PREVALENCE AND PREDICTORS OF OPIOID USE DISORDER

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FOLLOWING PRESCRIPTION OF OPIOIDS FOR CHRONIC NONCANCER

PAIN: A SYSTEMATIC REVIEW AND META-ANALYSIS OF

OBSERVATIONAL STUDIES

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TITLE: Prevalence and predictors of opioid use disorder following prescription of opioids for chronic noncancer pain: A systematic review and meta-analysis of observational studies

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LAY ABSTRACT

Opioids are commonly prescribed for patients with chronic pain that is not due to cancer; however, long-term opioid use inevitably leads to physical dependence and may result in addiction. Prior studies have reported extremely variable rates of opioid use disorder (OUD) following prescription for chronic noncancer pain, ranging from less than 1% to more than 50%, which has led to considerable confusion. My systematic review found moderate certainty evidence that the prevalence of OUD following prescription for chronic pain is 5.8% (95% CI: 2.8% to 9.5%). Patients who were younger, current smokers, males, and had a history of mental health disorders, had a higher risk of developing OUD. These findings will help support shared care decision-making between patients with chronic pain considering opioid therapy and their healthcare providers.

ABSTRACT

BACKGROUND

Despite the many harms and limited efficacy of opioids in managing chronic noncancer pain (CNCP), they are commonly prescribed for these patients in North America. One of the harms associated with prolonged opioid use is opioid use disorder (OUD); however, the risk of addiction is uncertain. We systematically reviewed observational studies to establish the prevalence of (OUD), and to explore factors associated with OUD in patients with CNCP.

METHODS

We searched MEDLINE, EMBASE, CINAHL, Cochrane Library, and PsycINFO from inception to December 2018 to identify studies that explored the prevalence of OUD or risk factors for OUD in patients with CNCP. Two specialists in addiction medicine reviewed each potentially eligible study, blinded to results, to ensure their outcome met DSM-5 criteria for OUD. We pooled estimates of OUD across eligible studies using random-effects models. When possible, we pooled estimates of association with OUD for all independent variables reported by more than one study.

RESULTS

Twenty-two studies reported the prevalence of OUD, and six studies reported the association of 36 factors with OUD in patients with CNCP. The pooled prevalence of OUD

was 20% (95% CI: 15% to 25%); however, we found evidence for small study effects (interaction p<0.001). When restricted to larger studies (≥900 patients), the pooled prevalence of OUD was 5.8% (95% CI: 2.8% to 9.5%; moderate certainty evidence). The prevalence of OUD was not associated with level of certainty of OUD criteria, under- or overestimation of instruments compared to DSM-5 criteria, severity of OUD, or risk of bias (interaction p values ranged from 0.34 to 0.92). Moderate certainty evidence demonstrated an association between OUD and male sex (OR 1.50 [95% CI: 1.05 to 2.14]; absolute risk increase (ARI) 2.7% [95% CI: 0.3% more to 5.8% more]), current smokers (OR 1.63; [95% CI: 1.25 to 2.12]; ARI 3.3% [1.3% more to 5.7% more]), and a history of mental health disorders (OR 1.49 [95% CI: 1.17 to 1.89]; ARI 2.6% [95% CI: 0.9% more to 4.6% more]). Low certainty evidence demonstrated an association between OUD and younger age (OR for every 10-year decrement, 1.60 [95% CI: 1.11 to 2.30]; ARI, 3.2% for every 10-year decrement [95% CI: 0.6% more to 6.6% more]). Moderate certainty evidence suggested no association between OUD and a history of alcohol abuse/dependence (OR 1.32 [95% CI: 0.84 to 2.07]; ARI 1.7% [95% CI: 0.9% less to 5.5% more]), and low certainty evidence suggested no association between OUD and a history of drug abuse (OR 1.51 [95% CI: 0.75 to 3.02]; ARI 2.7% [95% CI: 1.4% less to 9.9% more]).

CONCLUSION

Moderate certainty evidence suggests that 6% of CNCP patients prescribed opioids will develop OUD. Younger men who smoke, with a history of mental health disorders, are at

higher risk. Additional research is needed to establish the association between OUD and a

history of drug or alcohol abuse.

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LIST OF ABBREVIATIONS

AAPM	American Academy of Pain Management
ABC	Addiction Behaviors Checklist
ARI	Absolute Risk Increase
CI	Confidence Intervals
CNCP	Chronic Noncancer Pain
COMM	Current Opioid Misuse Measure
DSM	Diagnostic and Statistical Manual of Mental Disorders
GBD	Global Burden of Disease
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HR	Hazard Ratio
ICD	International Classification of Diseases
IQR	Interquartile Range
LR	Likelihood Ratio
NIDA	National Institute of Drug Abuse
OR	Odds Ratio
OUD	Opioid Use Disorder
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RR	Relative Risk
SOAPP-R	Screener and Opioid Assessment for Patients with Pain
WHO	World Health Organization

DECLARATION OF ACADEMIC ACHIEVEMENT

As the primary author of this Master's thesis, I was responsible for the majority of the work. I drafted the original protocol for this systematic review in conjunction with Drs. Jason Busse and Li Wang. My responsibilities included: developing the timeline for the project; designing the search strategy in collaboration with our research librarian (Rachel Couban); coordinating the reviewers (Ms. Elena Kum, Dr. Elie Isenberg-Grzeda, Gwendolyn Lovsted, Ms. Atefeh Noori, Dr. Patrick Jiho Hong, Dr. Yasir Rehman, Mr. Mahmood Amin Lari, Ms. Kayli Culig, Dr. Nooralhuda Bakaa, and Ms. Alexandra Nieuwesteeg); coordinating the addiction medicine specialists (Drs. James MacKillop and Jennifer Brasch), designing the screening forms; retrieving all titles and abstracts; and designing the data abstraction forms in conjunction with Dr. Wang. As the first reviewer, I was involved in the screening of every article and abstracted data for each included study. I calculated the kappa statistic for inter-rater reliability. In conjunction with Dr. Wang, I helped design the statistical analysis plan, and Dr. Wang performed the meta-analyses. I wrote every section of the manuscript for this systematic review.

CHAPTER 1: INTRODUCTION

1.1 Burden of Chronic Noncancer Pain

Chronic noncancer pain (CNCP) includes any painful condition that is not associated with malignant disease and lasts for three months or longer.[1] CNCP is a leading cause of disability worldwide. In fact, it is estimated that up to 22% of primary care patients worldwide live with CNCP,[2-4] with back pain being the most common cause.[5] In the 2015 Global Burden of Disease (GBD) study, neck pain and low back pain were the leading causes of disability in most countries, and the second leading causes of disability after ischemic heart disease in high-income countries.[6] In the 2017 GBD study, low back pain remained the second leading cause of disability after ischemic heart disease in high-income countries.[7] CNCP interferes with activities of daily living and has a major negative impact on quality of life and physical function,[8] and is the leading cause of health resource utilization among working-age adults.[9-12] It is expected that the burden of CNCP will increase as the population ages.

1.2 The Opioid Epidemic

Opioids are commonly prescribed for acute pain, palliative care, and CNCP. In patients with CNCP, long-term opioid use is associated with adverse events including opioid-induced hyperalgesia, vomiting, physiological dependence, nonfatal and fatal overdose, and opioid use disorder.[13-19] Furthermore, the effectiveness of long-term opioid use in patients living with chronic pain remains controversial;[19-22] a recent systematic review of

96 trials (26,169 patients) found that opioid use was associated with statistically significant but small improvements in pain (mean difference [MD] −0.69cm on the 10cm Visual Analogue Scale, 95% confidence interval [CI]: −0.82cm to −0.56cm) and physical functioning (MD 2.04 points on the 100-point Short Form-36 Physical Component Score, 95% CI: 1.41 to 2.68 points).[19] The 2017 Canadian Guideline for Opioids for Chronic Pain recommends optimization of nonpharmacologic therapy and nonopioid pharmacotherapy before opioids are considered, and restriction of the prescribed dose to less than 90mg morphine equivalents daily (and ideally less than 50mg morphine equivalent dose [MED]) for patients with CNCP who initiate opioid therapy.[22]

Despite the many harms and limited efficacy of opioids in managing CNCP, the rates of opioid prescribing have quadrupled in the United States over the past three decades,[13,23,24] and Canada has the second highest rate per capita of opioid prescribing in the world when measured using defined daily doses.[25] In the United States, 47,600 Americans died of opioid overdose in 2017[26] and in Canada, there were 4,460 opioid-related deaths in 2018, with most deaths attributed to fentanyl or fentanyl analogues.[27]

1.3 Prevalence of Opioid Use Disorder

Historically, the rates of problematic prescription opioid use have been difficult to estimate in patients with CNCP, partly due to the lack of universally accepted definitions and criteria for terms such as misuse, abuse, dependence and addiction.[28,29] This has led to inconsistencies in determining the prevalence of addiction in patients with CNCP who are

prescribed opioids, with reported rates ranging between 0.2% and 31%.[21,30-33] Until 2013, the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)[34] diagnosed clinically harmful substance use as either "substance abuse disorder" or "substance dependence disorder," two separate diagnoses with the former putatively reflecting a lower severity variant. This separation of "substance abuse" and "substance dependence" has led to confusion and substantial conceptual issues. In 2013, as a result of the conceptual issues raised in the DSM-IV, the DSM-5 largely combined these two diagnoses into a single category of Substance Use Disorder, which includes the diagnosis of Opioid Use Disorder (OUD).[35] The DSM-5 also changed the diagnostic threshold, removed the "legal problems" criterion and added "craving" as a criterion.[35] The impact of these changes in the diagnostic criteria on estimates of OUD is not entirely clear; there is conflicting evidence as to whether or not these changes affect the prevalence of OUD.[36,37] In the DSM-5, a diagnosis of OUD is made when patients meet two or more criteria from a list of 11, with a qualifier of "mild," "moderate," or "severe" (Figure 1).[35] If two to three criteria are met, it is considered mild; if four to five criteria are met, it is considered moderate; and if six or more criteria are met, it is considered severe.[35] Two criteria (tolerance and withdrawal) are not considered to meet the DSM-5 diagnosis of OUD if opioids are taken solely under medical supervision.[35]

A 2008 literature review[30] reported that the rate of opioid abuse/addiction, which they sorted into 3 groups: "addiction development on exposure to opioids," "demonstration of adverse drug-related behaviors," and "urine toxicology results," was 3.3%. However, there

are some limitations to this review: they combined rates of abuse with addiction, they simply took the weighted average of "alleged addiction" for all studies without considering variability, they did not perform meta-analyses, and they did not assess overall certainty of the evidence.[30]

A 2010 systematic review[21] assessed the safety, efficacy and effectiveness of long-term opioids for CNCP and reported that the prevalence of addiction, which was not defined by the authors, was 0.3%. However, on review of the two included studies, one[38] reported rates of "drug-seeking behavior" which were classified as possible drug abuse or dependence, and the other[39] reported the rate of requesting dose increases, but neither of those definitions met DSM-IV diagnostic criteria for opioid abuse or dependence.

A 2015 systematic review[31] assessed the prevalence of problematic opioid use in patients with chronic pain and reported that the rate of addiction, which they defined as "pattern of continued use with experience of, or demonstrated potential for, harm (e.g. 'impaired control over drug use, compulsive use, continued use despite harm, and craving')," ranged between 8% and 12% (95% CI: 3% to 17%).[31] However, they combined studies with different definitions of misuse, abuse and addiction without considering the nuanced language used in meeting diagnostic criteria for standardized definitions such as the DSM-IV[34] or DSM-5[35] or the International Classification of Diseases (ICD).[40] Furthermore, Vowles et al.[31] did not assess overall certainty of the evidence, or perform meta-analyses.

1.4 Predictors of Opioid Use Disorder

A 2008 systematic review[41] attempted to determine predictors of opioid abuse and misuse in patients with chronic pain, which they did not clearly define. They concluded that, although some studies had suggested that male gender, history of substance abuse, history of psychiatric disorders, and history of legal problems may be risk factors for opioid misuse, no set of predictor variables was sufficient to identify chronic pain patients at risk for opioid misuse or abuse. This review did not assess risk of bias for the included studies, nor overall certainty of evidence, and they did not perform meta-analyses.

A 2019 systematic review[42] investigated factors associated with opioid addiction in patients with mostly chronic pain and found that a history of OUD or other substance use disorder (likelihood ratio (+LR) range, 17-22), personality disorder (+LR 27, 95% CI: 18 to 41), somatoform disorder (+LR 12, 95% CI: 7.18-18), psychotic disorder (+LR 11, 95% CI: 8.5-14), and concomitant prescription of certain psychiatric medications (+LR, 17, 95% CI: 15 to 18), were all associated with a higher risk of opioid addiction. They also found that the absence of a mood disorder was associated with a lower risk of opioid addiction (-LR 0.50, 95% CI: 0.45 to 0.52).[42] However, this review did not assess the overall certainty of evidence nor report absolute measures of association to optimize interpretation of their findings. Another 2019 systematic review[43] investigated risk factors for prescription opioid misuse in patients with mostly chronic pain and found that current or previous substance use (OR 3.55, 95% 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) were associated with the development of opioid misuse. This review also did

not report absolute measures of association to optimize interpretation of their findings.

1.5 Rationale for This Study

Given the wide variability in the reported prevalence rates of OUD following prescription

of opioids for CNCP, and the limitations of previous systematic reviews, there is a need to

review the literature in this area. Therefore, the primary objective of this systematic review

is to establish the prevalence of OUD following prescription of opioids for CNCP. The

secondary objective is to explore the predictors of OUD following prescription of opioids

for CNCP.

CHAPTER 2: METHODS

2.1 Protocol Registration

We completed our systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement,[44] and registered our protocol with PROSPERO (registration number: CRD42019119184). Before performing our analysis, we included additional subgroup analyses to explore whether the following subgroups would be associated with higher rates of OUD: 1) DSM-5 criteria without conditional exclusions (i.e., including tolerance and withdrawal criteria) vs. criteria with these exclusions; 2) male vs. female sex; 3) instruments that our clinical experts felt may overestimate or underestimate rates of OUD compared to DSM-5; 4) lower vs. higher threshold for OUD; and 5) smaller vs. larger studies. We also conducted additional meta-regressions to explore whether a higher proportion of patients who were 1) males; 2) current smokers; 3) had a history of mental health disorders, 4) had a history of drug abuse, and 5) had a history of alcohol abuse; were associated with higher rates of OUD.

2.2 Data Sources and Search Strategy

We developed our search strategy with a health sciences librarian and systematically searched MEDLINE, EMBASE, CINAHL, Cochrane Library, and PsychINFO from inception to December 2018. There were no restrictions based on language of publication. We first developed a highly sensitive search strategy in MEDLINE and then modified it for use in other databases (Appendix 2). We also screened the reference lists of eligible

studies and previous reviews[31,42,43] When needed, we contacted authors for eligibility clarification, data verification, or to request missing data.

2.3 Eligibility Criteria

We included observational studies that evaluated the prevalence and/or predictors of OUD following prescription of opioids in adults aged 18 or older with CNCP. Eligible studies for establishing the prevalence of OUD included prospective or retrospective cohort studies and cross-sectional studies. For establishing predictors of OUD, eligible studies included prospective or retrospective cohort studies and case-control studies that explored, in an adjusted model, the association between independent factors and OUD. We excluded conference proceedings, editorials, narrative and systematic reviews, randomized controlled trials, and case series. When study populations overlapped by >50% among articles, we included only the study with the largest sample size and longest follow-up.

2.4 Study Selection

Pairs of reviewers, independently and in duplicate, screened titles and abstracts of identified citations and full texts of potentially eligible studies using standardized pilot-tested forms with detailed instructions (Appendix 3). Reviewers resolved disagreements by discussion, or through an arbitrator when disagreement remained. Two experts in addiction medicine, blinded to study results, independently adjudicated the case definition for each study according to the DSM-5 diagnostic criteria for OUD[35] into one of four groups: "OUD-strong certainty," "OUD-less certainty," "not OUD but a related outcome of clinical

interest," and "no outcomes of interest." For the purpose of this thesis, we only included studies that the clinical experts adjudicated as "OUD-strong certainty" or "OUD-less certainty." Our clinical experts also independently adjudicated whether each outcome would likely systematically "overestimate," "underestimate," or "provide similar rates" compared to the DSM-5 criteria for OUD.[35] We chose the outcome that would likely provide similar rates to DSM-5 criteria for OUD. Disagreements between the two experts were resolved by reaching consensus through discussion or by a third expert. We used online systematic review software (DistillerSR, Evidence Partners, Ottawa, Canada) to facilitate literature screening.

