Annals of Internal Medicine REVIEW

Predictors of Prolonged Opioid Use After Initial Prescription for Acute Musculoskeletal Injuries in Adults

A Systematic Review and Meta-analysis of Observational Studies

John J. Riva, DC, MSc; Salmi T. Noor, BHSc, MSc; Li Wang, PhD; Vahid Ashoorion, MD, MSc, PhD; Farid Foroutan, HBSc, PhD; Behnam Sadeghirad, PharmD, MPH, PhD; Rachel Couban, MA, MISt; and Jason W. Busse, DC, PhD

Background: Opioids are frequently prescribed for acute musculoskeletal injuries and may result in long-term use and consequent harms.

Purpose: To explore factors associated with persistent opioid use after its prescription for acute musculoskeletal injury.

Data Sources: Searches of multiple electronic databases, without language restrictions, from inception to 6 January 2020, and reference lists of selected articles.

Study Selection: Observational studies of adults with opioid prescriptions for outpatient acute musculoskeletal injuries, in an adjusted model, that explored risk factors for prolonged use.

Data Extraction: 6 reviewers, working in pairs, independently extracted data, rated the quality of studies, and evaluated the certainty of evidence.

Data Synthesis: 14 cohorts with 13 263 393 participants were included. The overall prevalence of prolonged opioid use after musculoskeletal injury for high-risk populations (that is, patients receiving workers' compensation benefits, Veterans Affairs claimants, or patients with high rates of concurrent substance use disorder) was 27% (95% CI, 18% to 37%). The prevalence among low-risk populations was 6% (CI, 4% to 8%; *P* for interaction < 0.001). Moderate-certainty evidence showed increased odds of persistent opioid use with older age (absolute risk increase [ARI] for every 10-year increase, 1.1% [CI, 0.7% to 1.5%]) and physical comorbidity (ARI, 0.9% [CI, 0.1% to 1.7%]). Low-certainty evidence suggested increased risk for persistent opioid use with past or current substance use disorder (ARI, 10.5% [CI, 4.2% to 19.8%]), prescriptions lasting more than 7 days (median ARI, 4.5%), and higher morphine milligram equivalents per day.

Limitation: Sparse, heterogeneous data with suboptimal adjustment for potential confounders.

Conclusion: Avoiding prescribing opioids for acute musculoskeletal injuries to patients with past or current substance use disorder, and restricting duration to 7 days or less and using lower doses when they are prescribed, are potentially important targets to reduce rates of persistent opioid use.

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For author, article, and disclosure information, see end of text.
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From 1996 to 2011, approximately 9% of the U.S. population reported a musculoskeletal injury. This amounted to 23 to 25 million reports each year, with older Americans reporting higher rates of injury than younger ones (1). Opioid analgesics are often prescribed to manage pain associated with acute musculoskeletal injuries and, from 2011 to 2015, 25% of U.S. patients presenting to an emergency department for a sprained ankle received a prescription for opioids (2). Acute use of opioids may lead to persistent use, which can be associated with misuse, dependence, addiction, and overdose. We conducted a systematic review to explore factors associated with prolonged opioid use in adults with acute musculoskeletal injuries managed in an outpatient setting. This review is part of the evidence base for a joint clinical practice guideline from the American College of Physicians and American Academy of Family Physicians.

METHODS

We reported our systematic review in accordance with the MOOSE (Meta-analysis of Observational Studies in Epidemiology) statement (3) and registered our protocol (PROSPERO: CRD42018104968) on 5 September 2018. We made the following changes to our protocol: We did not impute data for statically nonsignificant predictors for which no data were reported, we did not conduct meta-regression for the relationship between length of follow-up and prevalence of prolonged opioid use because of limited variability in length of follow-up across studies, and we used the QUIPS (Quality In Prognosis Studies) checklist (4) to assess risk of bias for individual studies.

Data Sources and Searches

We searched MEDLINE, EMBASE, Web of Science, and Google Scholar from inception to 6 January 2020, without language restrictions, with terms related to prolonged opioid use, prognosis, and acute musculoskeletal injuries (see the summary of search strategy and results in the **Supplement**, available at Annals.org). We reviewed reference lists of eligible studies for additional articles.

