Risk Factors for Misuse of Prescribed Opioids: A Systematic Review and Meta-Analysis

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Study objective: Increasing opioid prescribing has been linked to an epidemic of opioid misuse. Our objective is to synthesize the available evidence about patient-, prescriber-, medication-, and system-level risk factors for developing misuse among patients prescribed opioids for noncancer pain.

Methods: We performed a systematic search of the scientific and gray literature for studies reporting on risk factors for prescription opioid misuse. Two reviewers independently reviewed titles, abstracts, and full texts; extracted data; and assessed study quality. We excluded studies with greater than 50% cancer patients, palliative patients, and illicit opioid initiation. When possible, we synthesized the effect sizes of dichotomous risk factors and their associations with opioid misuse, using inverse-variance random-effects meta-analysis. We calculated the mean difference between opioid misusers and nonmisusers for continuous risk factors. When studies lacked homogeneity, we synthesized their results qualitatively.

Results: Of 9,629 studies, 65 met our inclusion criteria. Among patients with outpatient opioid prescriptions, the following factors were associated with the development of misuse: any current or previous substance use (odds ratio [OR] 3.55; 95% confidence interval [CI] 2.62 to 4.82), any mental health diagnosis (OR 2.45; 95% CI 1.91 to 3.15), younger age (OR 2.19; 95% CI 1.81 to 2.64), and male sex (OR 1.23; 95% CI 1.10 to 1.36).

Conclusion: Although clinicians should endeavor to offer alternative pain management strategies to all patients, those who are younger, are male patients, and report a history of or current substance use or mental health diagnoses were associated with a greater risk of developing opioid misuse. Clinicians should consider prioritizing alternative pain management strategies for these higher-risk patients. [Ann Emerg Med. 2019;74:634-646.]

Please see page 635 for the Editor's Capsule Summary of this article.

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INTRODUCTION

Background

In 2006, opioid addiction prevention became a public health priority because the United States experienced sharply increasing death tolls from overdoses.[1] The most recent surge in opioid-related deaths in Canada and the United States has been attributed to the entry of fentanyl and fentanyl analogues into the illicit market.[2,3] However, this was preceded by increasing opioid prescribing and an increasing population of individuals addicted to prescribed opioids.[4-7] In 2014, it was reported that 75% of recent heroin users identified a prescription opioid as their first opioid of abuse.[8]

Importance

Although policies to promote responsible opioid prescribing have been implemented across North America to prevent inappropriate use at the population level,[9,10] opioids continue to be used frequently for acutely painful medical and surgical conditions.[11] Alternatives are commonly less effective or contraindicated, and access to nonpharmacologic strategies such as acupuncture or regional anesthetic procedures is limited.[12] As a result, patients with painful conditions that may be amenable to alternative treatment options are commonly exposed to prolonged treatment with opioids. Identifying and prioritizing high-risk patients for alternative pain management strategies may enable prescribers to minimize opioid use in high-risk patients in particular to reduce their risk of developing misuse.

Two previous systematic reviews investigated predictors of developing opioid misuse among patients with chronic pain.[13,14] One found that 3.3% to 14.5% of long-term prescription-opioid users became addicted after being exposed to opioids for an average of 22 months.[13] In the

Editor's Capsule Summary

What is already known on this topic

Injudicious opioid prescribing is linked to misuse and adverse outcomes.

What question this study addressed

What risk factors in opioid-naive patients are associated with subsequent opioid misuse?

What this study adds to our knowledge

This systematic review of 67 studies found that current or previous substance use, mental health diagnoses, and younger age are associated with greater risk of developing problematic opioid use after an initial prescription.

How this is relevant to clinical practice

There may be a group of patients needing an even more cautious approach to opioid prescribing.

other study, risk factors were measured inconsistently and demonstrated mixed effects.[14] Neither review examined opioid-naive patients, for whom risk factors may be different.[14]

Goals of This Investigation

Our main objective was to synthesize the available evidence about patient-, provider-, drug-, and system-level risk factors for the development of opioid misuse among patients prescribed opioids. Specific objectives included synthesizing the available evidence about these risk factors overall and among subgroups of opioid-naive patients, and to explore the effect of study design and outcome ascertainment on the associations.