2.5 Risk of Bias Assessment and Data Abstraction

Pairs of reviewers trained in research methodology used standardized pilot-tested forms and a detailed instruction manual to extract data from all eligible studies, independently and in duplicate (Appendix 4). We collected information regarding study characteristics (i.e., author name, year of publication, study design, sample size, length of follow-up), intervention characteristics (i.e., type, dose and frequency and duration of opioid prescribed), and outcome data for prevalence rates of OUD, and predictors of OUD. We used outcome data from the longest follow-up time point reported for our analyses. When possible, rates of OUD data were recorded directly from the study text. When no specific rate was reported, a calculation was performed based on the number of patients meeting criteria for our case definition of OUD divided by the sample size.

Pairs of reviewers independently assessed risk of bias for all eligible studies guided by the Users' Guides to The Medical Literature criteria (Appendix 5).[45] The following criteria were assessed: (1) representativeness of the study population, (2) validity of outcome assessment, and (3) the proportion of missing data. We considered ≥20% loss to follow-up to represent a high risk of bias. We also assessed whether or not predictive models were appropriately adjusted. We defined a model as appropriately adjusted if it included age, sex, current or former substance abuse, and comorbid mental illness or psychotropic medication use as independent variables. Reviewers resolved disagreements through discussion or through an arbitrator.

2.6 Data Synthesis and Statistical Analysis

We used the kappa (k) statistic to measure inter-rater agreement of full-text screening.[46] Values of 0 to 0.20 represent slight agreement, 0.21 to 0.40 represent fair agreement, 0.41 to 0.60 represent moderate agreement, 0.61 to 0.80 represent substantial agreement, and >0.80 represents almost perfect agreement.[46]

We pooled the prevalence of OUD among eligible studies using random-effects models after performing a Freeman-Tukey Double Arcsine transformation to stabilize the variance.[47] If a study reported multiple definitions of opioid abuse, dependence or OUD, we chose the definition based on clinical interview over self-report, and where more than one was based on clinical interview, we chose the more recent nosological system (Appendix 6). When possible, we pooled all factors associated with OUD that were

reported by more than one study and presented ORs and associated 95% CI. If a study reported multiple regression models for different OUD-related outcomes, we chose the one that most closely approximated the DSM-5 definition of OUD (Appendix 6). When studies provided the measure of association as a RR or hazard ratio, we converted them to an OR if the baseline risk (i.e., the proportion of patients in the reference or unexposed group who did not have OUD at follow-up) was available.[48,49]

We calculated a single OR for converting categorical variables to continuous variables (i.e., age) using methods described in Appendix 7. If studies reported separate RR estimates for subgroups, we pooled related associations using the inverse variance method to generate an overall measure of association.[50] We used random-effects models for all meta-analyses. We used the following three criteria to identify predictors that were not amenable to pooling and showed promise for future research: 1) a statistically significant association with OUD of $p \leq 0.01$; 2) a large magnitude of association (OR ≥ 2.0 or ≤ 0.5); and 3) a sample size ≥ 500. To avoid overestimating the strength of association, we used an OR of 1 for predictors that were tested in bivariable analyses but were excluded from adjusted analyses because of nonsignificance or were included in multivariable analyses with the only information provided that they were not significant. We imputed an associated variance for all such predictors using the hot deck approach.[51] To facilitate interpretation, we calculated the absolute risk increase (ARI) for each predictor amenable to meta-analysis. We performed all statistical analyses using Stata statistical software version 15 (StataCorp, College Station, TX). All comparisons were 2-tailed, with a threshold p of 0.05.

2.7 Small Study Effects

We explored for small study effects by visual assessment of asymmetry of the funnel plot for the pooled prevalence of OUD, and for each pooled predictor and calculation of Begg's rank correlation test[52] and Egger's test,[53] when there were at least 10 studies in a meta-analysis. The funnel plots were developed with the prevalence of OUD on the horizontal axis, and the standard error or inverse variance on the vertical axis.

2.8 Subgroup Analyses and Sensitivity Analyses

We examined heterogeneity associated with all pooled analyses through visual assessment of forest plots.[54] We explored seven subgroup hypotheses to explain variability between studies, assuming larger associations with: 1) DSM-5 criteria without conditional exclusions (i.e., including tolerance and withdrawal criteria); 2) male sex; 3) instruments that our clinical experts considered to be "OUD-less certainty," such as the World Health Organization's (WHO) definition of addiction, authors' own definition of opioid abuse/addiction, National Institute of Drug Abuse's (NIDA) definition of prescription misuse or abuse, self-reported addiction, Portenoy's criteria, or a combination of the Current Opioid Misuse Measure (COMM) and the Addiction Behaviors Checklist (ABC); 4) instruments that would tend to overestimate rates of OUD compared to DSM-5, such as authors' own definition of opioid abuse/addiction, the NIDA's definition of prescription misuse or abuse, and a combination of the COMM and ABC; 5) lower threshold to designate OUD; 6) smaller studies; and 7) studies at higher risk of bias, on a criterion-by-criterion basis. We also conducted meta-regression to explore whether a higher proportion

of patients who were 1) males; 2) current smokers; 3) had a history of mental health disorders; 4) had a history of drug abuse; or 5) had a history of alcohol abuse; were associated with higher rates of OUD. We prioritized within-study subgroup analyses when possible to reduce risk of confounding, and between-study when not. We conducted subgroup analyses only if each subgroup contained two or more studies.

When possible, we performed sensitivity analyses to examine the effect of imputing data for nonsignificant predictors, and of converting categorical data for age to continuous data.

2.9 Certainty of Evidence

We used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology to summarize the quality of evidence on an outcome-by-outcome basis as high, moderate, low or very low.[54] Given a 5.8% baseline risk of OUD for patients prescribed opioids, after consulting with our clinical experts we estimated that a 2% increase in absolute risk would likely be sufficient to address modifiable risk factors, which can be directly targeted in an effort to reduce rates of OUD. We further estimated that an absolute increase in risk of 3% for a nonmodifiable factor would be sufficient to identify high-risk candidates for intervention. Therefore, we rated down for imprecision if the 95% CI associated with the ARI included 2% for modifiable risk factors or 3% for nonmodifiable risk factors.

CHAPTER 3: RESULTS

3.1 Literature Search Results

We identified a total of 12,013 unique records and retrieved 521 potentially eligible articles in full-text; of these, 11 cohort studies,[55-65] 12 cross-sectional studies,[66-77] and 1 case-control study[78] proved eligible for our review (Appendix 8, Figure 2). We excluded 7 studies with overlapping populations (Appendix 9). We also excluded 155 studies that were included in other reviews for the following reasons: (1) 100 studies did not use an outcome that met DSM-5 OUD criteria, (2) 40 studies were not restricted to CNCP patients prescribed opioid therapy, (3) 12 studies had ineligible study deigns for our review, and (4) 3 had overlapping populations with studies already included in our review (Appendix 10, Table 1). There was near perfect agreement (k = 0.85) among reviewers at the full-text review stage. We successfully contacted four of five authors to confirm eligibility[77,79,80] or to verify data.[55]

3.2 Description of Included Studies

Among our 24 eligible studies, 18 were conducted in the United States,[55-62,65-68,71,74-78] two in Australia,[63,64] one in Denmark,[72] one in Spain,[69] one in Israel,[70] and one in the United Kingdom[73] (Appendix 11, Table 2). Among the 22 studies[55-62,64-77] that reported prevalence of OUD following prescription of opioids for CNCP, the median sample size was 456 (interquartile range [IQR], 76 to 2,892). Among the 6 studies[55,58,61-63,78] that explored predictors of OUD, the median sample size was 1,198 (IQR, 89 to 2,752).

Only four studies[64,66,76,78] reported OUD as defined by DSM-5 criteria as their outcome, two[64,76] of which used DSM-5 OUD with conditional exclusions (i.e. excluding tolerance and withdrawal criteria). Seven studies[56,57,69-71,74,77] reported DSM-IV opioid abuse and/or dependence as their outcome, one study reported DSM-III opioid abuse and dependence,[73] two studies[63,72] reported ICD-10 opioid dependence and addiction, five studies[55,59-61,65] reported ICD-9 opioid abuse and/or dependence, one study[62] reported the World Health Organization's definition of opioid addiction, one study[68] reported the authors' own definition of opioid abuse, one study[58] reported the National Institute of Drug Abuse (NIDA)'s definition of prescription opioid misuse or abuse, one study[67] reported self-reported opioid addiction, and one study[75] reported opioid misuse as defined by a combination of the Current Opioid Misuse Measure (COMM) and the Addiction Behaviors Checklist (ABC).

After our clinical experts adjudicated the case definitions of the included studies, they considered 19 studies[55-57,59-61,63-66,69-74,76-78] to be "OUD – strong certainty" and five studies[58,62,67,68,75] to be "OUD – less certainty."

3.3 Risk of Bias Assessment

Two studies[74,78] were deemed to be at high risk of bias for not having a representative study population (Appendix 12, Table 3). Four studies[58,62,67,68] were deemed to be at high risk of bias for not using a valid outcome measure (Appendix 12, Table 3). Fifteen studies either

failed to report loss to follow up[60-62,65,68,74-77] or reported ≥20% loss to follow up[55,59,66,70,72,73] (Appendix 12, Table 3). Only three[55,60,61] of the six predictor studies[55,58,61-63,78] reported an adequately adjusted regression models (Appendix 12, Table 3). We were unable to assess for small study effects as there were less than 10 predictor studies (Appendix 13, Table 4).

3.4 Prevalence of Opioid Use Disorder

Twenty-two studies[55-62,64-77] reported prevalence of OUD, which ranged from 0.2% to 62%. The overall pooled prevalence rate was 20% (95% CI: 15% to 25%; Appendix 14, Figure 3). Only the use of DSM-5 criteria with conditional exclusions (excluding tolerance and withdrawal criteria) explained within-study heterogeneity, suggesting that DSM-5 criteria with conditional exclusions results in lower rates of OUD (22%, 95% CI: 20% to 23%) compared to DSM-5 criteria without conditional exclusions (27%, 95% CI: 26% to 29%; interaction p<0.001; Appendix 14, Figure 4). Meta-regression found evidence of small study effects (p=0.02; Appendix 14, Figures 5 & 6). After exploring the distribution, we identified that studies with <900 patients found systematically higher rates of OUD (34%, 95% CI: 24% to 45%) compared to studies with >900 patients (5.8%, 95% CI: 2.8% to 9.6%; interaction p<0.001; Appendix 14, Figure 7). Therefore, we focused on the nine large studies[55,58-61,64,65,71,76] with a pooled prevalence of 5.8% (95% CI: 2.8% to 9.6%), and we used this rate as the baseline risk for OUD. No significant between-study subgroup effects were detected for certainty of OUD criteria (Figure 8), under- or overestimation of instruments compared to DSM-5 criteria (Appendix 14, Figure 9), severity of OUD

(Appendix 14, Figure 10), sex (Appendix 14, Figure 11), and risk of bias (interaction p values ranged from 0.34 to 0.92; Appendix 14, Figures 12 and 13), or meta-regression for prevalence of OUD and loss to follow-up (interaction p=0.46; Appendix 14, Figure 14).

3.5 Predictors of Opioid Use Disorder

Six studies[55,58,61-63,78] involving 20,404 patients reported the association of 36 independent variables with OUD, five[55,58,61,63,78] of which were suitable for meta-analysis.

3.5.1 Sociodemographic Factors

We found low certainty evidence for a significant association between higher prevalence of OUD and younger age (OR for every 10-year decrement, 1.60 [95% CI: 1.11 to 2.30]; ARI, 3.2% for every 10-year decrement [95% CI: 0.6% more to 6.6% more]; Appendix 15, Figure 15; Table 4). We found moderate certainty evidence for a significant association between OUD and current smokers (OR 1.63 [95% CI: 1.25 to 2.12] ARI 3.3% [95% CI: 1.3% more to 5.7% more]; Appendix 15, Figure 16; Table 4), and male sex (OR 1.50 [95% CI: 1.05 to 2.14]; ARI 2.7% [95% CI: 0.3% more to 5.8% more]; Appendix 15, Figure 17; Table 4).

3.5.2 Clinical Factors

We found moderate certainty evidence for a significant association between OUD and history of mental health disorder (OR 1.49 [95% CI: 1.17 to 1.89]; ARI 2.6% [95% CI: 0.9% more to 4.6% more]; Appendix 15, Figure 18; Table 4). We did not find significant

subgroup effects for the associations of history of mental health disorders (interaction p=0.91 for optimally adjusted models vs. not optimally adjusted models; Appendix 16, Figure 19). Moderate certainty evidence showed no significant association between OUD and history of alcohol abuse/dependence (OR 1.32 [95% CI: 0.84 to 2.07]; ARI 1.7% [95% CI: 0.9% less to 5.5% more]; Appendix 17, Figure 20; Table 4). Low certainty evidence showed no significant association between OUD and history of drug abuse (OR 1.51 [95% CI: 0.75 to 3.02]; ARI 2.7% [95% CI: 1.4% less to 9.9% more]; Appendix 17, Figure 21; Table 4).

3.6 Subgroup Analyses, Meta-Regression, and Sensitivity Analyses

No additional subgroup analysis or meta-regression was significant, aside from those described above. We could not perform sensitivity analyses for the effect of imputing data for nonsignificant predictors as there was only one study.

CHAPTER 4: DISCUSSION

4.1 Summary of Principal Findings

We found moderate certainty evidence that approximately 6% of CNCP patients prescribed opioid therapy will develop OUD. The prevalence of addiction is increased by 3% for male sex (moderate certainty evidence), 3% each for current smoking status (moderate certainty evidence) or a history of mental health disorder (moderate certainty evidence), and may be increased by 3% for every 10-year decrement (low certainty evidence). Moderate certainty evidence showed no significant association between OUD and history of alcohol abuse/dependence, low certainty evidence showed no significant association between OUD and history of drug abuse. Investigators have tested 30 additional predictors that could not be statistically pooled (Appendix 18, Table 5; and Appendix 19, Table 6). Of these, non-adherence to opioids in the past 3 months warrants additional study.

4.2 Strengths

Our findings are strengthened by the use of explicit eligibility criteria and a comprehensive search that identified 16 studies that were not included in previous systematic reviews.[31,42,43] We also had two experts in addiction medicine adjudicate the case definitions of each potentially eligible study, and we only included those studies that our experts agreed met DSM-5 diagnostic criteria for OUD. We assessed risk of bias in individual studies and used the GRADE approach[36] to appraise the certainty of evidence.

We presented both relative risk increases and absolute risk increases, which more clearly convey the importance of associations.

4.3 Limitations

Our review has some limitations. First, there was substantial variability among included studies in the measurement of the prevalence of OUD as many studies used different instruments and diagnostic criteria to measure OUD. We attempted to mitigate this by having two experts in addiction medicine adjudicate the case definitions of each included study to determine the certainty (strong vs. less certainty) of meeting DSM-5 OUD criteria and we conducted subgroup analyses. We were only able to explain some of the variability by using the DSM-5 criteria with conditional exclusions (i.e. without tolerance and withdrawal criteria), and by small study effects. Second, given that some of the large studies used ICD codes from registry data, it's unclear whether all patients were individually assessed adequately for ICD criteria based on clinical interview, so it's possible that there may be systematic underreporting of OUD in the registry data. Third, one study[63] reported that history of illicit drug dependence was not associated with OUD (OR 0.75, [95% CI: 0.35 to 1.58]); however, inclusion of both illicit and prescription drug abuse in their adjusted model may have resulted in an interaction. We have contacted the study authors to explore this issue further.