Study Selection

Six reviewers (J.J.R., S.T.N., V.A., F.F., B.S., R.C.) worked in pairs to screen, independently and in dupli-

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cate, the titles and abstracts of identified citations from an EndNote library (version 7.8 [Thomson Reuters]) and, subsequently, the full texts of potentially eligible studies. Reviewers resolved disagreements by discussion or with the help of an adjudicator when consensus could not be reached. We included observational studies that explored risk factors for prolonged opioid use—as defined by authors—after an initial prescription for an acute musculoskeletal injury (≤4 weeks) in an inception cohort of adults (prospective or retrospective) using an adjusted analysis. Studies were ineligible if they enrolled hospitalized patients, patients with injuries requiring surgery, or patients experiencing acute flare-ups of chronic conditions; their reference group was nonopioid users; more than 20% of enrolled patients had nonacute musculoskeletal injuries and the study reported only aggregate results; or all adjusted models contained statistically significant predictors collected more than 30 days after prescription. In such instances, the status of the predictor may be a result, rather than a cause, of prolonged opioid use. When we were able to ascertain that a study included an opioid-naive, acute pain population but were not able to determine the proportion of patients presenting with musculoskeletal injuries, we included these studies and downgraded the certainty of evidence for indirectness.

Data Extraction and Risk of Bias Assessment

Using standardized, pilot-tested data extraction forms (Microsoft Excel 2011), pairs of reviewers (J.J.R., S.T.N., J.W.B.) extracted data and used the QUIPS tool (J.J.R., B.S.) to assess risk of bias from articles, independently and in duplicate (4). Predictive models were considered at low risk of bias if they adjusted for, at a minimum, age, sex, and injury severity. Disagreements were resolved by discussion to achieve consensus or, if consensus could not be reached, by an arbitrator. We extracted information for inception cohorts within study populations when required. For example, the cohort study by Berecki-Gisolf and colleagues reported on 54 931 injured workers; however, only 8267 received an opioid prescription after their injury (5).

Data Synthesis and Analysis

Among eligible studies, we pooled the prevalence of prolonged opioid use and used the Freeman–Tukey transformation to stabilize the variance (6). Without this transformation, very high or very low prevalence estimates can produce CIs that contain values lower than 0% or greater than 100%. When studies reported prevalence of prolonged opioid use according to methods proposed by Deyo and colleagues (7) and Shah and colleagues (8, 9), we prioritized the latter approach (defined as discontinuation of opioid treatment with ≥180 continuous days without opioid use from the end date of the last prescription) on the basis of independent consultation with 2 clinical experts in addiction medicine. When possible, unless there was large heterogeneity present, we pooled all factors assessed for an association with prolonged opioid use that were reported by more than 1 study using random-effects models and the DerSimonian–Laird method (10). We presented pooled measures of association as odds ratios (ORs) and the absolute risk increase (ARI), both with associated 95% CIs, to facilitate interpretation. When the association for age was reported using categories, we assumed the association between age and the dependent variable (persistent opioid use) was linear in each age category and the associations across categories were independent of each other. We used the Bucher approach to calculate the OR and CI for each age category (11) and pooled the ORs using the inverse variance method to produce a single OR for each study (12). We used the pooled prevalence from studies that enrolled patients representative of the general population to derive a baseline risk of 6% for prolonged opioid use after prescription for an acute musculoskeletal injury.

We explored the consistency of association between our pooled results and studies reporting the same predictors that were not possible to pool. We used 3 criteria to identify predictors that were not amenable to pooling and that showed promise for future research: a sample size of more than 500 participants, a highly statistically significant association with prolonged opioid use ($P \leq 0.01$), and a large magnitude of association (OR of ≥2.0 or ≤0.5).

If more than 1 adjusted model exploring risk factors for prolonged use was reported in a single study, we used only the most adjusted model to avoid clustering. We evaluated heterogeneity for all pooled estimates through visual inspection of forest plots because statistical tests of heterogeneity can be misleading when sample sizes are large and CIs are therefore narrow (13). We performed all statistical analyses using Stata, version 13.1 (StataCorp). All comparisons were 2-tailed, with a P value less than 0.05 considered statistically significant.

Subgroup Analyses

We generated 4 a priori hypotheses to explain variability between studies, assuming larger associations with higher-risk populations, studies at greater risk of bias, longer duration of follow-up, and indirect populations. We defined high-risk populations as patients receiving wage replacement benefits (14) or defined as high risk by the study authors (that is, high prevalence of workers' compensation recipients, Veterans Affairs claimants, or patients with concurrent substance use disorder). We considered Veterans Affairs populations to be at higher risk for prolonged opioid use because of higher rates of substance use disorder and posttraumatic stress disorder among this population than the general public (15). We did not conduct subgroup analyses if there was only 1 study in a given subgroup. We reported pooled associations with a combination of direct and potentially indirect study populations when there was no statistically significant subgroup effect between studies; otherwise, we reported only pooled estimates from direct populations.

Certainty of Evidence

We used the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach to summarize the certainty of evidence for all meta-analyses (16–18). Given a 6% baseline risk for

prolonged opioid use after surgery, we estimated that a 2.5% increase in absolute risk would likely be sufficient to address modifiable risk factors in the context of a clinical encounter for the management of an acute musculoskeletal injury, and a 5% increase in risk for a nonmodifiable factor would be sufficient to identify high-risk candidates for intervention. We therefore downgraded for imprecision when the CI overlapped an absolute risk difference of 2.5% for modifiable factors or 5% for nonmodifiable factors. We assessed publication bias if there were at least 10 studies that contributed to a meta-analysis (12).