MATERIALS AND METHODS

We conducted a systematic review of the literature adhering to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines, as well as the Meta-analysis of Observational Studies in Epidemiology guidelines, for the reporting of systematic reviews. We described detailed methods in a published protocol (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=96250).[15]

Data Collection and Processing

We published our search strategy (Appendix E1, available online at http://www.annemergmed.com) and information sources.[15] We conducted our search from July 2017 to February 2018. We searched 9 electronic reference databases, including MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects, the Cumulative Index to Nursing and Allied Health Literature, the Science Citation Index (Web of Science Core Collection), PsycINFO, Social Sciences Citation Index (Web of Science Core Collection), and the Sociology Collection. We conducted snowballing searches for cited and citing studies of all articles meeting our inclusion criteria, using the Web of Science Core Collection and ScienceDirect (Elsevier). We searched for ongoing studies in the ISRCTN registry, ClinicalTrials.gov, EU Clinical Trials Register and South African National Clinical Trials Register, Open Trials, and the Quebec Pain Registry. We completed a gray literature search for unpublished studies, using combinations of search terms and concepts derived from our electronic reference database search using Google. We reviewed the top 100 results for each search for articles meeting inclusion criteria. We also searched for articles in conference proceedings of the World Congress on Pain and the International Conference and Exhibition on Pain Medicine, and by looking through the tables of contents for all published issues of *Pain Medicine*, *Pain Research and Management*, *Anesthesia and Analgesia*, and the *Journal of Pain and Symptom Management* since 1964. We also searched the Web sites of key medical associations, addiction and pain agencies, and government. Finally, we contacted study authors and experts in the field for additional unpublished studies.

Two independent reviewers screened publications for inclusion (A.C., J.P.H., S.A.W., or S.A.K.). We included all potentially relevant titles or abstracts identified by either reviewer or both of them in the full-text review (Figure). We resolved disagreements relating to the inclusion or exclusion of full texts through discussion until reaching consensus. A third reviewer adjudicated the record if consensus could not be reached (A.C., J.P.H., S.A.W., or S.A.K.).

We described our study selection criteria for this systematic review by using modified population, intervention, control, outcome (PICO) criteria based instead on the population, outcome, topic, and study design of included studies.

Study Selection

We included studies in which adults or children were first exposed to an opioid through a prescription. We excluded studies in which all patients reported first being exposed to illicit opioids, were prescribed opioids for cancer pain, or were receiving palliative care. If studies did not disaggregate the patient population according to the context of their first exposure, we attempted to contact

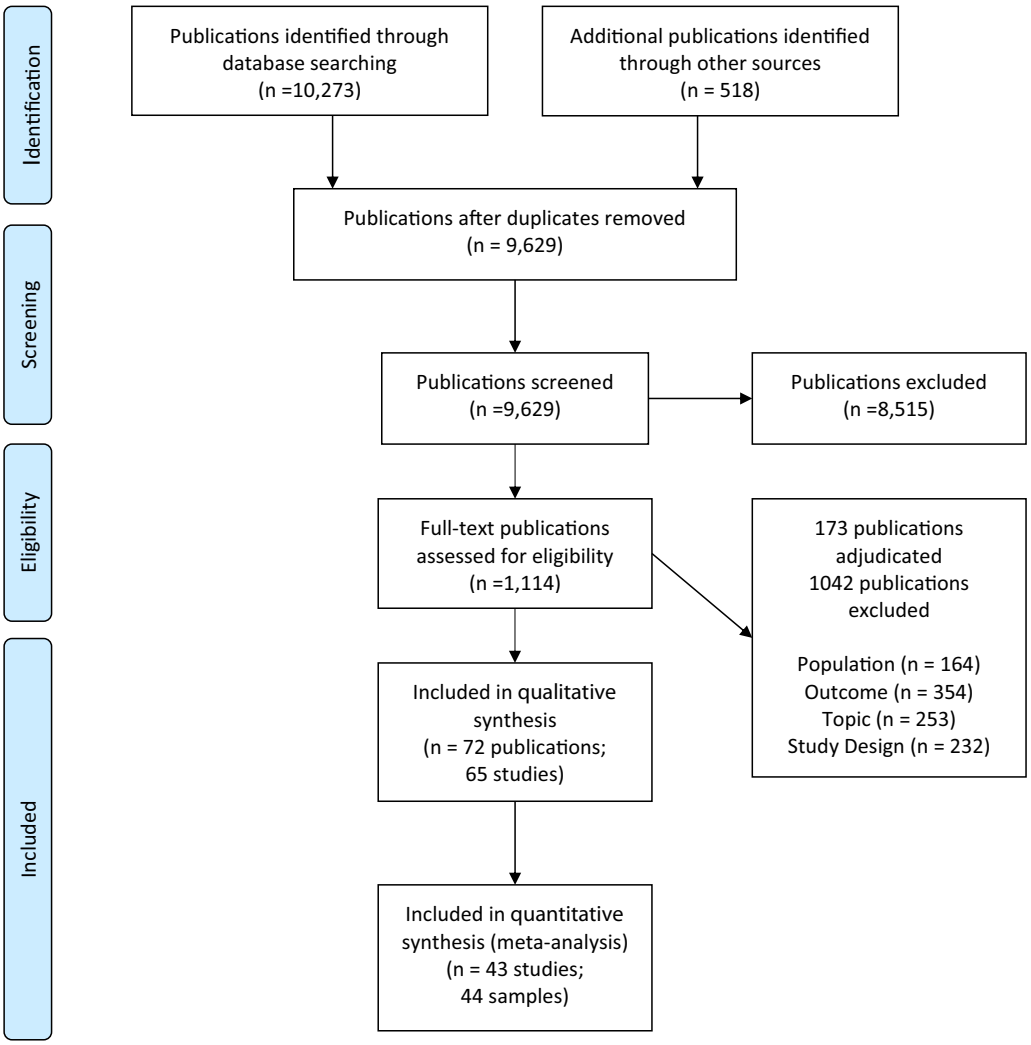

Figure. Study selection flow.