4.4 Comparison with Existing Systematic Reviews and Meta-Analyses

Previous systematic reviews[21,30,31,33] have evaluated the prevalence of prescription opioid dependence or addiction in patients with CNCP, with reported rates ranging between 0.3% and 31%. However, those reviews had limitations, such as combining studies with different definitions opioid misuse, abuse, and addiction without considering the nuanced language used in meeting diagnostic criteria for standardized definitions such as the DSM-IV, DSM-5 or ICD; and in some cases,[30,31] they were unable to perform meta-analyses and did not assess overall certainty of the evidence.[30,31] Indeed, our review found substantial variability in the reported rates of the included studies, ranging from 0.2% to 62%; this amount of variability is consistent with previous reviews.[21,30,31,33] Our review is the first to have clinical experts adjudicate the case definitions of each potentially eligible study, conduct meta-analyses, and attempt to explain some of the variability. The results of our review may be different from previous reviews because: 1) previous reviews included 155 studies that were not included in our review; 2) our search included 16 studies that were not included in previous reviews; and 3) some of the previous reviews did not perform meta-analyses or attempt to explain some of the variability. We performed several subgroup analyses and found no subgroup effects for OUD prevalence from certainty of DSM-5 OUD criteria, different instruments, severity of OUD, sex, risk of bias and loss to follow-up.

Previous systematic reviews[41,42] have also qualitatively and quantitatively summarized risk factors for prescription opioid addiction in patients with CNCP. We confirmed and

quantified two of these associations: male sex and history of mental health disorders. We have also identified two additional predictors: younger age, and current smokers. In addition, while several studies[58,61,81-83] have reported that a history of substance abuse may be one of the most consistent predictors of misuse, we found low certainty evidence that history of alcohol abuse/dependence, and very low certainty evidence that history of drug abuse are not associated with OUD; however, the association was very imprecise which could be due to the small sample size of the included studies, or due to underreporting of substance use and abuse. It's also possible that one of the studies[63] had problems with their adjusted model – there may be an interaction between history of illicit drug abuse and history of legal past drug abuse (i.e. benzodiazepine). We were unable to confirm the association of concomitant psychiatric medication as suggested in a previous review[42] use due to the lack of reporting of this factor in the included studies.

Our review adds clarity to the contentious debate regarding the risk of OUD following prescription for CNCP, which some experts have suggested is less than 1% while others advocate a prevalence of 60% or greater. Our findings will better support evidence-based, shared-care decision making between patients with CNCP considering opioid therapy and their healthcare providers.

4.5 Future Research

High quality observational studies, using diagnostic criteria for DSM-5 OUD with conditional exclusions, are required to confirm our results and to explore history of substance abuse as a risk factor for developing OUD following prescription for CNCP.

CHAPTER 5: CONCLUSIONS

We found moderate certainty evidence that 6% of patients prescribed opioids for CNCP will develop OUD. Young males, current smokers, and those with a history of mental health disorders, may be at higher risk of developing OUD. Future research using diagnostic criteria for DSM-5 OUD with conditional exclusions, should further explore the prevalence of OUD, and explore history of substance abuse as a risk factor for developing OUD following prescription of opioids for CNCP.

REFERENCES

1. Merksey H, Bogduk N. *Task Force on Taxonomy of the International Association for the Study of Pain. Classification of chronic pain. 2nd Edition.* 2nd ed: International Association for the Study of Pain; 1994.

2. Gureje O, Von Korff M, Simon GE, Gater R. Persistent pain and well-being: a World Health Organization Study in Primary Care. *Jama.* 1998;280(2):147-151.

3. Clark JD. Chronic pain prevalence and analgesic prescribing in a general medical population. *Journal of pain and symptom management.* 2002;23(2):131-137.

4. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. *European journal of pain (London, England).* 2006;10(4):287-333.

5. Deyo RA, Weinstein JN. Low back pain. *The New England journal of medicine.* 2001;344(5):363-370.

6. Kassebaum N, Arora M, Barber R, et al. Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet.* 2016;388(10053):1603-1658. doi: 1610.1016/S0140-6736(1616)31460-X.

7. Kyu H, Abate D, Abate K, et al. Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet.* 2018;392(10159):1859-1922. doi: 1810.1016/S0140-6736(1818)32335-32333.

8. Hogan ME, Taddio A, Katz J, Shah V, Krahn M. Health utilities in people with chronic pain using a population-level survey and linked health care administrative data. *Pain.* 2017;158(3):408-416.

9. Loeser JD. Economic implications of pain management. *Acta anaesthesiologica Scandinavica.* 1999;43(9):957-959.

10. Lynch ME. The need for a Canadian pain strategy. *Pain research & management.* 2011;16(2):77-80.

11. Initiative OM. The White Paper on opioids and pain: a pan-European challenge: the European White Paper on the use of opioids in chronic pain management. *J Pain Palliat Care Pharmacother.* 2006;20(3):79-87.

12. *The high price of pain: the economic impact of persistent pain in Australia.* Sydney, Australia: MBF Foundation and University of Sydney Pain Management Research Institute;2007.

13. Prevention CfDCa. Prescription opioid overdose data. http://www.cdc.gov/drugoverdose/data/overdose.html. Published 2016. Accessed April 11, 2018.

14. Lee M, Silverman SM, Hansen H, Patel VB, Manchikanti L. A comprehensive review of opioid-induced hyperalgesia. *Pain physician.* 2011;14(2):145-161.
15. Atluri S, Sudarshan G, Manchikanti L. Assessment of the trends in medical use and misuse of opioid analgesics from 2004 to 2011. *Pain physician.* 2014;17(2):E119-128.
16. Birnbaum HG, White AG, Schiller M, Waldman T, Cleveland JM, Roland CL. Societal costs of prescription opioid abuse, dependence, and misuse in the United States. *Pain medicine (Malden, Mass).* 2011;12(4):657-667.
17. Martell BA, O'Connor PG, Kerns RD, et al. Systematic review: opioid treatment for chronic back pain: prevalence, efficacy, and association with addiction. *Annals of internal medicine.* 2007;146(2):116-127.
18. Passik SD. Issues in long-term opioid therapy: unmet needs, risks, and solutions. *Mayo Clinic proceedings.* 2009;84(7):593-601.
19. Busse J, Wang L, Kamaleldin M, et al. Opioids for Chronic Noncancer Pain: A Systematic Review and Meta-analysis. *Jama.* 2018;320(23):2448-2460. doi: 2410.1001/jama.2018.18472.
20. Chou R, Turner JA, Devine EB, et al. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. *Annals of internal medicine.* 2015;162(4):276-286.
21. Noble M, Treadwell JR, Tregear SJ, et al. Long-term opioid management for chronic noncancer pain. *The Cochrane database of systematic reviews.* 2010(1):Cd006605.
22. Busse JW, Craigie S, Juurlink DN, et al. Guideline for opioid therapy and chronic noncancer pain. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne.* 2017;189(18):E659-e666.
23. (CDC) CfDCaP. Vital signs: overdoses of prescription opioid pain relievers---United States, 1999--2008. *MMWR Morbidity and mortality weekly report.* 2011;60(43):1487-1492.
24. Abuse NIoD. America's addiction to opioids: heroin and prescription drug abuse. https://www.drugabuse.gov/about-nida/legislative-activities/testimony-to-congress/2016/americas-addiction-to-opioids-heroin-prescription-drug-abuse. Published 2014. Accessed April 11, 2018.
25. Board INC. *Narcotic drugs: Estimated world requirements for 2016 and statistics for 2014.*: International Narcotics Control Board;2015.
26. WONDER Database. Centers for Disease Control and Prevention; 2018. https://wonder.cdc.gov. Accessed September 11, 2019.
27. National Report: Apparent Opioid-related Deaths in Canada. 2019. https://health-infobase.canada.ca/datalab/national-surveillance-opioid-mortality.html. Accessed September 11, 2019.

28. Savage SR. Assessment for addiction in pain-treatment settings. *The Clinical journal of pain.* 2002;18(4 Suppl):S28-38.

29. Smith SM, Dart RC, Katz NP, et al. Classification and definition of misuse, abuse, and related events in clinical trials: ACTTION systematic review and recommendations. *Pain.* 2013;154(11):2287-2296.

30. Fishbain DA, Cole B, Lewis J, Rosomoff HL, Rosomoff RS. What percentage of chronic nonmalignant pain patients exposed to chronic opioid analgesic therapy develop abuse/addiction and/or aberrant drug-related behaviors? A structured evidence-based review. *Pain medicine (Malden, Mass).* 2008;9(4):444-459.

31. Vowles KE, McEntee ML, Julnes PS, Frohe T, Ney JP, van der Goes DN. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. *Pain.* 2015;156(4):569-576.

32. Boscarino JA, Rukstalis M, Hoffman SN, et al. Risk factors for drug dependence among out-patients on opioid therapy in a large US health-care system. *Addiction (Abingdon, England).* 2010;105(10):1776-1782.

33. Minozzi S, Amato L, Davoli M. Development of dependence following treatment with opioid analgesics for pain relief: a systematic review. *Addiction (Abingdon, England).* 2013;108(4):688-698. doi: 610.1111/j.1360-0443.2012.04005.x. Epub 02012 Oct 04018.

34. Association AP. *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).* 4th ed: American Psychiatric Association; 1995.

35. Association AP. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5).* 5th ed: American Psychiatric Association; 2013.

36. Boscarino JAR, MR; Hoffman, SN; Han, JJ; Erlich, PM; Ross, S; Gerhard, GS; Stewart, WF. Prevalence of prescription opioid-use disorder among chronic pain patients: comparison of the DSM-5 vs. DSM-4 diagnostic criteria. *J Addict Dis.* 2011;30(3):185-194. doi: 110.1080/10550887.10552011.10581961.

37. Peer K, Rennert, L., Lynch, K. G., Farrer, L., Gelernter, J., & Kranzler, H. R. Prevalence of DSM-IV and DSM-5 alcohol, cocaine, opioid, and cannabis use disorders in a largely substance dependent sample. *Drug Alcohol Depend.* 2013;127(1-3):215-219. doi: 210.1016/j.drugalcdep.2012.1007.1009. Epub 2012 Aug 1019.

38. Portenoy RK, Farrar JT, Backonja MM, et al. Long-term use of controlled-release oxycodone for noncancer pain: results of a 3-year registry study. *The Clinical journal of pain.* 2007;23(4):287-299. doi: 210.1097/AJP.1090b1013e31802b31582f.

39. Anderson VC, Burchiel KJ. A prospective study of long-term intrathecal morphine in the management of chronic nonmalignant pain. *Neurosurgery.* 1999;44(2):289-300; discussion 300-281. doi: 210.1097/00006123-199902000-199900026.

40.   International classification of diseases for mortality and morbidity statistics (11th Revision). In. Geneva: World Health Organization; 2018.

41.   Turk DC, Swanson KS, Gatchel RJ. Predicting opioid misuse by chronic pain patients: a systematic review and literature synthesis. *The Clinical journal of pain.* 2008;24(6):497-508.

42.   Klimas J, Gorfinkel L, Fairbairn N, et al. Strategies to Identify Patient Risks of Prescription Opioid Addiction When Initiating Opioids for Pain: A Systematic Review. *JAMA Netw Open.* 2019;2(5):e193365. doi: 193310.191001/jamanetworkopen.192019.193365.

43.   Cragg A, Hau JP, Woo SA, et al. Risk Factors for Misuse of Prescribed Opioids: A Systematic Review and Meta-Analysis. *Ann Emerg Med.* 2019;19(19):30342-30347.

44.   Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Annals of internal medicine.* 2009;2009 Aug 18;151(4):264-269.

45.   Randolph AC, D; Guyatt, G. Prognosis. In: *Users' guides to the medical literature: a manual for evidence-based clinical practice.* 3 ed. New York: McGraw-Hill; 2015:421-429.

46.   Viera AJ, Garrett JM. Understanding interobserver agreement: the kappa statistic. *Family medicine.* 2005;37(5):360-363.

47.   Freeman M, Tukey J. Transformations Related to the Angular and the Square Root. 1950.

48.   Wang Z. Converting Odds Ratio to Relative Risk in Cohort Studies with Partial Data Information. 2013.

49.   Grant R. Converting an odds ratio to a range of plausible relative risks for better communication of research findings. *BMJ (Clinical research ed).* 2014;348:f7450.(doi):10.1136/bmj.f7450.

50.   Higgins J, Green S. Cochrane handbook for systematic reviews of interventions version 5.1.0 [updated March 2011]. Cochrane. https://training.cochrane.org/handbook. Published 2011. Accessed October 18, 2019, 2019.

51.   Gelman A, Hill J. *Chapter 25. Missing-data imputation. Data Analysis Using Regression and Multilevel/Hierarchical Models.* New York, NY: Cambridge University Press; 2007.

52.   Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics.* 1994;50(4):1088-1101.

53.   Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ (Clinical research ed).* 1997;315(7109):629-634.

54.   Iorio A, Spencer FA, Falavigna M, et al. Use of GRADE for assessment of evidence about prognosis: rating confidence in estimates of event rates in broad categories of patients. *BMJ (Clinical research ed).* 2015;350:h870.

55.   Young-Wolff KC, Klebaner D, Weisner C, Von Korff M, Campbell CI. Smoking Status and Opioid-related Problems and Concerns Among Men and Women on Chronic Opioid Therapy. *The Clinical journal of pain.* 2017;33(8):730-737. doi: 710.1097/AJP.0000000000000461.

56.   Huffman KL, Shella ER, Sweis GW, Griffith SD, Scheman J, Covington EC. Nonopioid substance use disorders and opioid dose predict therapeutic opioid addiction. *The journal of pain : official journal of the American Pain Society.* 2015;16(2):126-134. doi: 110.1016/j.jpain.2014.1010.1011. Epub 2014 Nov 1018.

57.   Huffman KL, Sweis GW, Gase A, Scheman J, Covington EC. Opioid use 12 months following interdisciplinary pain rehabilitation with weaning. *Pain medicine (Malden, Mass).* 2013;14(12):1908-1917. doi: 1910.1111/pme.12201. Epub 12013 Aug 12205.

58.   Hylan TR, Von Korff M, Saunders K, et al. Automated prediction of risk for problem opioid use in a primary care setting. *The journal of pain : official journal of the American Pain Society.* 2015;16(4):380-387. doi: 310.1016/j.jpain.2015.1001.1011. Epub 2015 Jan 1029.

59.   Hoffman EM, Watson JC, St Sauver J, Staff NP, Klein CJ. Association of Long-term Opioid Therapy With Functional Status, Adverse Outcomes, and Mortality Among Patients With Polyneuropathy. *JAMA Neurol.* 2017;74(7):773-779. doi: 710.1001/jamaneurol.2017.0486.

60.   Edlund MJ, Martin BC, Russo JE, DeVries A, Braden JB, Sullivan MD. The role of opioid prescription in incident opioid abuse and dependence among individuals with chronic noncancer pain: the role of opioid prescription. *The Clinical journal of pain.* 2014;30(7):557-564. doi: 510.1097/AJP.0000000000000021.

61.   Edlund MJ, Steffick D, Hudson T, Harris KM, Sullivan M. Risk factors for clinically recognized opioid abuse and dependence among veterans using opioids for chronic non-cancer pain. *Pain.* 2007;129(3):355-362. doi: 310.1016/j.pain.2007.1002.1014. Epub 2007 Apr 1020.

62.   Bouckoms A, Masand P, Murray GB, Cassem EH, Stern TA, Tesar GE. Chronic Nonmalignant Pain Treated with Long-Term Oral Narcotic Analgesics. *Annals of Clinical Psychiatry.* 1992;4(3):185-192.

63.   Campbell G, Nielsen S, Larance B, et al. Pharmaceutical Opioid Use and Dependence among People Living with Chronic Pain: Associations Observed within the Pain and Opioids in Treatment (POINT) Cohort. *Pain medicine (Malden, Mass).* 2015;16(9):1745-1758. doi: 1710.1111/pme.12773. Epub 12015 May 12722.