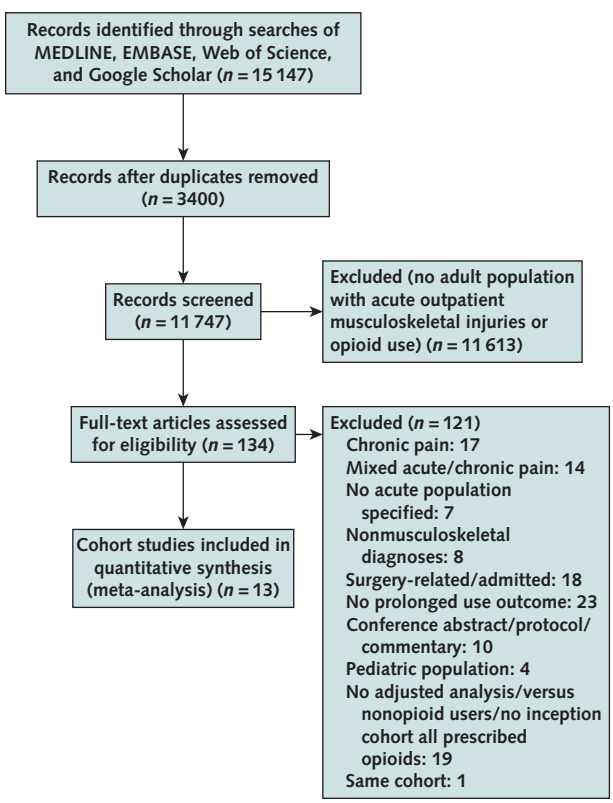
Role of the Funding Source

This systematic review was a sponsor-initiated study, supported by a grant from the National Safety Council (principal investigator: J.W.B.). The funder had no role in the conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

RESULTS

Of 11 747 unique records, we retrieved 134 full-text articles for review; 13 retrospective studies representing 14 cohorts (13 263 393 patients) proved eligible (2, 5, 7–9, 19–28) (Figure 1). We successfully contacted 6 of 8 authors to confirm eligibility (2, 7, 27, 29–31). Eleven studies enrolled patients from the United States (2, 7–9, 19–27), 1 enrolled patients from Australia (5), and 1 enrolled patients from Malaysia (28), and included patients receiving workers' compensation benefits, Veterans Affairs claimants, and injuries in the general population. Ten studies considered multiple acute pain reports (5, 7–9, 19, 20, 22, 23, 25–28), and 2 restricted their study population to low back pain (21, 24) or ankle sprains (2). The median length of follow-up was 12 months (range, 3 to 24 months). One study did not report a source of funding (21), whereas the remaining 12 reported financial support from not-for-profit sources. The definition of prolonged opioid use varied across studies (Table 1).

Figure 1. Evidence search and selection.



Risk of Bias

All studies were at risk of bias for at least 1 domain. Two studies could not confirm that patients were opioid naive at the time of enrollment (5, 26) and, for all studies, despite matching the time of injury with an opioid prescription, there remained the possibility that opioids were prescribed for an indication aside from an acute musculoskeletal injury. Loss to follow-up was low among studies (range, <1% to 10%) in which this information was reported; 1 study (8, 9) did not report the proportion of missing outcome data. Two studies reported that important confounders (for example, substance use disorder) may have been underestimated because of limitations of their registry data (26, 27), and only 1 study (19, 20) was able to confirm prolonged opioid use was related to initial musculoskeletal injury. Nine studies did not report adequately adjusted regression models (5, 7, 19–22, 24, 26–28), and 3 studies used data-driven adjusted regression models in which not all selected factors were included in their final model (Supplement Table 1, available at Annals.org) (19–21, 25).

Prevalence of Prolonged Opioid Use

The overall pooled prevalence of prolonged opioid use across included studies was 10.6% (95% CI, 5.9% to 16.5%); however, substantial heterogeneity was associated with this estimate. Eight studies enrolled patients from the general public (low risk) (2, 7–9, 23–25, 27, 28); 3 studies (with 4 cohorts) enrolled Veterans Affairs claimants, patients receiving workers' compensation benefits, or high proportions of patients with substance use disorder (high risk) (5, 21, 22); and 2 enrolled a mixed population of patients, with at least some receiving wage replacement benefits (uncertain risk) (19, 20, 26). Subgroup analysis revealed no difference in rate of prolonged opioid use among studies enrolling low-risk and uncertain-risk patients (5.7% [CI, 3.6% to 8.3%] vs. 5.3% [CI, 5.1% to 5.5%]; P for interaction = 0.85), and we therefore included studies of uncertain risk in the low-risk category. Subgroup analysis found that high-risk patients were more likely to develop prolonged opioid use (26.9% [CI, 18.2% to 36.6%]) than low-risk patients (5.9% [CI, 4.0% to 8.2%]; P for interaction < 0.001) (Figure 2).