study authors for patient-level data; if they were unavailable, we included studies in which greater than 50% of patients met our inclusion criteria. We identified studies enrolling opioid-naive patients and considered patients opioid naive if they had experienced an opioid washout period of any length in the time leading up to study recruitment.

Our primary outcome of interest was opioid misuse, including any aberrant drug behavior, opioid abuse, or opioid addiction or dependence, as described in our published protocol.[15] We defined misuse as evidence of any aberrant drug behavior[16] or any component of the definitions of opioid addiction or dependence from the most recent versions of the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*[17] or *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*.[18]

We included studies that ascertained opioid misuse using any method presented in the literature. Outcome ascertainment methods included clinical opinion, use of chart or administrative records, urine toxicology screening, patient self-report, family or clinic staff report, opioid agreement violation, or enrollment in a rehabilitation program. Two reviewers classified each included study by its method of outcome ascertainment into 1 of 3 categories: diagnosed by a health care practitioner, reported by the patient, or derived algorithmically from behaviors recorded in patient or administrative records.

We included studies that reported on any risk factor for opioid misuse. We synthesized risk factors reported in a similar way by more than one study. As a result, we have reported on several risk factors that appear to overlap (eg, conditions collapsed together versus on their own) but were measured in different ways across studies. Risk factors could

be self-reported or ascertained by health care providers, by chart reviews, or from administrative databases.

We included observational and experimental studies, including randomized controlled trials and cross-sectional, prospective, or retrospective cohort or case-control studies.[19,20]

Two reviewers extracted relevant data from each included study (A.C., J.PH., S.A.W., or S.A.K.). When studies reported results of multiple regressions in overlapping samples, we collected risk factor data from the largest extractable sample in which the proportion of the population misusing opioids was reported. When studies applied multiple outcome definitions on the same sample, we used the most inclusive definition meeting our inclusion criteria. We attempted to contact study authors for missing information and clarifications by e-mail.

Two reviewers independently appraised each included study for potential sources of bias (A.C. and S.A.K.). Reviewers used versions of the National Institute for Health and Care Excellence tool, depending on study design,[21] assessing each study for sources of confounding and selection and measurement bias. In cases of disagreement, the reviewers discussed their rating until reaching consensus. A third reviewer adjudicated cases in which consensus was not easily reached (J.P.H.).

Data Analysis

We synthesized the odds ratios (ORs) from individual studies by using inverse-variance weighted random-effects meta-analysis. Whenever available, adjusted ORs were pooled from individual studies by converting them to log(ORs) and standard errors, using the calculator function in Cochrane's Review Manager software (version 5.3; Cochrane, London, UK). When primary studies did not report adjusted ORs, we used the calculator to convert unadjusted ORs calculated from raw frequencies to log(ORs) and estimate their standard errors. We produced inverse-variance, weighted, pooled mean differences for continuous risk factors. We produced 95% confidence intervals (CIs) for all estimates and displayed individual and pooled effect sizes with forest plots. We assessed statistical heterogeneity with the I^2 statistic. We conducted subgroup analyses to explore the effect of opioid-naive status, outcome ascertainment method, and study design on our results. We also performed post hoc sensitivity analyses to explore the effect of study sample size on statistical heterogeneity. We used Review Manager (version 5.3) for quantitative data analyses. We synthesized findings qualitatively if studies presented data we could not extract, measured risk factors in different ways, or were deemed clinically heterogeneous.

We presented the results of our meta-analysis with a Grading of Recommendations Assessment, Development and Evaluation summary of findings table to place our estimates in context of the quality of evidence. We rated the confidence of our findings from high when synthesizing findings from experimental studies to low when synthesizing data from observational studies.[22,23] We assessed the quality of evidence according to the number, sample size, and quality of the component studies; how closely they met our inclusion criteria; and the consistency and generalizability within them. We downgraded estimates that significantly changed in size or direction in sensitivity analyses by risk of bias, inconsistency, indirectness, imprecision, or publication bias by one level for each issue down to a minimum rating of very low confidence. We used funnel plots to assess for publication bias if we had more than the necessary 10 included studies.