64.   Degenhardt L, Bruno R, Lintzeris N, et al. Agreement between definitions of pharmaceutical opioid use disorders and dependence in people taking opioids for chronic non-cancer pain (POINT): a cohort study. *Lancet Psychiatry.* 2015;2(4):314-322. doi: 310.1016/S2215-0366(1015)00005-X. Epub 02015 Mar 00031.

65.   Coutinho AD, K. G, Fuldeore RM, Landsman-Blumberg PB, Gandhi S. Long-term opioid users with chronic noncancer pain: Assessment of opioid abuse risk and relationship with healthcare resource use. *J Opioid Manag.* 2018;14(2):131-141. doi: 110.5055/jom.2018.0440.

66.   Boscarino JA, Hoffman SN, Han JJ. Opioid-use disorder among patients on long-term opioid therapy: impact of final DSM-5 diagnostic criteria on prevalence and correlates. *Subst Abuse Rehabil.* 2015;6:83-91.(doi):10.2147/SAR.S85667. eCollection 82015.

67.   Callinan CE, Neuman MD, Lacy KE, Gabison C, Ashburn MA. The Initiation of Chronic Opioids: A Survey of Chronic Pain Patients. *The journal of pain : official journal of the American Pain Society.* 2017;18(4):360-365. doi: 310.1016/j.jpain.2016.1011.1001. Epub 2016 Dec 1013.

68.   Chabal C, Erjavec MK, Jacobson L, Mariano A, Chaney E. Prescription opiate abuse in chronic pain patients: clinical criteria, incidence, and predictors. *The Clinical journal of pain.* 1997;13(2):150-155.

69.   Coloma-Carmona A, Carballo JL, Rodriguez-Marin J, Perez-Carbonell A. Withdrawal symptoms predict prescription opioid dependence in chronic pain patients. *Drug Alcohol Depend.* 2019;195:27-32.(doi):10.1016/j.drugalcdep.2018.1011.1013. Epub 2018 Dec 1013.

70.   Feingold D, Goor-Aryeh I, Bril S, Delayahu Y, Lev-Ran S. Problematic Use of Prescription Opioids and Medicinal Cannabis Among Patients Suffering from Chronic Pain. *Pain medicine (Malden, Mass).* 2017;18(2):294-306. doi: 210.1093/pm/pnw1134.

71.   Fleming MF, Davis J, Passik SD. Reported lifetime aberrant drug-taking behaviors are predictive of current substance use and mental health problems in primary care patients. *Pain medicine (Malden, Mass).* 2008;9(8):1098-1106. doi: 1010.1111/j.1526-4637.2008.00491.x. Epub 02008 Aug 00418.

72.   Hojsted J, Nielsen PR, Guldstrand SK, Frich L, Sjogren P. Classification and identification of opioid addiction in chronic pain patients. *European journal of pain (London, England).* 2010;14(10):1014-1020. doi: 1010.1016/j.ejpain.2010.1004.1006. Epub 2010 May 1021.

73.   Kouyanou K, Pither CE, Wessely S. Medication misuse, abuse and dependence in chronic pain patients. *J Psychosom Res.* 1997;43(5):497-504. doi: 410.1016/s0022-3999(1097)00171-00172.

74.   Lovejoy TI, Dobscha SK, Turk DC, Weimer MB, Morasco BJ. Correlates of prescription opioid therapy in Veterans with chronic pain and history of substance use disorder. *J Rehabil Res Dev.* 2016;53(1):25-36. doi: 10.1682/JRRD.2014.1610.0230.

75.   McHugh RK, Weiss RD, Cornelius M, Martel MO, Jamison RN, Edwards RR. Distress Intolerance and Prescription Opioid Misuse Among Patients With

Chronic Pain. *The journal of pain : official journal of the American Pain Society.* 2016;17(7):806-814. doi: 810.1016/j.jpain.2016.1003.1004. Epub 2016 Apr 1014.

76.   Von Korff M, Walker RL, Saunders K, et al. Prevalence of prescription opioid use disorder among chronic opioid therapy patients after health plan opioid dose and risk reduction initiatives. *Int J Drug Policy.* 2017;46:90-98.(doi):10.1016/j.drugpo.2017.1005.1053. Epub 2017 Jun 1027.

77.   Wunsch MJ, Cropsey KL, Campbell ED, Knisely JS. OxyContin use and misuse in three populations: substance abuse patients, pain patients, and criminal justice participants. *J Opioid Manag.* 2008;4(2):73-79.

78.   Gardner RA, Brewer KL, Langston DB. Predicting opioid use disorder in patients with chronic pain who present to the emergency department. *Inj Prev.* 2019;25(5):386-391. doi: 310.1136/injuryprev-2018-042723. Epub 042018 Apr 042726.

79.   Cepeda MS, Fife D, Kihm MA, Mastrogiovanni G, Yuan Y. Comparison of the risks of shopping behavior and opioid abuse between tapentadol and oxycodone and association of shopping behavior and opioid abuse. *The Clinical journal of pain.* 2014;30(12):1051-1056. doi: 1010.1097/AJP.0000000000000067.

80.   Dunn KE, Barrett FS, Fingerhood M, Bigelow GE. Opioid Overdose History, Risk Behaviors, and Knowledge in Patients Taking Prescribed Opioids for Chronic Pain. *Pain medicine (Malden, Mass).* 2017;18(8):1505-1515. doi: 1510.1093/pm/pnw1228.

81.   Ives TJ, Chelminski PR, Hammett-Stabler CA, et al. Predictors of opioid misuse in patients with chronic pain: a prospective cohort study. *BMC Health Serv Res.* 2006;6:46.(doi):10.1186/1472-6963-1186-1146.

82.   Michna E, Ross EL, Hynes WL, et al. Predicting aberrant drug behavior in patients treated for chronic pain: importance of abuse history. *Journal of pain and symptom management.* 2004;28(3):250-258. doi: 210.1016/j.jpainsymman.2004.1004.1007.

83.   Schieffer BM, Pham Q, Labus J, et al. Pain medication beliefs and medication misuse in chronic pain. *The journal of pain : official journal of the American Pain Society.* 2005;6(9):620-629. doi: 610.1016/j.jpain.2005.1004.1004.

Appendix 1: Diagnostic Criteria for Opioid Use Disorder

- Opioids are often taken in larger amounts or over a longer period than was intended
- There is persistent desire or unsuccessful efforts to cut down or control opioid use
- A great deal of time spent is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects
- Craving, or a strong desire or urge to use opioids
- Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school or home
- Continued use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids
- Important social, occupational, or recreational activities are given up or reduced because of opioid use
- Recurrent opioid use in situations in which it is physically hazardous
- Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance
- Tolerance*, as defined by either of the following:
    - A need for markedly increased amounts of opioids to achieve intoxication or desired effect
    - A markedly diminished effect with continued use of the same amount of an opioid
- Withdrawal*, as manifested by either of the following:
    - The characteristic opioid withdrawal syndrome
    - Opioids (or a closely related substance) are taken to relieve or avoid withdrawal symptoms

*Tolerance and withdrawal criteria are not considered to be met for those taking opioids solely under appropriate medical supervision

If 2-3 criteria are met, it is considered mild; if 4-5 criteria are met, it is considered moderate; and if >6 criteria are met, it is considered severe

Figure 1. DSM-5 Diagnostic Criteria for Opioid Use Disorder.

Appendix 2: Full Literature Search Strategies

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present Search Strategy:

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1   (chronic adj4 pain*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (58045)
2   Chronic Pain/ (9465)
3   exp Osteoarthritis/ (54524)
4   osteoarthrit*.mp. (75940)
5   osteo-arthritis.mp. (367)
6   degenerative arthrit*.mp. (1219)
7   exp Arthritis, Rheumatoid/ (104646)
8   exp Neuralgia/ (17701)
9   Diabetic Neuropathies/ (13598)
10   (neuropath* adj5 (pain* or diabet*)).mp. (36896)
11   neuralg*.mp. (23754)
12   zoster.mp. (19214)
13   Irritable Bowel Syndrome/ (6064)
14   (IBS or irritable colon or irritable bowel).mp. (14340)
15   Migraine Disorders/ (23013)
16   migraine.mp. (34504)
17   Fibromyalgia/ (7563)
18   fibromyalg*.mp. (10314)
19   complex regional pain syndromes/ or exp causalgia/ or exp reflex sympathetic dystrophy/ (5219)
20   (complex regional pain syndromes or causalgia).mp. (2139)
21   Pain, Intractable/ (6021)
22   Phantom Limb/ (1736)
23   Hyperalgesia/ (10022)
24   ((noncancer* or non-cancer*or chronic* or recurrent or persist* or non-malign*) adj3 pain).mp. (16501)
25   or/1-24 (373978)
26   exp back pain/ or exp failed back surgery syndrome/ or exp low back pain/ (34809)
27   Radiculopathy/ or radiculopathy.mp. (8051)
28   musculoskeletal pain/ or headache/ (27885)
29   exp Arthralgia/ (10983)
30   exp Headache Disorders/ (31162)
31   headache*.mp. (83325)
32   Temporomandibular Joint Dysfunction Syndrome/ (4837)
33   ((TMJ or TMJD) and pain*).mp. (2432)
34   whiplash.mp. or exp whiplash injury/ (3755)

35   exp Cumulative Trauma Disorders/ (12608)
36   exp Peripheral Nervous System Diseases/dt [Drug Therapy] (12956)
37   Pain Measurement/de [Drug Effects] (6350)
38   (backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or fibromyalgi* or myodyni* or neuralgi* or ischialgi* or crps or rachialgi*).ab,ti. (39747)
39   ((back or discogen* or bone or musculoskelet* or muscle* or skelet* or spinal or spine or vertebra* or joint* or arthritis or Intestin* or neuropath* or neck or cervical* or head or facial* or complex or radicular or cervicobrachi* or orofacial or somatic or shoulder* or knee* or hip or hips) adj3 pain).mp. (143905)
40   ((medication* or opioid* or opiate* or narcotic*) and pain).mp. (69406)
41   or/26-40 (351154)
42   (acute or emergency or preoperative or postoperative).ti,ab. (1699616)
43   41 not 42 (287522)
44   25 or 43 (558819)
45   exp Analgesics, Opioid/ (103601)
46   (opioid* or opiate*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (113980)
47   (alfentanil or alphaprodine or beta-casomorphin$ or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (143699)
48   or/45-47 (199130)
49   exp Narcotics/ (111485)
50   narcotic*.mp. (57151)
51   (adolonta or Anpec or Ardinex or Asimadoline or Alvimopam or amadol or biodalgic or biokanol or Codinovo or contramal or Demerol or Dicodid or Dihydrocodeinone or dihydromorphinone or dihydrohydroxycodeinone or dihydrone or dilaudid or dinarkon or dolsin or dolosal or dolin or dolantin or dolargan or dolcontral or duramorph or duromorph or duragesic or durogesic or eucodal or Fedotzine or Fentanest or Fentora or Fortral or Hycodan or Hycon or Hydrocodone or Hydrocodeinonebitartrate or hydromorphon or hydroxycodeinon or isocodeine or isonipecain or jutadol or laudacon or l dromoran or levodroman or levorphan or levo-dromoran or levodromoran or lexir or lidol or lydol or morfin or morfine or morphia or morphin or morphinium or morphinene or morphium or ms contin or n-methylmorphine or n methylmorphine or nobligan or numorphan or oramorph or oxycodeinon or oxiconum or oxycone or oxycontin or palladone or pancodine or pethidine or phentanyl or prontofort or robidone or skenan or

sublimaze or sulfentanyl or sulfentanil or sufenta or takadol or talwin or theocodin or tramadol or tramadolhameln or tramadolor or tramadura or tramagetic or tramagit or tramake or tramal or tramex or tramundin or trasedal or theradol or tiral or topalgic or tradol or tradolpuren or tradonal or tralgiol or tramadorsch or tramadin or tramadoc or ultram or zamudol or zumalgic or zydol or zytram).mp. (9560)

52   or/45-51 (227662)

53   prognosis/ (443467)

54   ep.fs. and (opioid or opiate or narcotic).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (8760)

55   survival analysis/ or kaplan-meier estimate/ or proportional hazards models/ (209273)

56   exp risk/ (1051450)

57   exp Regression Analysis/ (377162)

58   "analysis of variance"/ or multivariate analysis/ (317730)

59   exp Probability/ (1202722)

60   exp epidemiologic methods/ (5449196)

61   exp epidemiologic studies/ (2133421)

62   exp sentinel surveillance/ (5721)

63   exp seroepidemiologic studies/ (21074)

64   exp cohort studies/ or retrospective studies/ (1722906)

65   exp cross-sectional studies/ (260312)

66   exp longitudinal studies/ (113643)

67   exp follow-up studies/ (586874)

68   exp prospective studies/ (466983)

69   sn.fs. and (opioid or opiate or narcotic).mp. (5716)

70   or/53-69 (5617858)

71   (prognosis or prognostic or predict* or risk*).mp. (3703309)

72   ((univariate or covariate or variance or covariance or multivariate or regression or adjusted or unadjusted or logistic or diagnostic) adj2 (analys* or model*)).mp. (959011)

73   (logistic adj2 regress*).mp. (221100)

74   (proportional or hazard* or bayes* or markov* or "odds ratio" or Cox or survival or kaplan-meier or estimate* or ANOVA or ANCOVA).mp. (2282826)

75   (prevalence or incidence or epidemiol* or survey or RAR or cohort or surveillance or seroprevalence or seroincidence or seroepidemiol* or screening).mp. (2741940)

76   rapid assessment.mp. (2983)

77   situation assessment.mp. (89)

78   situational assessment.mp. (37)

79   or/53-78 (8844797)

80   exp Prescription Drug Misuse/ (10792)

81   exp opioid-related disorders/ (22452)

82   "Drug and Narcotic Control"/ (8274)

83   substance abuse detection/ (8271)

84   Drug Utilization/sn [Statistics & Numerical Data] (5563)
85   Inappropriate Prescribing/sn [Statistics & Numerical Data] (800)
86   or/80-85 (52992)
87   Drug-Seeking Behavior/ (947)
88   Behavior, Addictive/ (7813)
89   Substance Withdrawal Syndrome/ (20364)
90   Poisoning/ (21657)
91   "Drug-Related Side Effects and Adverse Reactions"/ (27960)
92   accidents/ or accidental falls/ or accidents, traffic/ (75052)
93   substance-related disorders/ (88275)
94   Opioid-Related Disorders/ (11177)
95   or/87-94 (241850)
96   (Opioid* or opiate* or narcotic* or analges* or prescription*).mp. (339581)
97   95 and 96 (31087)
98   86 or 97 (67600)
99   ((Opioid* or opiate* or narcotic* or analges* or prescription*) adj3 (abuse or addict* or dependen* or misuse or diversion or aberrant or monitoring or (prob* adj2 "drug use"))).mp. (17024)
100   (behav* adj3 (nonmedical or nontherapeutic or abberant)).mp. (23)
101   or/98-100 (73768)
102   44 and 52 and 79 and 101 (3360)
103   animals/ not humans/ (4405034)
104   exp Animal Experimentation/ (8611)
105   exp Animals, Laboratory/ (810005)
106   exp Models, Animal/ (505475)
107   exp Rodentia/ (3009067)
108   (rat or rats or mouse or mice).ti. (1253582)
109   or/103-108 (5238572)
110   102 not 109 (3539)

Database: PsycINFO <1987 to March Week 3 2018>
Search Strategy:
----
1   (chronic adj4 pain*).mp. (18923)
2   chronic pain/ (11638)
3   exp arthritis/ (3568)
4   osteoarthrit*.mp. (1731)
5   osteo-arthritis.mp. (7)
6   degenerative arthrit*.mp. (13)
7   exp neuralgia/ (848)
8   exp neuropathy/ (5809)
9   (neuropath* adj5 (pain* or diabet*)).mp. (6216)
10   neuralg*.mp. (1377)

