁵ 2017	Spine surgery (discectomy, decompression, lumbar posterolateral arthrodesis, or lumbar interbody arthrodesis)	Major
Westermann et al, ²⁴ 2017	Rotator cuff repair	Major
Rosenbloom et al, ¹² 2017	Traumatic musculoskeletal injury and corrective surgery	Major
Brummett et al, ¹⁰ 2017	Major surgical procedures included ventral incisional hernia repair, colectomy, reflux surgery, bariatric surgery, and hysterectomy. Minor surgical procedures included varicose vein removal, laparoscopic cholecystectomy, laparoscopic appendectomy, hemorrhoidectomy, thyroidectomy, transurethral prostate surgery, parathyroidectomy, and carpal tunnel.	Major and minor
Fuzier et al, ²⁶ 2018	Carpal tunnel surgery	Minor
Carroll et al, ¹⁵ 2012	Mastectomy, lumpectomy, thoracotomy, total knee replacement, or total hip replacement	Major
Pugely et al, ²³ 2018	Cervical spine surgery	Major
Politzer et al, ⁴ 2018	Total knee arthroplasty	Major
Swenson et al, ²⁹ 2018	Hysterectomy	Major
Namba et al, ¹⁶ 2018	Total knee arthroplasty	Major
Bennett et al, ¹³ 2019	Post-bariatric body contouring surgical procedures	Minor
Westermann et al, ²⁵ 2019	Hip arthroscopy	Minor
Goesling et al, ¹⁷ 2016	Total knee and total hip arthroplasty	Major
Lindestrand et al, ¹⁴ 2015	Hip fracture surgery	Major
Mulligan et al, ²⁷ 2016	Ankle and foot reconstruction	Major

Source	Type of surgery	Surgery classification
Rao et al, ¹⁸ 2018	Shoulder arthroplasty	Major
Singh and Lewallen, ³² 2010	Primary total hip arthroplasty	Major
Singh and Lewallen, ³⁰ 2012	Primary total knee arthroplasty	Major
Singh and Lewallen, ³¹ 2014	Revision total knee arthroplasty	Major
Valdes et al, ³³ 2015	Total joint replacement	Major
Rozet et al, ²⁸ 2014	Knee arthroscopy	Minor
Kim et al, ²² 2017	Hip or knee arthroplasty	Major
Hansen et al, ⁶ 2017	Total knee arthroplasty	Major
Inacio et al, ⁷ 2016	Total hip arthroplasty	Major
Hadlandsmayth et al, ⁸ 2018	Total knee arthroplasty	Major

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

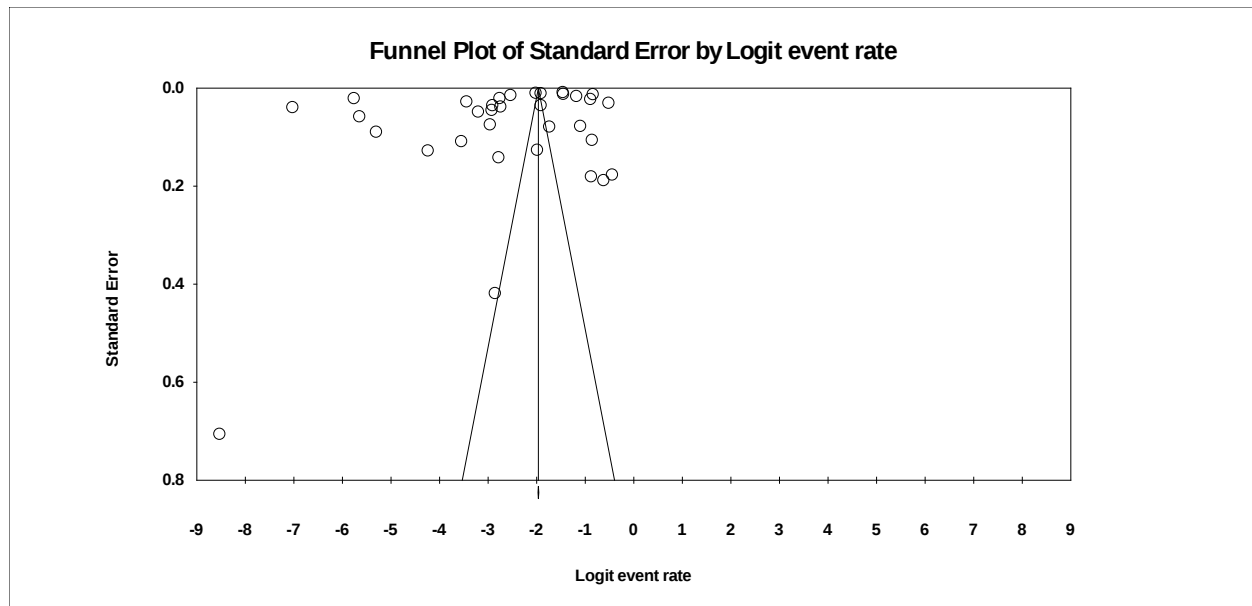
Risk factors	Studies, n	References for all studies	Primary analyses Pooled OR (95% CI)	Removed study, reference	Pooled OR (95% CI), One-study removed
Demographic characteristics					
BMI ^b					
< 25	NA	NA	1 [Reference]	NA	1 [Reference]
25 – 29.9	4	8,30–32	1.04 (0.52, 2.10)	30	1.26 (0.50, 3.14)
30 – 34.9	3	30–32	1.21 (0.61, 2.38)	31	1.46 (0.67, 3.20)
35 – 39.9	3	30–32	0.63 (0.31, 1.30)	31	0.78 (0.35, 1.79)
≥ 40	3	30–32	0.98 (0.42, 2.33)	32	0.80 (0.20, 3.51)
Gender					
Male	NA	NA	1 [Reference]	NA	1 [Reference]
Female	14	4,6,8–11,16–18,20,21,26,32,33	1.16 (1.08, 1.25)	4	1.15 (1.07, 1.24)
Race/ethnicity					
White	NA	NA	1 [Reference]	NA	1 [Reference]
African American	7	2,8,10,16,18,19,29	1.02 (0.92, 1.13)	18	1.06 (0.96, 1.17)
Asian	4	10,16,18,19	0.68 (0.45, 1.03)	19	0.82 (0.54, 1.25)