RESULTS

Main Results

We screened 9,629 articles, of which 1,114 proceeded to full-text review (Figure). We included 65 studies of 1 or more independent data sets reported across 72 publications.[9,24-94] Table E1 (available online at http://www.annemergmed.com) describes the characteristics of included studies. Almost one quarter of the studies limited their study populations to opioid-naive patients (15/65).[24,26,28,34,37,38,42,50,57,59,68,70-73] The most common designs were retrospective cohort (n=27), cross-sectional (n=18), prospective cohort (n=10), and case-control studies (n=5), followed by one randomized controlled trial (n=1). We reclassified 4 studies reported as retrospective cohorts as retrospective cross-sectional studies because the authors assessed risk factors and study outcomes simultaneously.[61,76,85,86] Most studies examined opioid use among patients with chronic noncancer pain (41/65), and 5 studies looked at prescription opioid use among patients with acute pain (eg, surgical or injury patients). Almost all studies were conducted in developed countries (63/65).

We included data from 43 studies reported in 46 publications in our meta-analysis (n=30,571,969 to 30,586,274) (Table E2, available online at http://www.annemergmed.com).[9,27,29,31-33,35,38,39,41-46,48,50,52-59,61-63,66-69,74,75,78,79,83-86,88,89,91-94] We performed meta-analysis on 27 risk factors that were dichotomous or were reported as dichotomous (Table 1). Sixteen patient characteristics were associated with increased odds of opioid misuse. These included male sex, younger than 40 years, mental-health-related factors, substance-use-related factors, and clinical variables (Appendix E2, available online at http://www.annemergmed.com[1,2,7-10,11-18,20,26]). Being employed and having arthritis were the only patient

Table 1. Pooled effect sizes and 95% CIs among outpatients with opioid prescriptions for each commonly reported risk factor with Grading of Recommendations Assessment, Development and Evaluation confidence rating.

Risk Factor	Reference Category	OR (95% CI)	No. of Samples	Heterogeneity (I^2), %	GRADE Ratings
Pooled odds of misuse for dichotomous risk factors					
Male sex*	Female sex	1.23 (1.10 to 1.36)	40	87	+000
<40 y	≥40 y	2.19 (1.81 to 2.64)	12	96	++00
Employed†	Unemployed	0.59 (0.46 to 0.75)	7	19	+000
Married	Not married	0.88 (0.70 to 1.12)	14	66	++00
White	Not white	1.23 (0.94 to 1.62)	15	64	++00
High school completion	No high school completion	0.99 (0.74 to 1.32)	9	28	++00
Depression	No depression	2.30 (1.92 to 2.77)	12	51	++00
Anxiety	No anxiety	2.14 (1.59 to 2.86)	11	81	++00
PTSD†	No PTSD	2.04 (1.03 to 4.06)	5	82	+000
Any mental health diagnosis	No mental health diagnosis	2.45 (1.91 to 3.15)	12	96	++00
Previous opioid use/abuse‡	No previous opioid use/abuse	3.83 (1.86 to 7.87)	10	97	+000
Any short-acting (IR) opioids*	Nonshort-acting (IR) opioids	2.40 (1.15 to 5.02)	4	99	+000
Recent benzodiazepine use	No benzodiazepine use	2.57 (1.23 to 5.38)	5	99	++00
NSAID use*	No NSAID use	1.83 (1.67 to 2.02)	3	66	+000
Alcohol use/abuse	No alcohol use/abuse	1.88 (1.41 to 2.50)	16	87	++00
Tobacco use/abuse	No tobacco use/abuse	1.72 (1.49 to 1.98)	11	61	++00
Illicit drug use history†	No illicit drug use history	4.21 (2.31 to 7.65)	6	80	+000
Any substance use	No substance use	3.55 (2.62 to 4.82)	19	90	++00
Any chronic pain	No chronic pain	0.92 (0.79 to 1.07)	5	75	++00
Back pain*	No back pain	1.29 (1.08 to 1.54)	12	80	+000
Headache disorder*	No headache disorder	1.10 (0.94 to 1.30)	9	34	+000
Fibromyalgia	No fibromyalgia	1.19 (0.89 to 1.58)	3	74	++00
Arthritis	No arthritis	0.81 (0.67 to 0.97)	7	82	++00
Neuropathic pain	No neuropathic pain	1.76 (1.01 to 3.05)	6	83	++00
Disability†,§	No disability	1.53 (0.91 to 2.57)	4	54	+000
Hepatitis C	No hepatitis C	2.31 (1.94 to 2.74)	3	0	++00
Liver disease†	No liver disease	0.92 (0.57 to 1.47)	3	35	+000