11   zoster.mp. (526)
12   irritable bowel syndrome/ (1052)
13   (IBS or irritable colon or irritable bowel).mp. (1752)
14   migraine headache/ (8243)
15   migraine.mp. (10761)
16   fibromyalgia/ (1767)
17   fibromyalg*.mp. (3036)
18   complex regional pain syndromes.mp. (55)
19   exp "Complex Regional Pain Syndrome (Type I)"/ (135)
20   (complex regional pain syndromes or causalgia).mp. (87)
21   somatosensory disorders/ (1248)
22   hyperalgesi*.mp. (3787)
23   somatoform pain disorder/ (706)
24   somatoform disorders/ (4960)
25   conversion disorder/ (760)
26   ((noncancer* or non-cancer*or chronic* or recurrent or persist* or non-malign*) adj3 pain).mp. (2924)
27   or/1-26 (53391)
28   back pain.mp. or exp Back Pain/ (4974)
29   radiculopathy.mp. (202)
30   musculoskeletal pain.mp. (1394)
31   Arthralgia.mp. (101)
32   headache.mp. or exp HEADACHE/ (17485)
33   ((TMJ or TMJD) and pain*).mp. (134)
34   WHIPLASH/ or whiplash.mp. (550)
35   (backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or fibromyalgi* or myodyni* or neuralgi* or ischialgi* or crps or rachialgi*).ab,ti. (5239)
36   ((back or discogen* or bone or musculoskelet* or muscle* or skelet* or spinal or spine or vertebra* or joint* or arthritis or Intestin* or neuropath* or neck or cervical* or head or facial* or complex or radicular or cervicobrachi* or orofacial or somatic or shoulder* or knee* or hip or hips) adj3 pain).mp. (17482)
37   ((medication* or opioid* or opiate* or narcotic*) and pain).mp. (11610)
38   or/28-37 (45785)
39   (acute or emergency or preoperative or postoperative).ti,ab. (99714)
40   38 not 39 (39712)
41   27 or 40 (69496)
42   exp opiates/ (19866)
43   (opioid* or opiate*).mp. (25083)
44   (alfentanil or alphaprodine or beta-casomorphin$ or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine

or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp. (22820)

45   exp narcotic drugs/ (22187)

46   narcotic*.mp. (3635)

47   (adolonta or Anpec or Ardinex or Asimadoline or Alvimopam or amadol or biodalgic or biokanol or Codinovo or contramal or Demerol or Dicodid or Dihydrocodeinone or dihydromorphinone or dihydrohydroxycodeinone or dihydrone or dilaudid or dinarkon or dolsin or dolosal or dolin or dolantin or dolargan or dolcontral or duramorph or duromorph or duragesic or durogesic or eucodal or Fedotzine or Fentanest or Fentora or Fortral or Hycodan or Hycon or Hydrocodone or Hydrocodeinonebitartrate or hydromorphon or hydroxycodeinon or isocodeine or isonipecain or jutadol or laudacon or l dromoran or levodroman or levorphan or levo-dromoran or levodromoran or lexir or lidol or lydol or morfin or morfine or morphia or morphin or morphinium or morphinene or morphium or ms contin or n-methylmorphine or n methylmorphine or nobligan or numorphan or oramorph or oxycodeinon or oxiconum or oxycone or oxycontin or palladone or pancodine or pethidine or phentanyl or prontofort or robidone or skenan or sublimaze or sulfentanyl or sulfentanil or sufenta or takadol or talwin or theocodin or tramadol or tramadolhameln or tramadolor or tramadura or tramagetic or tramagit or tramake or tramal or tramex or tramundin or trasedal or theradol or tiral or topalgic or tradol or tradolpuren or tradonal or tralgiol or tramadorsch or tramadin or tramadoc or ultram or zamudol or zumalgic or zydol or zytram).mp. (833)

48   or/42-47 (39293)

49   prognosis/ (7080)

50   epidemiology/ (43635)

51   risk assessment/ or risk factors/ (80915)

52   exp statistical regression/ (5558)

53   "analysis of variance"/ (1431)

54   exp multivariate analysis/ (14106)

55   exp variability measurement/ (3218)

56   exp "ANALYSIS OF COVARIANCE"/ (1113)

57   exp statistical probability/ (5730)

58   maximum likelihood/ or "goodness of fit"/ (2486)

59   (prognosis or prognostic or predict* or risk*).mp. (648209)

60   ((univariate or covariate or multivariate or variance or covariance or regression or adjusted or unadjusted or logistic or diagnostic) adj2 (analys* or model*)).mp. (145007)

61   (ANOVA or ANCOVA).mp. (20777)

62   (logistic adj2 regress*).mp. (46677)

63   (proportional or hazard* or bayes* or markov* or "odds ratio" or Cox or survival or kaplan-meier or estimate).mp. (121596)

64   adjust*.ti,ab. (110179)

65   or/49-64 (888990)

66   drug dependency/ (11173)

67   drug abuse/ (41605)

68   drug rehabilitation/ (16431)
69   "substance use disorder"/ (5494)
70   self-medication/ (639)
71   prescription drugs/ (3738)
72   drug overdoses/ (1293)
73   exp drug addiction/ (10358)
74   or/66-73 (69689)
75   drug seeking/ (811)
76   addiction/ (9345)
77   drug withdrawal/ (4362)
78   toxic disorders/ (1111)
79   "side effects (drug)"/ (22256)
80   drug tolerance/ (3380)
81   exp accidents/ (11062)
82   exp "death and dying"/ (26955)
83   suicide/ or self-destructive behavior/ or attempted suicide/ or self-injurious behavior/ or suicidal ideation/ or suicide prevention/ (36387)
84   or/75-83 (111272)
85   (Opioid* or opiate* or narcotic* or analges* or prescription*).mp. (50064)
86   84 and 85 (5965)
87   74 or 86 (73586)
88   ((Opioid* or opiate* or narcotic* or analges* or prescription*) adj3 (abuse or addict* or misuse or overdose or poison* or diversion or aberrant or monitoring or mortality or death or suicide or coroner or (prob* adj2 "drug use"))).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (5110)
89   87 or 88 (74707)
90   41 and 48 and 65 and 89 (971)

Database: Embase <1974 to 2018 March 28>
Search Strategy:
----
1   (chronic adj4 pain*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word] (95680)
2   Chronic Pain/ (49834)
3   exp Osteoarthritis/ (111728)
4   osteoarthrit*.mp. (121670)
5   osteo-arthritis.mp. (446)
6   degenerative arthrit*.mp. (1507)
7   exp Arthritis, Rheumatoid/ (184566)
8   exp Neuralgia/ (93437)
9   Diabetic Neuropathies/ (14142)

10   (neuropath* adj5 (pain* or diabet*)).mp. (64665)
11   neuralg*.mp. (28393)
12   zoster.mp. (34729)
13   Irritable Bowel Syndrome/ (6221)
14   (IBS or irritable colon or irritable bowel).mp. (27877)
15   Migraine Disorders/ (15847)
16   migraine.mp. (61539)
17   Fibromyalgia/ (17497)
18   fibromyalg*.mp. (18803)
19   complex regional pain syndromes/ or exp causalgia/ or exp reflex sympathetic dystrophy/ (6731)
20   (complex regional pain syndromes or causalgia).mp. (1320)
21   Pain, Intractable/ (2970)
22   Phantom Limb/ (94)
23   Hyperalgesia/ (17414)
24   ((noncancer* or non-cancer*or chronic* or recurrent or persist* or non-malign*) adj3 pain).mp. (23901)
25   or/1-24 (640522)
26   exp back pain/ or exp failed back surgery syndrome/ or exp low back pain/ (93935)
27   Radiculopathy/ or radiculopathy.mp. (12290)
28   musculoskeletal pain/ or headache/ (195025)
29   exp Arthralgia/ (51252)
30   exp Headache Disorders/ (267096)
31   headache*.mp. (243984)
32   Temporomandibular Joint Dysfunction Syndrome/ (9530)
33   ((TMJ or TMJD) and pain*).mp. (3303)
34   whiplash.mp. or exp whiplash injury/ (4954)
35   exp Cumulative Trauma Disorders/ (18598)
36   exp Peripheral Nervous System Diseases/dt [Drug Therapy] (6637)
37   Pain Measurement/de [Drug Effects] (0)
38   (backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or fibromyalgi* or myodyni* or neuralgi* or ischialgi* or crps or rachialgi*).ab,ti. (58834)
39   ((back or discogen* or bone or musculoskelet* or muscle* or skelet* or spinal or spine or vertebra* or joint* or arthritis or Intestin* or neuropath* or neck or cervical* or head or facial* or complex or radicular or cervicobrachi* or orofacial or somatic or shoulder* or knee* or hip or hips) adj3 pain).mp. (242617)
40   ((medication* or opioid* or opiate* or narcotic*) and pain).mp. (118308)
41   or/26-40 (688528)
42   (acute or emergency or preoperative or postoperative).ti,ab. (2306609)
43   41 not 42 (572046)
44   25 or 43 (1006993)
45   exp Analgesics, Opioid/ (301003)

46   (opioid* or opiate*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word] (168834)

47   (alfentanil or alphaprodine or beta-casomorphin$ or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word] (267453)

48   or/45-47 (380965)

49   exp Narcotics/ (253161)

50   narcotic*.mp. (46499)

51   (adolonta or Anpec or Ardinex or Asimadoline or Alvimopam or amadol or biodalgic or biokanol or Codinovo or contramal or Demerol or Dicodid or Dihydrocodeinone or dihydromorphinone or dihydrohydroxycodeinone or dihydrone or dilaudid or dinarkon or dolsin or dolosal or dolin or dolantin or dolargan or dolcontral or duramorph or duromorph or duragesic or durogesic or eucodal or Fedotzine or Fentanest or Fentora or Fortral or Hycodan or Hycon or Hydrocodone or Hydrocodeinonebitartrate or hydromorphon or hydroxycodeinon or isocodeine or isonipecain or jutadol or laudacon or l dromoran or levodroman or levorphan or levo-dromoran or levodromoran or lexir or lidol or lydol or morfin or morfine or morphia or morphin or morphinium or morphinene or morphium or ms contin or n-methylmorphine or n methylmorphine or nobligan or numorphan or oramorph or oxycodeinon or oxiconum or oxycone or oxycontin or palladone or pancodine or pethidine or phentanyl or prontofort or robidone or skenan or sublimaze or sulfentanyl or sulfentanil or sufenta or takadol or talwin or theocodin or tramadol or tramadolhameln or tramadolor or tramadura or tramagetic or tramagit or tramake or tramal or tramex or tramundin or trasedal or theradol or tiral or topalgic or tradol or tradolpuren or tradonal or tralgiol or tramadorsch or tramadin or tramadoc or ultram or zamudol or zumalgic or zydol or zytram).mp. (48824)

52   or/45-51 (395061)

53   prognosis/ (532035)

54   ep.fs. and (opioid or opiate or narcotic).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word] (6587)

55   survival analysis/ or kaplan-meier estimate/ or proportional hazards models/ (106675)

56   exp risk/ (2117100)

57   exp Regression Analysis/ (394190)

58   "analysis of variance"/ or multivariate analysis/ (287111)

59   exp Probability/ (81233)

60   exp epidemiologic methods/ (2874401)
61   exp epidemiologic studies/ (2874401)
62   exp sentinel surveillance/ (2045)
63   exp seroepidemiologic studies/ (3394)
64   exp cohort studies/ or retrospective studies/ (725167)
65   exp cross-sectional studies/ (246401)
66   exp longitudinal studies/ (110417)
67   exp follow-up studies/ (1268532)
68   exp prospective studies/ (435935)
69   sn.fs. and (opioid or opiate or narcotic).mp. (0)
70   or/53-69 (6153957)
71   (prognosis or prognostic or predict* or risk*).mp. (5123001)
72   ((univariate or covariate or variance or covariance or multivariate or regression or adjusted or unadjusted or logistic or diagnostic) adj2 (analys* or model*)).mp. (1121056)
73   (logistic adj2 regress*).mp. (328554)
74   (proportional or hazard* or bayes* or markov* or "odds ratio" or Cox or survival or kaplan-meier or estimate* or ANOVA or ANCOVA).mp. (3008726)
75   (prevalence or incidence or epidemiol* or survey or RAR or cohort or surveillance or seroprevalence or seroincidence or seroepidemiol* or screening).mp. (4972797)
76   rapid assessment.mp. (3976)
77   situation assessment.mp. (134)
78   situational assessment.mp. (63)
79   or/53-78 (11049729)
80   exp Prescription Drug Misuse/ (7235)
81   exp opioid-related disorders/ (14719)
82   "Drug and Narcotic Control"/ (11327)
83   substance abuse detection/ (49703)
84   [Drug Utilization/sn [Statistics & Numerical Data]] (0)
85   [Inappropriate Prescribing/sn [Statistics & Numerical Data]] (0)
86   or/80-85 (79385)
87   Drug-Seeking Behavior/ (2028)
88   Behavior, Addictive/ (31010)
89   Substance Withdrawal Syndrome/ (11981)
90   Poisoning/ (180094)
91   "Drug-Related Side Effects and Adverse Reactions"/ (148905)
92   accidents/ or accidental falls/ or accidents, traffic/ (101071)
93   substance-related disorders/ (23368)
94   Opioid-Related Disorders/ (4827)
95   or/87-94 (447990)
96   (Opioid* or opiate* or narcotic* or analges* or prescription*).mp. (600444)
97   95 and 96 (32625)
98   86 or 97 (105760)

99   ((Opioid* or opiate* or narcotic* or analges* or prescription*) adj3 (abuse or addict* or dependen* or misuse or diversion or aberrant or monitoring or (prob* adj2 "drug use"))).mp. (30969)
100   (behav* adj3 (nonmedical or nontherapeutic or abberant)).mp. (39)
101   or/98-100 (116386)
102   44 and 52 and 79 and 101 (5533)
103   animals/ not humans/ (1328803)
104   exp Animal Experimentation/ (2194467)
105   exp Animals, Laboratory/ (579423)
106   exp Models, Animal/ (1122548)
107   exp Rodentia/ (3460613)
108   (rat or rats or mouse or mice).ti. (1467574)
109   or/103-108 (5082747)
110   102 not 109 (5390)
111   (chronic adj4 pain*).mp. (95680)
112   chronic pain/ (49834)
113   exp osteoarthritis/ (111728)
114   osteoarthrit*.mp. (121670)
115   osteo-arthritis.mp. (446)
116   degenerative arthrit*.mp. (1507)
117   exp rheumatoid arthritis/ (184566)
118   exp neuralgia/ (93437)
119   diabetic neuropathy/ (21509)
120   (neuropath* adj5 (pain* or diabet*)).mp. (64665)
121   neuralg*.mp. (28393)
122   zoster.mp. (34729)
123   irritable colon/ (22406)
124   (Irritable Bowel Syndrome or IBS).mp. (21310)
125   exp migraine/ (55666)
126   migraine.mp. (61539)
127   fibromyalgia/ (17497)
128   fibromyalg*.mp. (18803)
129   reflex sympathetic dystrophy.mp. (2313)
130   (complex regional pain syndromes or causalgia).mp. (1320)
131   intractable pain/ (4425)
132   phantom limb.mp. or agnosia/ or phantom pain/ or amputation stump/ (7911)
133   hyperalgesia/ (17414)
134   ((noncancer* or non-cancer*or chronic* or recurrent or persist* or non-malign*) adj3 pain).mp. (23901)
135   or/111-134 (647408)
136   exp backache/ (93935)
137   radiculopathy.mp. or exp radiculopathy/ (34830)
138   musculoskeletal pain/ (8699)
139   exp arthralgia/ (51252)