Risk factors	Studies, n	References for all studies	Primary analyses Pooled OR (95% CI)	Removed study, reference	Pooled OR (95% CI), One-study removed
Hispanic	5	2,10,16,18,19	0.92(0.80, 1.05)	19	1.02 (0.98, 1.06)
Preoperative medication use					
Antidepressants	6	1–3,8,9,22	1.42 (1.11, 1.81)	3	1.38 (1.05, 1.80)
Benzodiazepines	5	1,3,8,9,22	1.53 (1.20, 1.95)	1	1.32 (1.11, 1.59)
Opioids	14	2,8,10,14,16–18,22–25,27–29	5.32 (2.94, 9.64)	2	4.97 (2.70, 9.16)
Substance use					
Alcohol abuse	8	3,10–12,19,21,22,27	1.55 (1.07, 2.25)	22	1.70 (1.15, 2.52)
Tobacco	10	1,2,10,11,13,19–22,27	1.55 (1.23, 1.96)	20	1.61 (1.26, 2.05)
Medical comorbidities					
Mental conditions					
Anxiety	9	2,10,12,13,16,18,30–32	1.14 (1.06, 1.23)	12	1.17 (1.06, 1.29)
Depression	15	2,3,7,12,16,18–21,23,25,29–32	1.54 (1.25, 1.91)	29	2.62 (1.71, 4.02)
Mood disorders	3	10,13,27	1.85 (1.11, 3.07)	27	1.19 (1.07, 1.32)
Psychiatric disorders	5	3,7,13,18,24	1.04 (0.95, 1.13)	13	1.42 (0.72, 2.79)
Unspecified mental disorders	5	10,11,13,16,26	1.45 (0.78, 2.68)	11	1.10 (0.91, 1.33)

Risk factors	Studies, n	References for all studies	Primary analyses Pooled OR (95% CI)	Removed study, reference	Pooled OR (95% CI), One-study removed
Pain conditions					
Arthritis	4	10,13,16,18	1.19 (0.93, 1.52)	10	1.07 (0.90, 1.26)
Back pain	11	1,6,7,10,16,18,21–24,33	2.05 (1.63, 2.58)	6	1.81 (1.44, 2.28)
Chronic pain	5	2,8,12,18,27	1.35 (1.04, 1.75)	8	1.64 (1.04, 2.58)
Fibromyalgia	7	1,16,18,21–24	1.43 (1.15, 1.79)	21	1.36 (1.03, 1.78)
Migraine	4	1,7,18,22	1.36 (1.02, 1.80)	18	1.58 (0.92, 2.69)
Neck pain	4	10,13,16,18	1.12 (1.02, 1.23)	16	1.13 (0.97, 1.32)
Osteoarthritis	3	16,18,26	1.03 (0.96, 1.09)	16	0.99 (0.90, 1.10)
Unspecified pain disorders	9	10,11,13,16–18,26,29,33	1.45 (1.21, 1.72)	33	1.27 (1.16, 1.61)
Other medical conditions					
Diabetes	5	7,9,18,26,27	1.09 (0.90, 1.31)	9	1.15 (0.81, 1.63)
Liver disease	4	7,16,18,19	1.23 (0.98, 1.54)	18	1.47 (0.92, 2.34)
Pulmonary disease	4	20,33	1.32 (1.07, 1.63)	16	1.48 (0.93, 2.35)
Renal disease	3	9,16,18	1.02 (0.97, 1.08)	16	0.97 (0.89, 1.06)
Substance abuse	11	1–3,8,11,12,16,18,21–23	1.58 (1.14, 2.21)	21	1.37 (1.17, 1.60)

^a For each risk factor reported by three or more studies, we recalculated the pooled effect by omitting one study each time. When the conclusion of the recalculated pooled estimate did not differ (on the basis of statistical significance) from the initial analysis, we presented one of the recalculated estimates; otherwise, the recalculated estimate(s) yielding a conclusion different from the primary analysis was presented. In all instances, our analyses were performed using a random-effects model. ^b Calculated as weight in kilograms divided by height in meters squared.

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



We plotted the standard error against the logit of the event rates of prolonged opioid use from the 33 eligible studies. Based on the results from the Egger's regression test, we have no evidence of small-study-effects (intercept: -20.99 [95%, -46.04% - 4.07%]; standard error: 12.28; $P = .0976$)

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