Predictors of Prolonged Opioid Use

The 13 studies eligible for review reported the association of 47 independent variables with prolonged

Table 1. Characteristics of Included Studies

Study, Year (Reference)	Population, Country	Definition of Prolonged Opioid Use	Follow- up	Risk of Bias	Funding Source and Competing Interests
Direct studies					
Berecki-Gisolf et al, 2014 (5)	Musculoskeletal work injuries (*n* = 8933), Australia	≥1 opioid prescription in the second year after injury	24 mo	High	Nonprofit; Transport Accident Commission and Institute for Safety, Compensation and Recovery Research
Delgado et al, 2018 (2)	Ankle sprains (*n* = 6463), United States	≥4 new opioid prescriptions 30–180 d after the initial prescription	6 mo	High	Nonprofit; National Institute on Drug Abuse, National Institutes of Health, and Leonard Davis Institute of Health Economics at the University of Pennsylvania PI reports honorarium for participating in an expert roundtable on innovative solutions for pain management convened by the UnitedHealth Group
Fritz et al, 2018 (21)	Low back pain (*n* = 707), United States	≥120 d or >90 d with ≥10 fills during 1 year	12 mo	High	Not reported
O'Hara et al, 2018 (26)	Musculoskeletal work injuries (*n* = 9596), United States	Filled an opioid prescription >90 d from the date of injury	12 mo	High	Nonprofit; Chesapeake Employers' Insurance Company
Durand et al, 2019 (19)	Musculoskeletal work injuries (*n* = 38 080), United States	Receiving an opioid on most days for a 90-d period, measured as ≥45 prescription-days in 90 d after injury	3 mo	High	Nonprofit; Centers for Disease Control and Prevention's Prescription Drug Overdose: Prevention for States Program Coinvestigator served as a consultant and receiving personal fees from Western University of Health Sciences, Southern California University of Health Sciences, RAND Corporation, and EBSCO Information Services
Harris et al, 2019 (24)	Low back pain (*n* = 3983), United States	Using the CONSORT (Consortium to Study Opioid Risks and Trends) criteria, prescription dates spanned ≥90 d from initial prescription to the run-out date of the last prescription, and included ≥120-d supply or ≥10 fills	9 mo	High	Nonprofit; U.S. Department of Health and Human Services, Penn Center for AIDS Research, Penn Mental Health AIDS Research Center, and Veterans Integrated Service Network 4 Mental Illness Research, Education, and Clinical Center PI named inventor on PCT patent application: "Genotype-guided dosing of opioid agonists"
Indirect opioid-naive population studies					
Deyo et al, 2017 (7)	Any acute pain condition (*n* = 536 767), United States	≥6 opioid fills in the 12 mo after the initiation month	12 mo	High	Nonprofit; National Institute on Drug Abuse and National Center for Advancing Translational Sciences PI reports receiving royalties from UpToDate for authoring topics on low back pain, and previous board membership at the nonprofit Informed Medical Decisions Foundation
Halbert et al, 2016 (23)	Any acute noncancer pain condition (*n* = 2995), United States	≥3 opioid prescriptions during consecutive survey periods during 1-y follow-up	12 mo	High	Nonprofit; Institutional National Research Service Award, Ryoichi Sasakawa Fellowship Fund, Division of General Medicine and Primary Care at Beth Israel Deaconess Medical Center, Harvard Catalyst–The Harvard Clinical and Translational Science Center, National Center for Advancing Translational Sciences, and National Institutes of Health
Hooten et al, 2015 (25)	Any acute pain condition (*n* = 293), United States	Episodes of prescribing lasting >90 d and ≥120 total days' supply	12 mo	High	Nonprofit; Rochester Epidemiology Project
Quinn et al, 2017 (27)	Any new noncancer pain condition (*n* = 10 311 961), United States	Filled prescriptions for >90-d opioid supply during a 6-mo window and required 6-mo window had no gaps of >32 days' supply	12–18 mo	High	Nonprofit; National Institute on Drug Abuse and Indiana Clinical and Translational Sciences Institute