Risk factor	Units of measure	Mean difference (95% CI)			
Pooled mean difference of continuous risk factors between patients misusing opioids vs not					
Age*	Years	−4.45 (−6.71 to −2.18)	25	99	+000
Pain duration†,§	Years	1.10 (−0.45 to 2.65)	4	0	+000
Recent pain severity	Scale of 0 to 10	0.28 (0.16 to 0.40)	7	0	++00
Time receiving opioids§	Years	1.87 (0.74 to 3.01)	3	0	+000
Opioid dose*,†	Milligram morphine equivalents/day	81.34 (38.71 to 123.96)	6	79	+000
Opioid supply	Days	147.27 (−32.95 to 327.48)	2	100	++00

GRADE, Grading of Recommendations Assessment, Development and Evaluation; *+OOO*, very low quality (we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect[23]); *++OO*, low quality (our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect); *PTSD*, posttraumatic stress disorder; *IR*, immediate release; *NSAID*, nonsteroidal anti-inflammatory drug.

*GRADE rating downgraded because of inconsistency in effect across studies.

†GRADE rating downgraded because of risk of indirectness (low generalizability).

‡GRADE rating downgraded because of risk of bias (low internal validity).

§GRADE rating downgraded because of risk of imprecision (small N).

Table 2. Associations between variables of interest and misuse among outpatients prescribed opioids, by opioid exposure status at baseline (n=number of samples).

Risk Factor	Reference Category	Naive (95% CI)	Tolerant (95% CI)
Pooled odds of misuse for dichotomously measured risk factors			
Male sex	Female sex	1.58 (1.23 to 2.02) [n=4; I^2=83%]	1.14 (0.94 to 1.39) [n=12; I^2=54%]
<40 y	≥40 y	5.42 (1.51 to 19.43) [n=2; I^2=95%]	2.31 (2.03 to 2.62) [n=3; I^2=19%]
Depression	No depression	2.38 (1.92 to 2.94) [n=1]	2.49 (1.63 to 3.80) [n=4; I^2=78%]
Anxiety	No anxiety	2.80 (2.23 to 3.52) [n=1]	2.79 (2.05 to 3.79) [n=3; I^2=0%]
Any mental health diagnosis	No mental health diagnosis	2.65 (1.31 to 5.38) [n=4; I^2=95%]	3.05 (2.56 to 3.64) [n=3; I^2=33%]
Previous opioid use/abuse	No previous opioid use/abuse	2.83 (0.97 to 8.23) [n=3; I^2=68%]	4.42 (2.33 to 8.41) [n=3; I^2=81%]
Benzodiazepine use	No benzodiazepine use	2.08 (0.88 to 4.93) [n=2; I^2=87%]	[n=0]
Alcohol use/abuse	No alcohol use/abuse	1.99 (0.58 to 6.89) [n=3; I^2=88%]	1.46 (1.07 to 1.99) [n=6; I^2=70%]
Tobacco use/abuse	No tobacco use/abuse	1.46 (1.03 to 2.08) [n=1]	2.03 (1.46 to 2.83) [n=5; I^2=43%]
Any substance use	No substance use	2.75 (1.54 to 4.92) [n=5; I^2=86%]	4.21 (2.55 to 6.97) [n=6; I^2=82%]
Any chronic pain	No chronic pain	0.82 (0.68 to 0.99) [n=1]	[n=0]
Back pain	No back pain	1.82 (1.48 to 2.24) [n=2; I^2=24%]	1.25 (1.11 to 1.40) [n=3; I^2=0%]
Headache disorder	No headache disorder	1.16 (0.90 to 1.50) [n=1]	1.27 (1.11 to 1.45) [n=2; I^2=0%]
Fibromyalgia	No fibromyalgia	1.28 (0.92 to 1.77) [n=2; I^2=83%]	[n=0]
Arthritis	No arthritis	0.74 (0.43 to 1.25) [n=2; I^2=95%]	0.74 (0.64 to 0.87) [n=2; I^2=0%]
Neuropathic pain	No neuropathic pain	1.15 (0.97 to 1.37) [n=2; I^2=0%]	[n=0]
Hepatitis C	No hepatitis C	1.56 (0.80 to 3.05) [n=1]	[n=0]
Liver disease	No liver disease	2.09 (0.62 to 7.03) [n=1]	[n=0]
	Units of measure		
Pooled mean difference between patients misusing vs not misusing opioids for continuously measured risk factors			
Age	Years	−14.85 (−18.95 to −10.75) [n=3; I^2=97%]	−4.85 (−8.32 to −1.39) [n=8, I^2=80%]
Opioid dose	Milligram morphine equivalents/day	44.80 (37.28 to 52.32) [n=1]	104.30 (56.85 to 151.75) [n=3; I^2=51%]
Opioid supply	Days	55.40 (47.67 to 63.13) [n=1]	[n=0]

characteristics associated with reduced odds of opioid misuse (Appendix E2, available online at http://www.annemergmed.com[3,23]). Being married, being white, having completed high school, and reporting chronic pain, headaches, fibromyalgia, neuropathic pain, liver disease, or any disability were not associated with opioid misuse (Appendix E2, available online at http://www.annemergmed.com[4-6,19,21,22,24,25,27]). Among 6 meta-analyzed continuous risk factors, younger age, increased pain, longer exposures to opioids, and greater opioid doses were associated with the development of misuse (Table 1; Appendix E2, available online at http://www.annemergmed.com[28-33]).