140   headache/ (187753)
141   headache*.mp. (243984)
142   temporomandibular joint disorder/ (12272)
143   ((TMJ or TMJD) and pain*).mp. (3303)
144   whiplash.mp. or whiplash injury/ (4954)
145   exp cumulative trauma disorder/ (18598)
146   ((medication* or opioid* or opiate* or narcotic*) and pain).mp. (118308)
147   or/136-146 (524025)
148   (acute or emergency or preoperative or postoperative).ti,ab. (2306609)
149   147 not 148 (429527)
150   135 or 149 (957893)
151   exp narcotic analgesic agent/ (301003)
152   (opioid* or opiate*).mp. (168834)
153   (alfentanil or alphaprodine or beta-casomorphin$ or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp. (267453)
154   (adolonta or Anpec or Ardinex or Asimadoline or Alvimopam or amadol or biodalgic or biokanol or Codinovo or contramal or Demerol or Dicodid or Dihydrocodeinone or dihydromorphinone or dihydrohydroxycodeinone or dihydrone or dilaudid or dinarkon or dolsin or dolosal or dolin or dolantin or dolargan or dolcontral or duramorph or duromorph or duragesic or durogesic or eucodal or Fedotzine or Fentanest or Fentora or Fortral or Hycodan or Hycon or Hydrocodone or Hydrocodeinonebitartrate or hydromorphon or hydroxycodeinon or isocodeine or isonipecain or jutadol or laudacon or l dromoran or levodroman or levorphan or levo-dromoran or levodromoran or lexir or lidol or lydol or morfin or morfine or morphia or morphin or morphinium or morphinene or morphium or ms contin or n-methylmorphine or n methylmorphine or nobligan or numorphan or oramorph or oxycodeinon or oxiconum or oxycone or oxycontin or palladone or pancodine or pethidine or phentanyl or prontofort or robidone or skenan or sublimaze or sulfentanyl or sulfentanil or sufenta or takadol or talwin or theocodin or tramadol or tramadolhameln or tramadolor or tramadura or tramagetic or tramagit or tramake or tramal or tramex or tramundin or trasedal or theradol or tiral or topalgic or tradol or tradolpuren or tradonal or tralgiol or tramadorsch or tramadin or tramadoc or ultram or zamudol or zumalgic or zydol or zytram).mp. (48824)
155   or/151-154 (381587)
156   prognosis/ (532035)
157   ep.fs. and (opioid or opiate or narcotic).mp. (6587)
158   epidemiology/ or pharmacoepidemiology/ (218146)
159   epidemiological data/ or survival/ (321002)

160   statistical analysis/ or "analysis of covariance"/ or "analysis of variance"/ or kaplan meier method/ or maximum likelihood method/ or exp multivariate analysis/ or exp regression analysis/ or univariate analysis/ (997331)

161   proportional hazards model/ (83835)

162   risk/ or risk assessment/ or risk factor/ (1614996)

163   probability/ (81233)

164   prediction/ (305112)

165   statistical model/ (147885)

166   disease association/ (468353)

167   disease duration/ (131049)

168   (prognosis or prognostic or predict* or risk*).mp. (5123001)

169   ((univariate or covariate or variance or covariance or multivariate or regression or adjusted or unadjusted or logistic or diagnostic) adj2 (analys* or model*)).mp. (1121056)

170   (logistic adj2 regress*).mp. (328554)

171   (proportional or hazard* or bayes* or markov* or "odds ratio" or Cox or survival or kaplan-meier or estimate or ANOVA or ANCOVA).mp. (2457022)

172   cohort analysis/ (357522)

173   cross-sectional study/ (246401)

174   retrospective study/ (629319)

175   prospective study/ (435935)

176   longitudinal study/ (110251)

177   follow up/ (1268532)

178   or/156-177 (8590393)

179   opiate addiction/ (14719)

180   narcotic dependence/ or morphine addiction/ (4332)

181   prescription drug diversion/ (254)

182   or/179-181 (18922)

183   drug abuse/ or analgesic agent abuse/ or drug misuse/ (56469)

184   drug control/ (12152)

185   drug monitoring/ (48764)

186   substance abuse/ (49703)

187   drug urine level/ (32577)

188   drug dose regimen/ (32250)

189   drug overdose/ (21810)

190   drug seeking behavior/ (2028)

191   drug dependence/ (47664)

192   addiction/ (50115)

193   drug withdrawal/ (157169)

194   withdrawal syndrome/ (28198)

195   intoxication/ (184322)

196   accident/ or falling/ or home accident/ or traffic accident/ (112567)

197   suicide/ or suicidal behavior/ or suicide attempt/ (80618)

198   or/183-197 (819572)

199   dt.fs. (3515110)

200   to.fs. (518918)
201   199 or 200 (3935570)
202   (Opioid* or opiate* or narcotic* or analges* or prescription*).ti,ab. (372428)
203   (Opioid* or opiate* or narcotic* or analges* or prescription*).ti. (124603)
204   198 and 202 (45807)
205   201 and 203 (36662)
206   182 or 204 or 205 (85402)
207   ((Opioid* or opiate* or narcotic* or analges* or prescription*) adj3 (abuse or addict* or misuse or overdose or poison* or diversion or aberrant or monitoring or mortality or death or suicide or coroner or (prob* adj2 "drug use"))).mp. (27607)
208   206 or 207 (89558)
209   150 and 155 and 178 and 208 (7612)
210   exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/ (25789772)
211   human/ or normal human/ or human cell/ (19494565)
212   210 and 211 (19446425)
213   210 not 212 (6343347)
214   animals/ not humans/ (1328803)
215   nonhuman/ (5379994)
216   exp Animal Experiment/ (2194467)
217   exp Experimental Animal/ (579423)
218   exp Rodent/ (3460613)
219   (rat or rats or mouse or mice).ti. (1467574)
220   214 or 215 or 216 or 217 or 218 or 219 (7714682)
221   209 not 213 (7426)
222   221 not 220 (7832)

Cochrane
Search Name: **Mar29_2018_Opioid**
Last Saved: 29/03/2018 15:38:03.391
Description:

ID   Search
#1   MeSH descriptor: [Chronic Pain] explode all trees
#2   (chronic pain) and (opioid or opiate or narcotic)
#3   MeSH descriptor: [Osteoarthritis] explode all trees
#4   "osteoarthrit*"
#5   "osteo-arthrit*"
#6   "degenerative arthrit*"
#7   MeSH descriptor: [Arthritis, Rheumatoid] explode all trees
#8   MeSH descriptor: [Neuralgia] explode all trees
#9   MeSH descriptor: [Diabetic Neuropathies] explode all trees
#10   (neuropath* N5 (pain* or diabet*))
#11   chronic N4 pain

#12   "neuralg*"
#13   "zoster"
#14   MeSH descriptor: [Irritable Bowel Syndrome] explode all trees
#15   (irritable (bowel or colon))
#16   "IBS"
#17   MeSH descriptor: [Migraine Disorders] explode all trees
#18   "migraine"
#19   MeSH descriptor: [Fibromyalgia] explode all trees
#20   fibromyalg*
#21   MeSH descriptor: [Complex Regional Pain Syndromes] explode all trees
#22   causalgia
#23   intractable pain
#24   MeSH descriptor: [Phantom Limb] explode all trees
#25   MeSH descriptor: [Hyperalgesia] explode all trees
#26   ((noncancer* or non-cancer*or chronic* or recurrent or persist* or non-malign*) N3 pain)
#27   {or #1-#26}
#28   MeSH descriptor: [Back Pain] explode all trees
#29   MeSH descriptor: [Radiculopathy] explode all trees
#30   "musculoskeletal pain"
#31   "radiculopathy"
#32   MeSH descriptor: [Arthralgia] explode all trees
#33   MeSH descriptor: [Headache] explode all trees
#34   "headache"
#35   MeSH descriptor: [Temporomandibular Joint Dysfunction Syndrome] explode all trees
#36   ((TMJ or TMJD) and pain*)
#37   MeSH descriptor: [Whiplash Injuries] explode all trees
#38   "whiplash"
#39   MeSH descriptor: [Cumulative Trauma Disorders] explode all trees
#40   MeSH descriptor: [Peripheral Nervous System] explode all trees
#41   backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or fibromyalgi* or myodyni* or neuralgi* or ischialgi* or crps or rachialgi*
#42   ((back or discogen* or bone or musculoskelet* or muscle* or skelet* or spinal or spine or vertebra* or joint* or arthritis or Intestin* or neuropath* or neck or cervical* or head or facial* or complex or radicular or cervicobrachi* or orofacial or somatic or shoulder* or knee* or hip or hips) N3 pain)
#43   {or #28-#42}
#44   acute or emergency or preoperative or postoperative
#45   #43 not #44
#46   #27 or #45
#47   "medication"
#48   "opioid"
#49   "opiate"

#50   "narcotic"
#51   {or #47-#50}
#52   "pain"
#53   #51 and #52
#54   #53 not #44
#55   #46 or #54
#56   MeSH descriptor: [Analgesics, Opioid] explode all trees
#57   "opioid"
#58   "opiate"
#59   MeSH descriptor: [Narcotics] explode all trees
#60   "narcotic"
#61   alfentanil or alphaprodine or beta-casomorphin$ or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol
#62   adolonta or Anpec or Ardinex or Asimadoline or Alvimopam or amadol or biodalgic or biokanol or Codinovo or contramal or Demerol or Dicodid or Dihydrocodeinone or dihydromorphinone or dihydrohydroxycodeinone or dihydrone or dilaudid or dinarkon or dolsin or dolosal or dolin or dolantin or dolargan or dolcontral or duramorph or duromorph or duragesic or durogesic or eucodal or Fedotzine or Fentanest or Fentora or Fortral or Hycodan or Hycon or Hydrocodone or Hydrocodeinonebitartrate or hydromorphon or hydroxycodeinon or isocodeine or isonipecain or jutadol or laudacon or l dromoran or levodroman or levorphan or levo-dromoran or levodromoran or lexir or lidol or lydol or morfin or morfine or morphia or morphin or morphinium or morphinene or morphium or ms contin or n-methylmorphine or n methylmorphine or nobligan or numorphan or oramorph or oxycodeinon or oxiconum or oxycone or oxycontin or palladone or pancodine or pethidine or phentanyl or prontofort or robidone or skenan or sublimaze or sulfentanyl or sulfentanil or sufenta or takadol or talwin or theocodin or tramadol or tramadolhameln or tramadolor or tramadura or tramagetic or tramagit or tramake or tramal or tramex or tramundin or trasedal or theradol or tiral or topalgic or tradol or tradolpuren or tradonal or tralgiol or tramadorsch or tramadin or tramadoc or ultram or zamudol or zumalgic or zydol or zytram
#63   {or #56-#62}
#64   MeSH descriptor: [Prognosis] explode all trees
#65   MeSH descriptor: [Epidemiology] explode all trees
#66   TX opioid* and MW "EP"
#67   TX opiate* and MW "EP"
#68   TX narcotic* and MW "EP"
#69   MeSH descriptor: [Survival Analysis] explode all trees
#70   MeSH descriptor: [Risk Assessment] explode all trees

#71   MeSH descriptor: [Risk Factors] explode all trees
#72   MeSH descriptor: [Regression Analysis] explode all trees
#73   MeSH descriptor: [Analysis of Variance] explode all trees
#74   MeSH descriptor: [Probability] explode all trees
#75   prognosis or prognostic or predict* or risk*
#76   N2 (analys* or model*)
#77   (univariate or covariate or variance or covariance or multivariate or regression or adjusted or unadjusted or logistic or diagnostic)
#78   logistic N2 regress*
#79   proportional or hazard* or bayes* or markov* or "odds ratio" or Cox or survival or kaplan-meier or estimate* or ANOVA or ANCOVA
#80   {or #64-#79}
#81   MeSH descriptor: [Substance-Related Disorders] explode all trees
#82   MeSH descriptor: [Drug Overdose] explode all trees
#83   MeSH descriptor: [Drug-Related Side Effects and Adverse Reactions] explode all trees
#84   MeSH descriptor: [Drug and Narcotic Control] explode all trees
#85   MeSH descriptor: [Substance Abuse Detection] explode all trees
#86   MeSH descriptor: [Behavior, Addictive] explode all trees
#87   MeSH descriptor: [Substance Withdrawal Syndrome] explode all trees
#88   MeSH descriptor: [Poisoning] explode all trees
#89   MeSH descriptor: [Drug-Related Side Effects and Adverse Reactions] explode all trees
#90   MeSH descriptor: [Accidents] explode all trees
#91   MeSH descriptor: [Accidental Falls] explode all trees
#92   MeSH descriptor: [Accidents, Home] explode all trees
#93   MeSH descriptor: [Accidents, Traffic] explode all trees
#94   MeSH descriptor: [Death] explode all trees
#95   MeSH descriptor: [Suicide] explode all trees
#96   {or #81-#95}
#97   Opioid* or opiate* or narcotic* or analges* or prescription*
#98   #96 and #97
#99   #55 and #63 and #80 and #98

Appendix 3: Full-Text Screening Form

1. Is the study design an observational study (prospective cohort, retrospective cohort, cross-sectional or case-control)?

If no, EXCLUDE.
If yes, go to next question.

2. Is the article about adults ≥18 years old who have chronic noncancer pain that were prescribed opioids? Chronic noncancer pain includes any painful condition that is not associated with cancer and lasts for three months or longer.

If a study enrolled a mixed clinical population, do include it if they met the above criteria, and if 1) the authors provided the results separately for the participants with chronic noncancer pain; or 2) at least 80% of a study's sample comprised participants with chronic noncancer pain.

If no, EXCLUDE.
If yes, go to next question.

3. Does the article explore either: 1) the prevalence of opioid abuse, misuse, addiction, withdrawal, problematic use, and/or opioid use disorder or similar; or 2) risk/predictive factors for opioid abuse, misuse, addiction, withdrawal, problematic use, and/or opioid use disorder or similar using adjusted/multivariate analyses?

Note: For studies looking ONLY at predictive factors, DO NOT include cross-sectional studies; but for studies looking at prevalence, DO include cross-sectional studies.

If no, EXCLUDE.
If yes, INCLUDE.

Appendix 4: Data Abstraction Forms

Study Characteristics

RefID	
Author	
Journal	
Year	
Study design	
Country	
Industry funding	
Sampling	
Source of data	
Representativeness of study population	
If not representative, state reason	
Recruitment (first year)	
Recruitment (last year)	

Patient Characteristics

Total # of patients at baseline	
Age, median (IQR) or mean (SD)	
Age groups	
% Female	
Instrument with pain scale	
Direction of pain scale	
Mean (SD) or median (IQR) pain score	
Duration of chronic pain, mean (SD) or median (IQR)	
Pain location/type	
Current or former substance use/abuse	
Comorbid mental illness or antipsychotic medication use	

Opioid Characteristics

Type of opioid	
Mode of administration	
Dose	
Frequency	
Duration of opioid use	

Follow-up and Statistical Analysis

Follow-up time, mean (SD) or median (IQR)	
Number of patients eligible	
Number of patients in final analysis	
Loss to follow-up number, %	
Adjusted predictors (if applicable)	
Age adjusted	
Gender adjusted	
Adjusted for current or former substance abuse?	
Adjusted for comorbid mental illness or antipsychotic medication use?	

OUD Prevalence Measurement

RefID	
Authors' OUD outcome	
Measurement tool	
Is it measured in a valid way?	
Our experts' OUD outcome category (strong or less certainty)	
DSM-5 instrument: 0-other instrument; 1-DSM-5	
Underestimate DSM-5 (1), similar as DSM-5 (2), or overestimate DSM-5 (3)	
Overall (# of prevalence)	
Population (total population or subgroup)	
Name of subgroup (if applicable)	
Subgroup factor (if applicable)	
OUD total prevalence (%)	
Number of events	
Denominator	
Source of results (table, figure or page #)	

Predictors of OUD

RefID	
Sample size	
OUD definition	
Our experts' OUD outcome category (strong or less certainty)	

Predictor name	
Predictor code	
Comparison	
Reference	
Source (table, figure or page #)	
Significant (yes or no)	
Effect measure (OR, RR, or HR)	
Lower limit confidence interval	
Upper limit confidence interval	
P-value for each predictor (all groups)	
P-value for each group level within	
Comments	
InOR	
seInOR	

Appendix 5: Risk of Bias Assessment

1) Representativeness of the study population: low risk of bias when using random sampling, consecutive sampling, or data collected from a national or international registry; high risk of bias when the source of study population was not reported or acquired through convenience sampling

2) Validity of outcome assessment: low risk of bias when OUD was measured by a validated instrument

3) Proportion of lost to follow-up: high risk of bias if $\geq$20%

4) Whether or not predictive models were optimally adjusted: low risk of bias if adjusted for, at minimum, age, gender, substance abuse, comorbid mental illness or antipsychotic medication use

Appendix 6: Criteria for Model Selection From Multiple Reported Regression Models

1) If a study reported multiple regression models for different OUD-related outcomes, we chose the one that most closely approximated the DSM-5 definition of OUD.