Continued on following page

Table 1–Continued

Study, Year (Reference)	Population, Country	Definition of Prolonged Opioid Use	Follow- up	Risk of Bias	Funding Source and Competing Interests
Shah et al, 2017 (8)	Any acute noncancer pain condition (*n* = 1 353 902), United States	Opioid treatment discontinuation was defined as ≥180 continuous days without opioid use from the end date of the last opioid prescription	12 mo	High	Nonprofit; University of Arkansas for Medical Sciences Translational Research Institute, National Institutes of Health, and Translational Training in Addiction
Hadlandsmyth et al, 2019 (22)	Any acute pain condition (cohort 1, *n* = 432 565; cohort 2, *n* = 523 396), United States	Deyo method: ≥6 opioid fills in the 12 mo after the initiation month Shah method: Opioid treatment discontinuation was defined as ≥180 continuous days without opioid use from the end date of the last opioid prescription	12 mo	High	Nonprofit; U.S. Department of Veterans Affairs, Veterans Health Administration, and the Health Services Research and Development Service
Zin et al, 2019 (28)	Any acute noncancer pain condition (*n* = 33 752), Malaysia	Opioids were prescribed for ≥90 d per year after the index prescription over 12-mo follow-up	12 mo	High	Nonprofit; The Ministry of Education Malaysia (Fundamental Research Grant Scheme)

PCT = Patent Cooperation Treaty; PI = principal investigator.

opioid use after prescription for an acute musculoskeletal injury, 3 of which were suitable for meta-analysis on the basis of our criteria.

Sociodemographic Factors

We found moderate-certainty evidence for small, but statistically significant, associations between prolonged opioid use and older age in adults (OR for every 10-year increase in age, 1.20 [CI, 1.12 to 1.27]; ARI, 1.1% [CI, 0.7% to 1.5%]) and greater physical comorbidity (OR, 1.16 [CI, 1.02 to 1.31]; ARI, 0.9% [CI, 0.1% to 1.7%]), as well as low-certainty evidence for a statistically significant association with past or present substance use disorder (OR, 3.14 [CI, 1.79 to 5.52]; ARI, 10.5% [CI, 4.2% to 19.8%]) (**Table 2**; **Supplement Figure**, available at Annals.org). Substance use disorder was typically defined using International Classification of Diseases, Ninth or 10th Revision codes, including general definitions, such as any drug abuse (2) or nonopioid use disorders (27) as well as more specific codes for alcohol, marijuana, methamphetamine, benzodiazepine, or cocaine use disorders (21, 25).

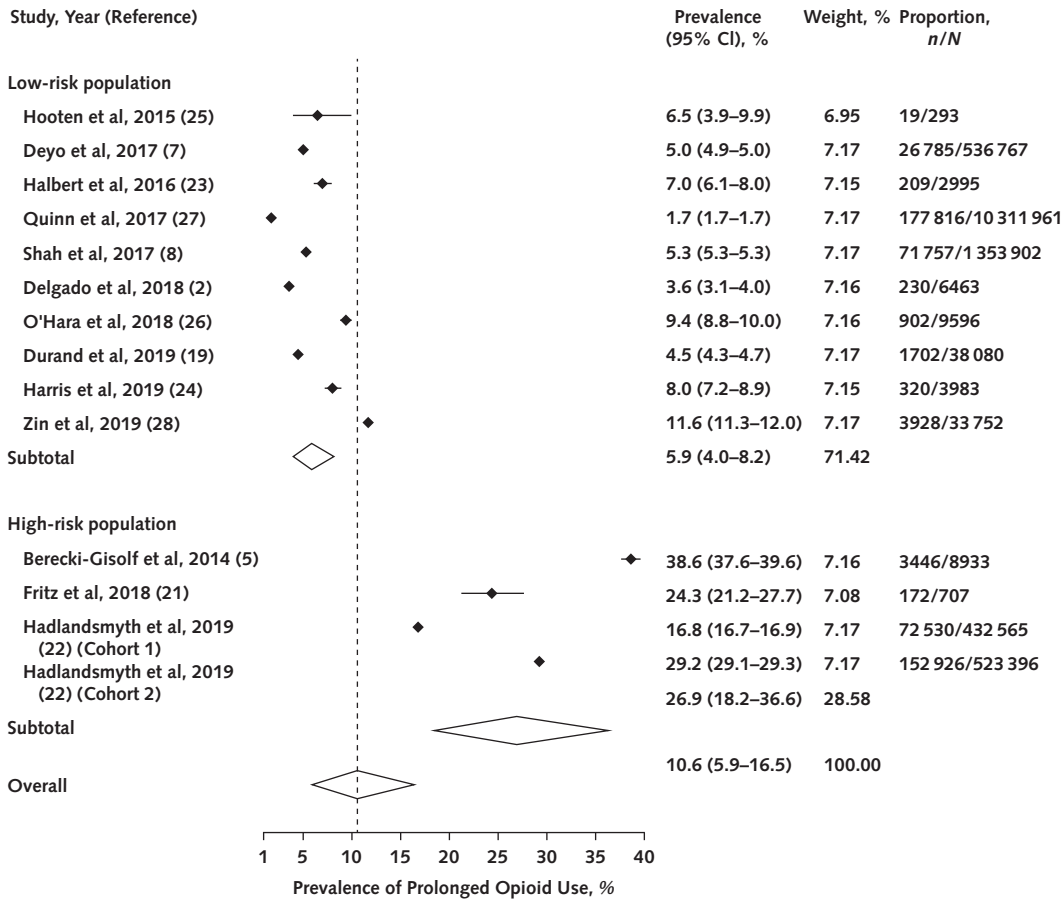
Among sociodemographic factors that were not amenable to pooling, 12 predictors were consistently associated with prolonged opioid use (**Supplement Table 2**, available at Annals.org), including sleep disorders, opioid use disorder, history of suicide attempt or self-injury, lower socioeconomic status, higher household income, rural residency, lower education level, early work disability lasting more than 2 weeks, permanent work disability, being injured in a motor vehicle accident, receipt of Medicaid, and incurring high hospital expenses. Medical claim–only costs were associated with a lower likelihood of prolonged opioid use (**Supplement Table 2**). Five of these factors (opioid use disorder, suicide attempt or self-injury history, early work disability lasting >2 weeks, receipt of Medicaid, and medical claim–only costs) met our criteria for promising predictors for future research. Six factors (sex, anxiety, depression, smoking status, occupation, and injury type) showed conflicting associations (**Supplement Table 3**, available at Annals.org), and 6 factors (race, alcohol use disorder, psychosis, episodic mood disorders, obesity, and non–full-time employment status) were consistently not associated with prolonged opioid use (**Supplement Table 4**, available at Annals.org).