We performed planned subgroup analyses to explore the effect of opioid-naive status, outcome ascertainment method, and study design on our effect size estimates (Table 2; Appendix E2, available online at http://www.annemergmed.com). Male sex, use of any short-acting opioids, nonsteroidal anti-inflammatory drug use, back pain, and headache disorders were the only effect sizes that varied significantly in any of the subgroup analyses, with only one change in effect direction for headache disorder by both study design and outcome ascertainment (Table 2; Appendix E2, available online at http://www.annemergmed.com). We also performed sensitivity analyses to explore the effect of study sample size on the heterogeneity of each meta-analysis. We observed that removal of studies with the narrowest CIs in each meta-analysis reduced heterogeneity without significant changes to most pooled estimates (data not shown).

In subgroup analyses to explore the effect of baseline opioid exposure (Table 2), we limited our analyses to studies that clearly defined their population as being either opioid naive or opioid tolerant (ie, long-term use). This reduced the heterogeneity of our estimates for most variables (Table 2; Appendix E2, available online at http://www.annemergmed.com). In these analyses, the same risk factors were associated with opioid misuse in opioid-naive and -nonnaive patients, although the association between each risk factor and opioid misuse tended to be highest among studies of opioid-naive patients. Mean age and opioid dose were lower among opioid-naive patients compared with opioid-tolerant ones.

The findings for most risk factors did not vary significantly by study design (Appendix E2, available online at http://www.annemergmed.com). Statistical heterogeneity was reduced for only 2 risk factors and not for any other variables we examined. The size and direction of effect of headache disorder on opioid misuse was protective in cross-sectional studies (OR 0.61; 95% CI 0.40 to 0.92), but not in retrospective cohorts (OR 1.23; 95% CI 1.10 to 1.37). This was the only variable that differed in the direction of its effect size between study designs.

Subgroup analysis by method of outcome ascertainment reduced heterogeneity for 9 variables, including sex, marital status, nonsteroidal anti-inflammatory drug use, previous opioid use, alcohol use, illicit drug use history, back pain, headache disorder, and arthritis (Appendix E2, available online at http://www.annemergmed.com). The association between these 9 risk factors and opioid misuse was consistently strongest in studies with practitioner-diagnosed misuse compared with self-reported or derived outcomes. Marital status, race, and back pain were all significantly associated with opioid misuse only when limited to studies with practitioner-diagnosed outcomes. Headache disorders were significantly protective in studies measuring patient-reported opioid misuse (OR 0.64; 95% CI 0.43 to 0.95) but a significant risk factor in studies with practitioner-diagnosed misuse outcomes (OR 1.23; 95% CI 1.10 to 1.38).

Tables 1 and 2 summarize the risk-of-bias assessments for all included studies. Greater than half of the meta-analyzed articles were rated as having high risk of bias compromising internal validity (28/47; 60%) because of measurement bias, uncontrolled confounding, or both. The most common reason for this was lack of adjustment for potential confounders in almost all studies (27/28; 96%). Sensitivity analyses removing studies at high risk of bias affected the reported effect size for only one variable (Table 1). Removing studies at high risk of bias because of compromised internal validity narrowed the CIs for being married (OR 0.55; 95% CI 0.40 to 0.74), having chronic pain (OR 0.80; 95% CI 0.72 to 0.89), headache disorders (OR 1.23; 95% CI 1.10 to 1.37), and a disability (OR 2.18; 95% CI 1.34 to 3.55), and they became statistically significant. The size and direction of effect remained constant for all other risk factors (Table 1).

Several studies were rated as having high risk of bias compromising external validity (19/47; 40%) because of selection bias or lack of generalizability to patients with noncancer pain (eg, specialized population). The most common reason was the recruitment of patients from one site only (12/19; 63%). Removal of studies with poor external validity showed minor effects on pooled estimates, with no significant changes in effect size or direction (Table 1).

During qualitative analysis, 2 of the 4 studies reporting on income level found low income to be associated with opioid misuse.[42,60] Three studies investigated the effect of publicly funded government insurance programs compared

with private insurance plans as risk factors for opioid misuse.[38,50,95] One found public insurance to be associated with misuse,[38] whereas 2 reported commercial insurance to be associated with misuse.[50,95]

Qualitative analyses of hypertension, body mass index, marijuana use, the site of reported pain, bipolar disorder, schizophrenia, personality disorders, and distance from prescriber found that these factors were not significantly or were inconsistently associated with opioid misuse.