2) If a study reported multiple definitions of opioid abuse, dependence or OUD, we chose the definition based on clinical interview over self-report, and where more than one were based on clinical interview, we chose the more recent nosological system over an older one (i.e. DSM-5, ICD-10, DSM-IV, ICD-9, etc).

3) If authors reported regression models for OUD at different time-points, we used the longest follow-up reported.[1]

4) If authors reported regression models for different populations, we used the model corresponding to the entire or largest population.

Reference:

1. Tendal B, Nuesch E, Higgins JP, et al: Multiplicity of data in trial reports and the reliability of meta-analyses: empirical study. BMJ 343:d4829, 2011.

Appendix 7: Methods to Convert Categorial Data to Continuous Data

When the association for age was reported according to 2 categories, we used the average of the upper and lower boundaries of each category to calculate a midpoint and assigned the reported odds ratio (OR) for each category to its respective midpoint. We then calculated the OR for every 10-year decrement in age, assuming a linear association with OUD.

When the association for age was reported for ≥3 categories, we assumed the association between age and the OUD was linear in each age category and the associations across categories were independent of each other. We used Bucher's approach to calculate the OR and 95% CI[1] for each age category and pooled the ORs using the inverse variance method to produce a single OR for each study.[2]

References

1. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol. 1997; 50: 683-691.

2. Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochranehandbook.org.

Appendix 8: PRISMA Flow Diagram of Study Selection

Identification

Citations identified through
database searching
(n = 13750)

Duplicates removed
(n = 1737)

Screening

Titles and abstracts screened
(n = 12013)

Citations excluded
(n = 11492)

Eligibility

Full-text articles assessed for
eligibility
(n = 521)

Full-text articles excluded   (n = 497)
  Not an observational study   (n = 66)
  Not all chronic non-cancer pain   (n = 173)
  patients prescribed opioids
  Not measuring OUD   (n = 251)
  Overlapping with other studies   (n = 7)

Included

Studies included in qualitative
synthesis
(n = 24)

Studies included in
quantitative synthesis (meta-
analysis)
(n = 24)

Figure 2. PRISMA flow diagram of study selection.

Appendix 9: Studies Excluded Due to Population Overlap

1. Boscarino JA, Rukstalis M, Hoffman SN, Han JJ, Erlich PM, Gerhard GS et al. Risk factors for drug   dependence among out-patients on opioid therapy in   a large US health-care system. Addiction. 2010 Oct;105(10):1776-82.
2. Boscarino JA, Rukstalis M, Hoffman SN, Han JJ, Erlich PM, Ross S et al. Prevalence of prescription opioid
use disorder among chronic pain patients: comparison of   the DSM-5 vs. DSM 4 diagnostic criteria. J Addict Dis. 2011 Jul-Sep;30(3):185-94.
3. Coloma-Carmona A, Carballo JL, Rodriguez-Marin J, Perez-Carbonell A. Use and dependence on opioid drugs in the Spanish population with chronic pain: Prevalence and differences according to sex. Rev Clin Esp. 2017;217(6):315-319. doi: 310.1016/j.rce.2017.1003.1007. Epub 2017 May 1010.
4. Edlund MJ, Martin BC, Fan MY, Devries A, Braden JB, Sullivan MD. Risks for opioid abuse and dependence among recipients of chronic opioid therapy: Results from the TROUP Study. Drug Alcohol Depend. 2010 Nov 1;112(1-2):90-8.
5. Fleming MF, Balousek SL, Klessig CL, Mundt MP, Brown DD. Substance use disorders in a primary care sample receiving daily opioid therapy. The journal of pain : official journal of the American Pain Society. 2007;8(7):573-582. doi: 510.1016/j.jpain.2007.1002.1432. Epub 2007 May 1011
6. Hojsted J, Nielsen PR, Kendall S, Frich L, Sjogren P. Validation and usefulness of the Danish version of the Pain Medication Questionnaire in opioid-treated chronic pain patients. Acta anaesthesiologica Scandinavica. 2011;55(10):1231-1238. doi: 1210.1111/j.1399-6576.2011.02523.x. Epub 02011 Sep 02527
7. Kovatch M, Feingold D, Elkana O, Lev-Ran S. Evaluation and comparison of tools for diagnosing problematic prescription opioid use among chronic pain patients. Int J Methods Psychiatr Res. 2017 Dec;26(4).

Appendix 10: Reasons for Excluded Studies That Were Included in Other Reviews

Table 1. Reasons for Excluded Studies That Were Included in Other Reviews

Reason for Exclusion	Number of Studies
Clinical experts determined that case definitions did not meet DSM-5 OUD criteria	100
Ineligible population for our review	40
Ineligible study design for our review	12
Overlapping populations with other studies	3
Total	155

Appendix 11: Baseline Characteristics of Included Studies

Table 2. Baseline characteristics of included studies

Author	Year	Country	Study design	Sample size	Age mean ±SD or median (range)	Length of follow-up (months)	Prevalence of OUD (%)	Authors' definition of OUD	Valid outcome measure	Experts' outcome category
Boscarino[66]	2015	USA	Cross-sectional	705	18-64, 79.3%; 65+, 20.7%	N/A	13.2	DSM-5 OUD	Yes	OUD – strong certainty
Bouckoms[62]	1992	USA	Prospective cohort	59	50 (24-79)	36	24	WHO opioid addiction	No	OUD – less certainty
Callinan[67]	2017	USA	Cross-sectional	115	53.3±13	N/A	9.6	Self-reported opioid addiction	No	OUD – less certainty
Campbell[63]	2015	Australia	Prospective cohort	1424	59 (49-68)	24	3.6	ICD-10 opioid dependence	Yes	OUD – strong certainty
Chabal[68]	1997	USA	Cross-sectional	76	48±13	N/A	61.6	Authors' own criteria of opioid abuse	No	OUD – less certainty
Coloma-Carmona[69]	2019	Spain	Cross-sectional	207	59±14.3	N/A	26.6	DSM-IV-TR opioid use disorder	Yes	OUD – strong certainty
Coutinho[65]	2018	USA	Retrospective cohort	21072	52.7±14.7	12	2.2	ICD-9 opioid abuse	Yes	OUD – strong certainty
Degenhardt[64]	2015	Australia	Prospective cohort	1422	58 (48-67)	24	2	DSM-5 OUD	Yes	OUD – strong certainty

Edlund[61]	2007	USA	Retrospective cohort	15160	<40, 4.2%; 40-49, 16.1%; 50-59, 35%; >60, 44.6%	36	2	ICD-9 opioid abuse/ dependence	Yes	OUD – strong certainty
Edlund[60]	2014	USA	Retrospective cohort	568640	18-30, 11.4%; 31-40, 19.8%; 41-50, 27.2%; 51-64, 29.5%; >=65, 12.1%	18	0.176	ICD-9 opioid abuse and dependence	Yes	OUD – strong certainty
Feingold[70]	2017	Israel	Cross-sectional	888	18-29, 9.1%; 30-44, 27.8%; 45-64, 39.1%; 65+, 24%	N/A	52.6	DSM-IV opioid dependence	Yes	OUD – strong certainty
Fleming[71]	2008	USA	Cross-sectional	904	48.3	N/A	11	DSM-IV opioid-specific substance use disorder	Yes	OUD – strong certainty
Gardner[78]	2019	USA	Case-control	89	43.6±14.1	12	50.5	DSM-5 OUD	Yes	OUD – strong certainty
Hoffman[59]	2017	USA	Retrospective cohort	2892	67.5±16.6	48	2.96	ICD-9 opioid dependence	Yes	OUD – strong certainty

Højsted[72]	2010	Denmark	Cross-sectional	207	53±13.3	N/A	14.4	ICD-10 opioid addiction	Yes	OUD – strong certainty
Huffman[57]	2013	USA	Retrospective cohort	120	49.5±13.7	12	32.5	DSM-IV-TR opioid addiction	Yes	OUD – strong certainty
Huffman[56]	2015	USA	Retrospective cohort	199	46.4±13.6	14	43.7	DSM-IV-TR opioid addiction and AAPM therapeutic opioid addiction	Yes	OUD – strong certainty
Hylan[58]	2015	USA	Retrospective cohort	2752	18-44, 21.2%; 45-64, 49.9%; >65, 28.9%	24	0.9	National Institute of Drug Abuse opioid abuse	No	OUD – less certainty
Kouyanou[73]	1997	UK	Cross-sectional	125	41±11	N/A	8	DSM-III-R opioid abuse and dependence	Yes	OUD – strong certainty
Lovejoy[74]	2016	USA	Cross-sectional	80	54.8	N/A	3.75	DSM-IV opioid abuse and dependence	Yes	OUD – strong certainty
McHugh[75]	2016	USA	Cross-sectional	51	54.6±8.4	N/A	60.8	COMM plus ABC opioid misuse	Yes	OUD – less certainty
Von Korff[76]	2017	USA	Cross-sectional	1588	20-44, 8.25%; 45-54, 16%; 55-64, 34.3%; 65-74, 28.1%; 75+, 13.7%	N/A	25.3	DSM-5 OUD without tolerance/withdrawal criteria	Yes	OUD – strong certainty

Wunsch[77]	2008	USA	Cross-sectional	34	43.9 (21-66)	N/A	62	DSM-IV opioid abuse/dependence	Yes	OUD – strong certainty
Young-Wolff[55]	2017	USA	Retrospective cohort	972	21-44 (197); 45-64 (512); 65+ (194)	22	7.5	ICD-9 opioid abuse and dependence	Yes	OUD – strong certainty

ABC: Addiction Behaviors Checklist; AAPM: American Academy of Pain Management; COMM: Current Opioid Misuse Measure; DSM: Diagnostic and Statistical Manual of Mental Disorders; ICD: International Statistical Classification of Diseases and Related Health Problems; NIDA: National Institute of Drug Abuse; N/A: not applicable; OUD: Opioid Use Disorder; UK: United Kingdom; USA: United States of America; WHO: World Health Organization

Appendix 12: Risk of Bias of Included Studies

Table 3. Risk of bias and statistical characteristics of included studies

Author	Year	Representative ness of study population	Validated outcome measure	Proportion of loss to follow up (%)	Valid predictor measurement	Model adjusted for age, gender, substance abuse, and mental illness or antipsychotic medication use	Independent variables chosen purposefully before analysis	All factors were included in final analysis
Boscarino	2015	Low	Low	High	N/A	N/A	N/A	N/A
Bouckoms	1992	Low	High	Low	Low	High	No	No
Callinan	2017	Low	High	Low	N/A	N/A	N/A	N/A
Chabal	1997	Low	High	Low	N/A	N/A	N/A	N/A
Campbell	2015	Low	Low	Low	Low	Low	Yes	No
Coloma-Carmona	2019	Low	Low	Low	N/A	N/A	N/A	N/A
Coutinho	2018	Low	Low	Low	N/A	N/A	N/A	N/A
Degenhardt	2015	Low	Low	Low	N/A	N/A	N/A	N/A
Edlund	2007	Low	Low	Low	Low	Low	Yes	Yes
Edlund	2014	Low	Low	Low	Low	Low	Yes	Yes
Feingold	2017	Low	Low	High	N/A	N/A	N/A	N/A
Fleming	2008	Low	Low	Low	N/A	N/A	N/A	N/A
Gardner	2019	High	Low	Low	Low	High	Yes	No
Hoffman	2017	Low	Low	High	N/A	N/A	N/A	N/A
Hojsted	2010	Low	Low	High	N/A	N/A	N/A	N/A
Huffman	2013	Low	Low	Low	N/A	N/A	N/A	N/A
Huffman	2015	Low	Low	Low	N/A	N/A	N/A	N/A
Hylan	2015	Low	High	Low	Low	High	Yes	No
Kouyanou	1997	Low	Low	High	N/A	N/A	N/A	N/A
Lovejoy	2016	High	Low	Low	N/A	N/A	N/A	N/A
McHugh	2016	Low	Low	Low	N/A	N/A	N/A	N/A
Von Korff	2017	Low	Low	Low	N/A	N/A	N/A	N/A
Wunsch	2008	Low	Low	Low	N/A	N/A	N/A	N/A
Young-Wolff	2017	Low	Low	High	Low	Low	Yes	Yes

N/A: not applicable

Appendix 13: GRADE Evidence Profiles

Table 4. GRADE Evidence Profile: Predictors of Opioid Use Disorder in Patients with Chronic Noncancer Pain

No. of Participants; No. of Studies; Follow-Up (months)	Quality Assessment						Summary of Findings		
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	Relative Effect, OR (95% CI)	Baseline Risk (%)	Anticipated Absolute Effects
									Risk Difference (95% CI)
Predictor 1. Age younger vs. older									
19329; 3; 24-60	No serious risk of bias$_a$	Serious inconsistency$_b$	No serious indirectness	Serious imprecision$_c$	Uncertain: only three studies	Low	1.6 (1.11 to 2.30)	5.8	3.2 more (0.6 more to 6.6 more) patients with per 10-year decrement of age developing OUD
Predictor 2. Current smoker yes vs. no									
4709; 4; 1-24	No serious risk of bias$_a$	No serious inconsistency	No serious indirectness	Serious imprecision$_c$	Uncertain: only three studies	Moderate	1.63 (1.25 to 2.12)	5.8	3.3 more (1.3 to 5.7 more) patients who are smokers developing OUD
Predictor 3. Sex male vs. female									
16577; 2; 24-60	No serious risk of bias$_a$	No serious inconsistency	No serious indirectness	Serious imprecision$_c$	Uncertain: only two studies	Moderate	1.50 (1.05 to 2.14)	5.8	2.7 more (0.3 to 5.8 more) male patients developing OUD

Predictor 4. History of mental health disorder yes vs. no									
19418; 4; 24-60	No serious risk of bias[a]	No serious inconsistency	No serious indirectness	Serious imprecision[c]	Uncertain: only four studies	Moderate	1.49 (1.17 to 1.89)	5.8	2.6 more (0.9 to 4.6 more) patients with history of mental health disorder developing OUD
Predictor 5. History of alcohol abuse/dependence yes vs. no									
4169; 2; 1-24	No serious risk of bias[a]	No serious inconsistency	No serious indirectness	Serious imprecision[cd]	Uncertain: only two studies	Moderate	1.32 (0.84 to 2.07)	5.8	1.7 more (0.9 less to 5.5 more) patients with history of alcohol abuse/dependence developing OUD
Predictor 6. History of drug abuse yes vs. no									
19329; 3; 24-60	No serious risk of bias[a]	Serious inconsistency[b]	No serious indirectness	Serious imprecision[cd]	Uncertain: only three studies	Low	1.51 (0.75 to 3.02)	5.8	2.7 more (1.4 less to 9.9 more) patients with history of drug abuse developing OUD

Abbreviations: CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; OUD, opioid use disorder; OR, odds ratio.

[a]We did not rate down for risk of bias, because our subgroup analyses and metaregression did not identify any significant difference between each risk of bias component and the estimates of association

[b]We rated down because of inconsistency, because the confidence intervals did not overlap

[c]We rated down because of imprecision, because the 95% CI associated with the risk difference included our threshold of 2% for modifiable factors and 3% for nonmodifiable factors, which means clinical actions on the basis of the estimates in the lower or upper boundary may be different.