Prescribing Factors

No prescribing factors were amenable to meta-analysis, but 4 factors were reported by several studies and showed a consistent association with increased risk for prolonged opioid use: prescribing opioids for more than 7 days (5 cohorts; 2 087 624 patients; median ARI, 4.5%; low-certainty evidence); higher morphine milligram equivalent dose (6 cohorts; 2 624 355 patients; ARI varied widely on the basis of dose and reference category; low-certainty evidence); long-acting versus short-acting opioids (3 cohorts; 1 924 421 patients; ARI range, 0.6% to 23.4%; very-low-certainty evidence); and more than 1 refill in the first month (3 cohorts; 1 230 243 patients; median ARI, 2.5%; very-low-certainty evidence) (**Supplement** Table 2).

Among factors reported by single studies, 5 were consistently associated with prolonged opioid use: primary care visit within 30 days of injury, non–emergency department prescriptions, hydrocodone versus oxycodone prescription, tramadol versus other opioids, and coprescription of benzodiazepine. Physical therapy within 30 days of injury was associated with a lower likelihood of prolonged opioid use (**Supplement** Table 2). Two of these factors (non–emergency department prescriptions and hydrocodone vs. oxycodone prescription) met our criteria as promising for future study.

Figure 2. Pooled prevalence of prolonged opioid use.



The figure shows a subgroup analysis of populations with high versus low risk for prolonged opioid use (P for interaction < 0.001). High-risk populations were injured workers receiving workers' compensation benefits (5), Veterans Affairs claimants (22), and patients with a high prevalence of substance use disorders (21).

Eight predictors were not associated with prolonged opioid use: 1) year sampled from 2012 to 2015; 2) U.S. region; 3) early diagnostic imaging; 4) visiting an emergency department; 5) surgeon or other specialist consultation; or coprescription with 6) nonsteroidal anti-inflammatory drugs, 7) muscle relaxants, or 8) oral steroids (**Supplement** Table 4).

DISCUSSION

The prevalence of prolonged opioid use after prescription for an acute musculoskeletal injury was 27% for high-risk populations (that is, workers' compensation patients receiving disability benefits, Veterans Affairs claimants, and patients with high prevalence of comorbid substance use disorder) and 6% among patients representative of the general population. We found moderate-certainty evidence that older age and greater physical comorbidity, and low-certainty evidence that past or present substance use disorder, are associated with prolonged opioid use after its prescription for acute musculoskeletal injury. The strongest of these associations was with past or present substance use disorder, with an absolute increase in prolonged opioid use of 11%. Among predictors that could not be pooled, prescribing opioids for more than 7 days, higher morphine milligram equivalent opioid doses, higher number of refills in the first month, non–emergency department prescriptions, hydrocodone versus oxycodone prescription, opioid use disorder, suicide attempt or self-injury history, early work disability lasting more than 2 weeks, receipt of Medicaid, and medical claim–only costs met our criteria for promising associations for future research.