LIMITATIONS

Our systematic review is not without limitations. We were only able to report on each of our findings independently and were unable to quantitatively explore interactions between risk factor variables (eg, between age and sex). All studies included in our quantitative syntheses were observational, and therefore our findings have the potential to be affected by residual and uncontrolled confounding. For example, hepatitis C was shown to be a risk factor for opioid misuse. However, it is more likely that illicit drug use is associated with both hepatitis C and opioid misuse. We were unable to assess provider- and system-level risk factors because we were unable to find enough studies examining these factors. It is possible that targeting factors at these levels—for example, targeting prescribing intensity at the provider level—would have a larger influence on reducing prescription opioid misuse than patient-level factors.[26]

Most of our analyses had high I^2 scores that improved marginally on subgroup analyses. Before meta-analysis, we removed all studies with clinically heterogeneous populations compared with other included studies (eg, we removed studies of inpatients with acute pain). We observed that the effect sizes reported by the remaining studies were mostly consistent in direction for each risk factor. As such, the high I^2 values reported in many of the meta-analyses could simply reflect the variation in sample sizes between the included studies. Many of the included studies had narrow CIs, which led to little overlap between studies reporting similar effects. We observed that removal of studies with the narrowest CIs in each meta-analysis reduced heterogeneity without significant changes to most pooled estimates, indicating that the high I^2 scores were likely due to variation in sample sizes of our included studies and less likely due to true heterogeneity between studies.[96]

DISCUSSION

Our main objective was to synthesize the available evidence on patient-, provider-, drug-, and system-level risk factors for the development of opioid misuse among patients prescribed opioids. Of the 33 factors we examined, we found that younger age, male sex, current licit or illicit substance use or a history of either one, and mental health diagnoses were consistently associated with an increased risk of developing opioid misuse.

One narrative review identified past or current substance abuse, untreated psychiatric disorders, and younger age, but not sex, as risk factors for opioid-use disorder.[97] Another narrative review identified these variables and male sex as important risk factors for opioid abuse or misuse.[98] In contrast, a systematic review of transnational trends in prescription drug misuse among women found significantly higher rates of misuse among women with mental health illness and among those misusing other substances, but stated that women abused prescription drugs at rates equal to or higher than those of men.[99]

We found that male outpatients were 23% more likely to misuse opioids compared with female outpatients. Previous research has not clarified whether male sex is a risk factor for opioid misuse. Our findings mirrored both the general sex and age trends in opioid substance use disorder and nonmedical opioid use prevalence from 2 nationally representative samples of adult Americans.[100,101] It is possible that this inconsistency in whether male sex is identified as a risk factor is due to an interaction between sex and age. Vasilenko et al[100] demonstrated that only younger male individuals were at higher risk of opioid substance use disorder compared with female individuals, whereas both sexes older than 60 years demonstrated similar rates of opioid substance use disorder.[100] The studies included in our review included a disproportionate number of younger patients, which could have strengthened the effect of male sex. It is also possible that the inconsistency in the literature is due to the outcome definition used. Back et al[101] found significantly higher rates of nonmedical opioid use in male individuals but similar rates of prescription opioid abuse or dependence in both sexes. The literature demonstrates that men typically engage in riskier behaviors (ie, taking drugs) to conform to social pressures compared with women, but that women who engage in these behaviors escalate more rapidly from casual drug use to abuse and addiction.[102-104] Because we used a more inclusive outcome definition, we may have been more likely to capture men misusing opioids recreationally who did not go on to develop opioid addiction. Increased prevalence of recreational opioid misuse among younger men could therefore explain the increased odds of opioid misuse among men in our review.

Our findings indicate that younger patients are at twice the risk of opioid misuse compared with older ones and that younger opioid-naive patients are 5 times more likely to misuse opioids than older ones. It has been argued that prescription drug misuse is common among younger individuals because of ease of access to these drugs from family and friends.[99] However, we found that younger individuals were still at greater risk of opioid misuse when prescription opioids were equally accessible across all age groups. This finding could be an example of survivorship bias, in which older opioid misusers have died or had the time to undergo lengthy treatment to overcome their addiction, whereas younger patients have not. However, if this were the case, we would not have observed increased risk for younger patients when the analyses were limited to opioid-naive patients. It is possible that younger patients are simply more vulnerable to addiction than older ones,[105] which is consistent with findings from a prospective study demonstrating that individuals regularly exposed to addictive substances in adolescence were more likely to continue to use substances later in life.[105-107]

Genetic and environmental influences are also known to affect substance use and misuse.[108] Therefore, it is not surprising that patients who previously used or misused nonopioid substances (eg, benzodiazepines, alcohol, tobacco) have been shown to be 2 to 4 times more prone to engaging in misuse when prescribed opioids than those who had never used or misused substances. However, studies measuring both substance use as a potential risk factor and opioid misuse as an outcome are also at risk of misclassifying substance users as opioid misusers because of crossover in definitions, ascertainment methods, or both. For example, concurrent abuse of alcohol or illicit drugs is listed as a diagnostic criterion for opioid aberrant drug behavior,[16] and evidence of illicit substances was often all that was required for a positive urine screen result for opioid misuse.[25,32,69,79,94] Fortunately, the only study included in this review that reported on alcohol and illicit drug use as risk factors for opioid misuse measured with a urine screen used a prospective cohort design. Therefore, it is unlikely that our pooled effect sizes for alcohol or illicit substance use were significantly affected.