Our finding of a relationship between older age in adults and prolonged use differs from a recent systematic review of children and adults on predictors of opioid misuse after prescription for acute or chronic pain; however, only 5 of the 64 included studies enrolled acute pain populations (32). A clinical practice guideline by the Centers for Disease Control and Prevention, which informed a Health Quality Ontario standard, recommends avoiding prescribing more than 7 days of opioids at one time for acute pain because of increased risk for prolonged use (33, 34). Others have, as we

found, reported that higher doses of opioids are associated with prolonged use (2), and our findings are consistent with recent reviews of opioid-naive patients receiving opioids for any pain condition that reported history of substance use disorder was significantly associated with the development of opioid use disorder (35) and opioid misuse (32). Our finding from a single study (2) that alcohol abuse was not associated with prolonged opioid use is likely because of the small number of patients with alcohol use disorder (73 of 6463), leading to high imprecision in the estimate of association.

We found limited evidence that physical therapy early in care was associated with lower risk for prolonged opioid use (21). A recent cross-sectional study of 88 985 opioid-naive patients with acute musculoskeletal pain found that early physical therapy was associated with lower risk for long-term opioid use and, among those prescribed opioids, a 10% reduction in the mean dose of opioids when compared with similar patients who did not receive early physical therapy (36). The effect of health care provider attending to care is further supported by a study of 377 629 Medicare beneficiaries presenting to an emergency department in which those who saw high-intensity opioid prescribers were more likely to progress to long-term opioid use than those visiting low-intensity prescribers (OR, 1.3 [CI, 1.23 to 1.37]) (37).

Strengths of our review include explicit eligibility criteria, a comprehensive search, and use of the GRADE approach to appraise the certainty of evidence. We have presented pooled measures of association as both relative and absolute risk increases, which we believe strengthens inferences about the importance of associations. Some authors have proposed inclusion of randomized controlled trials in prognostic reviews (38); however, we included only observational studies because of concerns that strict inclusion criteria used in many randomized trials would limit their generalizability.

Our study also has limitations, including imprecision for the prevalence of prolonged opioid use among high-risk populations and some risk of bias for most studies. One study that explored the same registry of Veterans Affairs claimants in 2011 and again in 2016 found that the prevalence of prolonged opioid use decreased from 29% to 17% (22), suggesting that recent changes to Veterans Affairs policies to curb opioid use have been effective (39–41). We were unable to pool predictors from 3 studies that reported only nonsignificant associations without accompanying data, and their inclusion would reduce the magnitude of associations for age, physical comorbidity, and past or present

Table 2. GRADE Evidence Profile of Pooled Predictors of Prolonged Opioid Use After Prescription for Acute Musculoskeletal Injuries

Sociodemographic Factor	Patients (Studies), Follow-up	Quality Assessment						Adjusted Relative Effect: OR (95% CI)	Anticipated Absolute Effect: Risk Difference* (95% CI)
		Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Certainty of Evidence		
Age (every 10-y increase in adults)†	29 016 patients (5 studies), 6–24 mo follow-up	Serious‡	Not serious	Not serious	Not serious	Uncertain; only 6 studies§	Moderate	1.20 (1.12–1.27)	1.1% more (0.7%–1.5%) patients per 10-y increase develop prolonged use
Past or present substance use disorder‖	10 319 424 patients (4 studies), 6–18 mo follow-up	Serious‡	Not serious	Not serious	Serious¶	Uncertain; only 5 studies**	Low	3.14 (1.79–5.52)	10.5% more (4.2%–19.8%) patients with substance use disorder†† develop prolonged use
Comorbidity index‡‡	7170 patients (2 studies), 6–12 mo follow-up	Serious‡	Not serious	Not serious	Not serious	Uncertain; only 3 studies§	Moderate	1.16 (1.02–1.31)	0.9% more (0.1%–1.7%) patients with higher numbers of comorbidities§§ develop prolonged use

GRADE = Grading of Recommendations Assessment, Development and Evaluation; OR = odds ratio.
* Baseline risk of 6% based on pooled prevalence of 10 low-risk population studies (Figure 2).
† From references 2, 5, 21, 24, and 26.
‡ Downgraded because of limitations reported in risk of bias summary (Supplement Table 1).
§ The study by Hooten and colleagues (25) (n = 293) was not included in the pooled estimate because there were no data reported for age or physical comorbidity; both reported no statistically significant association with prolonged opioid use in an adjusted model.
‖ From references 2, 21, 25, and 27.
¶ Downgraded because 95% CI crossed 5% threshold for a nonmodifiable factor in the context of a clinical encounter for the management of an acute musculoskeletal injury.
** The study by O'Hara and colleagues (26) (n = 9596) was not included in the pooled estimate because there were no data reported for substance use disorder, which was noted to show no statistically significant association with prolonged opioid use in an adjusted model.
†† Substance use disorder was defined using International Classification of Diseases, Ninth or 10th Revision codes, including general codes, such as any drug abuse (2) or nonopioid use disorders (27), as well as more specific codes, including alcohol, marijuana, methamphetamine, benzodiazepine, or cocaine use disorders (21, 25).
‡‡ From references 2 and 21.
§§ The study by Delgado and colleagues (2) measured comorbidity using the total number of Elixhauser comorbidities. The most common comorbidities represented in the sample were hypertension (23%), uncomplicated diabetes (9%), chronic pulmonary disease (9%), hypothyroidism (7%), and obesity (6%). The study by Fritz and colleagues (21) measured comorbidity using the Charlson Comorbidity Index and classified patients as having multiple comorbid conditions if the score was ≥2. Obesity was present in 26% of patients with long-term opioid use; other comorbidities were not reported.

substance use disorder with prolonged opioid use (1 study for each predictor). However, the 1 study that was excluded from our pooled estimate for past or present substance use disorder acknowledged that its registry data underreported rates of comorbid mental illness (26) and identified only 60 of 9596 patients (0.6%) with substance use disorders. We found sparse information to inform the associations of some predictors, and data from our review came from patient or claim registries in which the reason for the original opioid prescription and subsequent prescriptions could typically not be definitively attributed to acute musculoskeletal injury.

Future research would benefit from prospective studies in which both the initial prescription for, and continued use of, opioids was confirmed to be associated with an acute musculoskeletal injury. Regression models for prolonged opioid use should include, at a minimum, age, sex, injury severity, past and present substance use disorder, physical comorbidity, payer (for example, workers' compensation or Medicaid), and opioid prescribing factors (for example, duration, number of refills, dose, and type of opioid). Only 15% of the 13 studies eligible for our review included all of these factors in their adjusted regression model (**Supplement Table 5**, available at Annals.org). Some regression models we reviewed included independent factors with few observations, resulting in highly imprecise measures of association. Future studies should set a threshold of a minimum number of observations per category for each independent factor (for example, ≥200) to provide some reassurance that each variable has sufficient discriminant power to detect an association with prolonged opioid use if an association exists. Studies should report multiple clinically meaningful categories for opioid duration and dose that reflect current legislative changes (42). Further, prolonged opioid use is a surrogate for patient-important outcomes, such as addiction, overdose, and death, which should also be captured and reported (43).

In conclusion, prolonged use is common among patients prescribed opioids for acute musculoskeletal injuries. Avoiding prescribing opioids for acute musculoskeletal injuries among patients with past or current substance use disorder, and restricting duration to 7 days or less and using lower doses when they are prescribed, are potentially important targets to reduce rates of persistent opioid use.

From McMaster University, Hamilton, Ontario, Canada (J.J.R., F.F.); University of Ottawa, Ottawa, Ontario, Canada (S.T.N.); Michael G. DeGroote National Pain Centre, McMaster University, Hamilton, Ontario, Canada (L.W., V.A., B.S., R.C.); and Michael G. DeGroote National Pain Centre, McMaster University, and Chronic Pain Centre of Excellence for Canadian Veterans, Hamilton, Ontario, Canada (J.W.B.).

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Corresponding Author: John J. Riva, DC, MSc, McMaster University, Department of Family Medicine, David Braley Health Sciences Centre, 100 Main Street West, 6th Floor, Hamilton, ON L8P 1H6, Canada; e-mail, rivaj@mcmaster.ca.

Current author addresses and author contributions are available at Annals.org.

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Current Author Addresses: Dr. Riva: McMaster University, David Braley Health Sciences Centre, 100 Main Street West, 6th Floor, Hamilton, ON L8P 1H6, Canada.
Ms. Noor: University of Ottawa, 451 Smyth Road #2044, Ottawa, ON K1H 8M5, Canada.
Drs. Wang, Ashoorion, Sadeghirad, and Busse and Ms. Couban: Michael G. DeGroote National Pain Centre, McMaster University, MDCL-2112, 1280 Main Street West, Hamilton, ON L8S 4K1, Canada.
Dr. Foroutan: McMaster University Medical Centre, 1280 Main Street West, 2C Area, Hamilton, ON L8S 4K1, Canada.

Author Contributions: Conception and design: J.J. Riva, J.W. Busse.
Analysis and interpretation of the data: J.J. Riva, S.T. Noor, L. Wang, F. Foroutan, J.W. Busse.
Drafting of the article: J.J. Riva, J.W. Busse.
Critical revision of the article for important intellectual content: J.J. Riva, L. Wang, B. Sadeghirad, J.W. Busse.
Final approval of the article: J.J. Riva, S.T. Noor, L. Wang, V. Ashoorion, F. Foroutan, B. Sadeghirad, R. Couban, J.W. Busse.
Statistical expertise: L. Wang, F. Foroutan, J.W. Busse.
Obtaining of funding: J.W. Busse.
Administrative, technical, or logistic support: J.J. Riva, B. Sadeghirad.
Collection and assembly of data: J.J. Riva, S.T. Noor, V. Ashoorion, B. Sadeghirad, R. Couban, J.W. Busse.