Our study found that individuals with mental health diagnoses were twice as likely to misuse prescribed opioids. Individuals may misuse prescribed drugs for psychological effects, to self-medicate for withdrawal symptoms, or to substitute or complement the use of other substances.[97,109] A study of US veterans found that prescription opioid and heroin use was most often motivated by the need to alleviate physical or emotional pain.[110] Patients with mental health diagnoses may misuse opioids to self-treat mental health symptoms (eg, anxiety, stress) or to counteract adverse effects of stimulant medications, or, conversely, could be more likely to receive a diagnosis of mental health illness once addicted. Finally, it is possible that patients with mental health diagnoses were misclassified as opioid misusers according to urine toxicology screening if their prescribed medication was on the list of banned substances in urine screens for opioid misuse (eg, benzodiazepines).

Recognizing the higher risk of opioid misuse associated with a previous or concurrent history of substance use and mental health diagnoses, Canadian guidelines recommend withholding prescribed opioids to patients with a history of substance use or mental illness.[111] US guidelines recommend extra monitoring and counseling for these patients but do not currently recommend against prescribing opioids to them.[112] We believe that more careful opioid prescribing in this group is warranted not only to reduce the risk of developing opioid misuse but also because patients with mental health diagnoses are overrepresented among those who are currently receiving prescribed opioids in the United States.[113] We suggest that practitioners carefully counsel patients who they believe require opioids and who have these risk factors, and that they minimize the use and duration of opioids prescribed. Our results show that not all patients are of equal risk. Although we suggest a careful approach to prescribing opioids for all patients who require pain relief beyond the emergency department, extra caution is warranted for those with high-risk features. We suggest that patients with high-risk features be prioritized for referral for alternative pain management strategies to assist in obtaining effective pain relief while minimizing the need for opioid analgesics.

In our sensitivity analyses, we found that some pooled effect sizes were higher and more precise when we included only studies in which health care practitioners diagnosed substance misuse compared with studies in which misuse outcomes were reported by patients or derived from aberrant drug-related behaviors recorded in patient charts or administrative data. Although self-reported outcomes may underestimate opioid misuse because of recall and social desirability biases, and administrative records may underreport drug-related behaviors and outcomes, we found little evidence thereof. We found associations between back pain and headache disorders and the risk of opioid misuse only when limiting our analyses to studies in which health care providers diagnosed opioid misuse. Although this could indicate that practicing health care providers may be more likely to associate these presentations with drug-seeking behavior, these associations were weak. However, effect sizes for all other risk factor

variables did not vary significantly during planned subgroup analyses, indicating that our findings were robust.

In summary, understanding risk factors for opioid misuse among patients who require analgesia has the potential to inform opioid prescribing. Of the risk factors examined, patients with concurrent substance use or mental health disorders or a history of either one were at highest risk for prescription opioid misuse. Clinicians should always prioritize nonopioid pain management strategies but, when an opioid is deemed absolutely necessary, should pay particular attention to these risk factors that place the patient at even greater risk of developing misuse.

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IMAGES IN EMERGENCY MEDICINE

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DIAGNOSIS:

Spontaneous diaphragmatic hernia with colonic incarceration. The chest radiograph (Figure 1) and chest CT (Figure 2) demonstrated findings of bowel herniation through the diaphragm on the right side. CT scan of the abdomen and pelvis (Figure 3) showed portal venous gas, concerning for bowel incarceration and colonic ischemia. The patient was taken to the operating room for urgent surgery and had reduction of her right-sided diaphragmatic hernia, primary diaphragmatic repair, and a right-sided hemicolectomy with ileocolic anastomosis. She was discharged home later that week without complications.

Spontaneous diaphragmatic hernia is a rare surgical emergency; its incidence is unknown.[1,2] Most diaphragmatic hernia cases occur in neonates or in the setting of trauma, and are less likely to be spontaneous in adults. Physical examination findings can include absent breath sounds unilaterally, nausea, and vomiting. Treatment involves urgent operative repair.

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2. Losanoff JE, Edelman DA, Salwen WA, et al. Spontaneous rupture of the diaphragm: case report and comprehensive review of the world literature. *J Thorac Cardiovasc Surg*. 2010;139:e127-e128.