[d]We rated down because of imprecision, because the 95% CI for the pooled effect overlapped 1 (no effect)

Appendix 14: Meta-Analysis of the Prevalence of Opioid Use Disorder at the Longest Follow-up

Author	Year		ES (95% CI)	% Weight	n/N
Bouckoms	1992		0.237 (0.147, 0.360)	4.10	14/59
Chabal	1997		0.618 (0.506, 0.719)	4.24	47/76
Kouyanou	1997		0.115 (0.064, 0.199)	4.31	10/87
Edlund	2007		0.020 (0.018, 0.022)	4.83	298/15160
Fleming	2008		0.110 (0.091, 0.132)	4.78	99/904
Wunsch	2008		0.618 (0.450, 0.761)	3.70	21/34
Hojsted	2010		0.144 (0.101, 0.202)	4.57	27/187
Huffman	2013		0.325 (0.248, 0.413)	4.44	39/120
Edlund	2014		0.002 (0.002, 0.002)	4.83	347/197269
Boscarino	2015		0.413 (0.377, 0.449)	4.76	291/705
Degenhardt	2015		0.208 (0.188, 0.230)	4.80	293/1409
Huffman	2015		0.437 (0.370, 0.507)	4.59	87/199
Hylan	2015		0.009 (0.006, 0.013)	4.81	25/2752
Lovejoy	2016		0.038 (0.013, 0.105)	4.27	3/80
McHugh	2016		0.608 (0.471, 0.730)	4.01	31/51
Callinan	2017		0.096 (0.054, 0.163)	4.43	11/115
Feingold	2017		0.526 (0.485, 0.568)	4.74	290/551
Hoffman	2017		0.030 (0.023, 0.038)	4.81	59/1993
Von Korff	2017		0.225 (0.205, 0.246)	4.80	357/1588
Young-Wolff	2017		0.079 (0.063, 0.098)	4.78	73/927
Coutinho	2018		0.022 (0.020, 0.024)	4.83	455/21072
Coloma-Carmona	2019		0.570 (0.502, 0.636)	4.60	118/207
Overall ($I^2 = 99.736\%$, p = 0.000)			0.196 (0.146, 0.251)	100.00	

0   .05   .1   .2   .3   .4   .5   .6   .7   .8

Figure 3. Overall prevalence of opioid use disorder.
*Used DSM-5 criteria with conditional exclusions (without tolerance and withdrawal criteria) for Degenhardt 2015 and Von Korff 2017
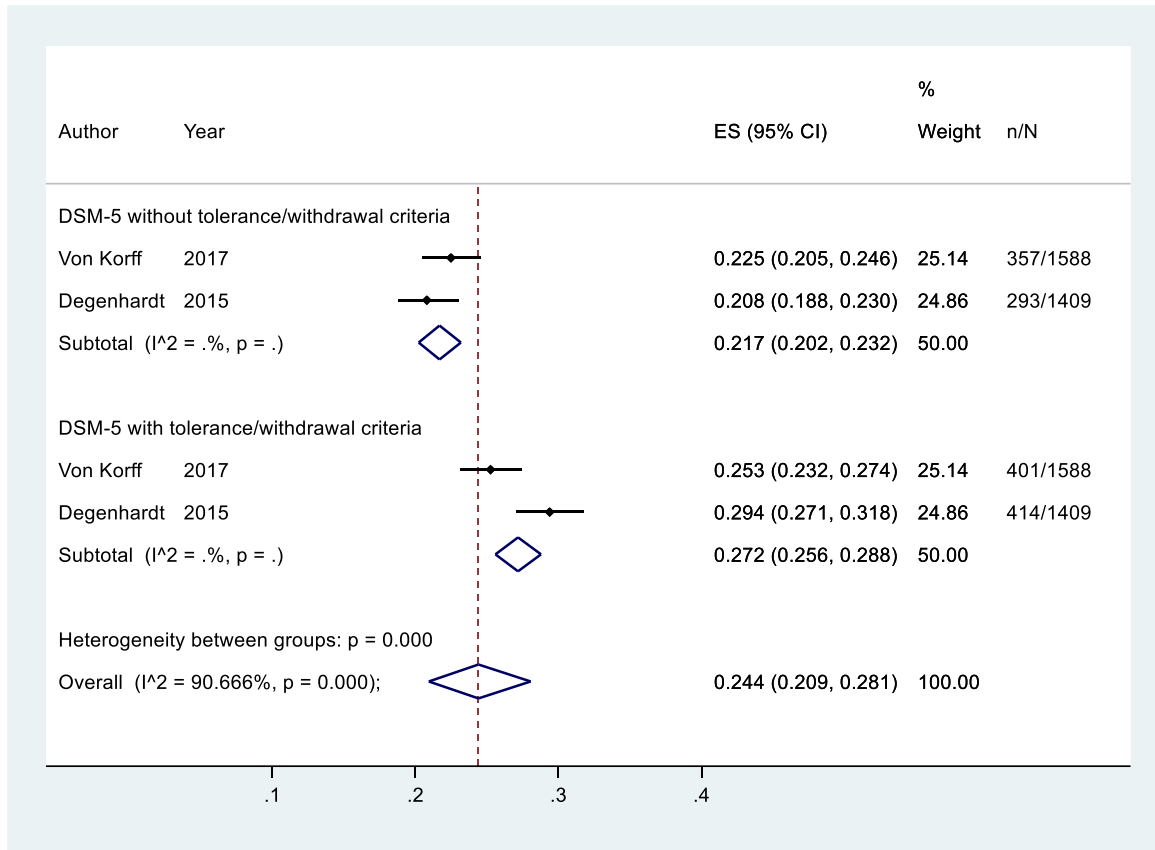
Figure 4. Subgroup analysis of prevalence of opioid use disorder: DSM-5 with vs. without tolerance and withdrawal criteria (interaction p<0.001) from within-study comparisons using Freeman-Tukey transformation.
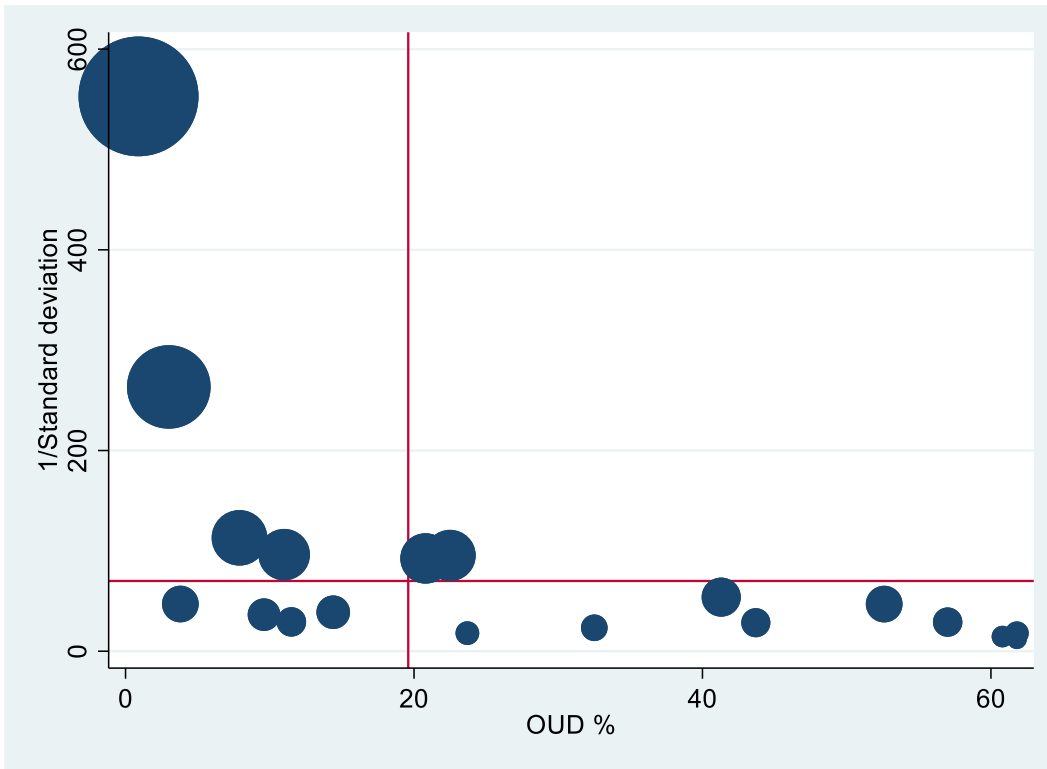
Figure 5. Funnel plot of proportion of opioid use disorder vs. 1/standard deviation (19 studies after excluding 3 studies with sample size >15000 (15,160, 21,072, and 197,269 with OUD % of 2%, 2.2% and 0.2% respectively.
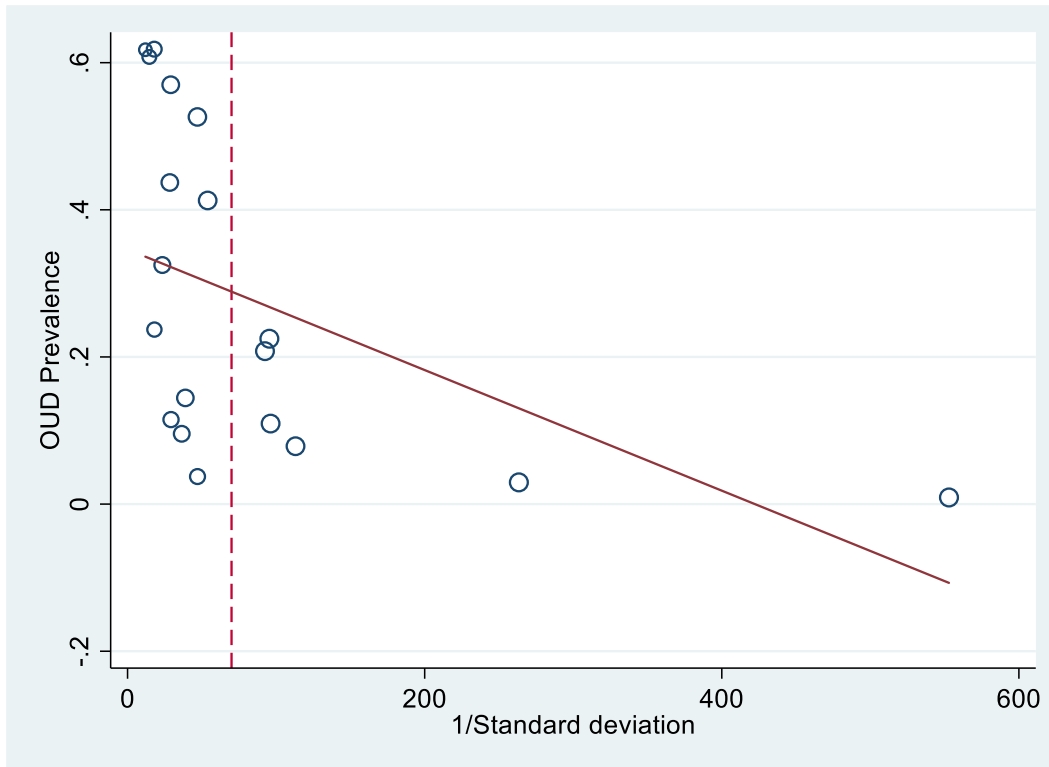
Figure 6. Meta-regression for opioid use disorder vs. 1/standard deviation (19 studies after excluding 3 largest studies with 15,160, 21,072, and 197,269 patients with OUD % of 2%, 2.2% and 0.2% respectively, P=0.02).

Figure 7. Subgroup analysis prevalence of opioid use disorder: Small (<900) vs. large studies (interaction p<0.001).

Author	Year		ES (95% CI)	% Weight	n/N
1a. OUD-strong certainty					
Kouyanou	1997		0.115 (0.064, 0.199)	4.31	10/87
Edlund	2007		0.020 (0.018, 0.022)	4.83	298/15160
Fleming	2008		0.110 (0.091, 0.132)	4.78	99/904
Wunsch	2008		0.618 (0.450, 0.761)	3.70	21/34
Hojsted	2010		0.144 (0.101, 0.202)	4.57	27/187
Huffman	2013		0.325 (0.248, 0.413)	4.44	39/120
Edlund	2014		0.002 (0.002, 0.002)	4.83	347/197269
Boscarino	2015		0.413 (0.377, 0.449)	4.76	291/705
Degenhardt	2015		0.208 (0.188, 0.230)	4.80	293/1409
Huffman	2015		0.437 (0.370, 0.507)	4.59	87/199
Lovejoy	2016		0.038 (0.013, 0.105)	4.27	3/80
Feingold	2017		0.526 (0.485, 0.568)	4.74	290/551
Hoffman	2017		0.030 (0.023, 0.038)	4.81	59/1993
Von Korff	2017		0.225 (0.205, 0.246)	4.80	357/1588
Young-Wolff	2017		0.079 (0.063, 0.098)	4.78	73/927
Coutinho	2018		0.022 (0.020, 0.024)	4.83	455/21072
Coloma-Carmona	2019		0.570 (0.502, 0.636)	4.60	118/207
Subtotal (I^2 = 99.788%, p = 0.000)			0.182 (0.127, 0.243)	78.41	
1b. OUD-less certainty					
Bouckoms	1992		0.237 (0.147, 0.360)	4.10	14/59
Chabal	1997		0.618 (0.506, 0.719)	4.24	47/76
Hylan	2015		0.009 (0.006, 0.013)	4.81	25/2752
McHugh	2016		0.608 (0.471, 0.730)	4.01	31/51
Callinan	2017		0.096 (0.054, 0.163)	4.43	11/115
Subtotal (I^2 = 98.900%, p = 0.000)			0.264 (0.031, 0.609)	21.59	
Heterogeneity between groups: p = 0.587					
Overall (I^2 = 99.736%, p = 0.000);			0.196 (0.146, 0.251)	100.00	

Figure 8. Subgroup analysis of prevalence of opioid use disorder: Strong vs. less certainty of DSM-5 criteria (interaction p=0.56).
***Used DSM-5 criteria with conditional exclusions (without tolerance and withdrawal criteria) for Degenhardt 2015 and Von Korff 2017**

Author	Year	OUD instrument	ES (95% CI)	% Weight	n/N
Underestimate OUD					
Bouckoms	1992	WHO Addiction	0.237 (0.147, 0.360)	6.91	14/59
Kouyanou	1997	DSM-III abuse/dependence	0.115 (0.064, 0.199)	7.22	10/87
Hojsted	2010	ICD-10 addiction	0.144 (0.101, 0.202)	7.62	27/187
Edlund	2014	ICD-9 OUD	0.002 (0.002, 0.002)	8.00	347/197269
Boscarino	2015	DSM-IV dependence	0.356 (0.322, 0.392)	7.89	251/705
Degenhardt	2015	ICD-10 use disorder	0.186 (0.167, 0.207)	7.95	265/1422
Huffman	2015	DSM-IV-TR and AAPM Therapeutic opioid addiction	0.437 (0.370, 0.507)	7.64	87/199
Callinan	2017	Self-reported	0.096 (0.054, 0.163)	7.40	11/115
Feingold	2017	DSM-IV dependence	0.526 (0.485, 0.568)	7.86	290/551
Hoffman	2017	ICD-9 dependence	0.030 (0.023, 0.038)	7.96	59/1993
Young-Wolff	2017	ICD-9 OUD	0.079 (0.063, 0.098)	7.92	73/927
Coutinho	2018	ICD-9 abuse	0.022 (0.020, 0.024)	7.99	455/21072
Coloma-Carmona	2019	DSM-IV-TR OUD	0.570 (0.502, 0.636)	7.65	118/207
Subtotal (I^2 = 99.774%, p = 0.000)			0.177 (0.113, 0.252)	100.00	
Similar estimate as DSM-5					
Edlund	2007	ICD-9 abuse/dependence	0.020 (0.018, 0.022)	12.76	298/15160
Fleming	2008	DSM-IV SUD	0.110 (0.091, 0.132)	12.72	99/904
Wunsch	2008	DSM-IV abuse/dependence	0.618 (0.450, 0.761)	11.65	21/34
Huffman	2013	DSM-IV addiction	0.325 (0.248, 0.413)	12.42	39/120
Boscarino	2015	DSM-5	0.413 (0.377, 0.449)	12.71	291/705
Degenhardt	2015	DSM-5 with tolerance/withdrawal criteria	0.294 (0.271, 0.318)	12.74	414/1409
Lovejoy	2016	DSM-IV abuse/dependence	0.038 (0.013, 0.105)	12.26	3/80
Von Korff	2017	DSM-5 with tolerance/withdrawal criteria	0.253 (0.232, 0.274)	12.74	401/1588
Subtotal (I^2 = 99.719%, p = 0.000)			0.224 (0.086, 0.403)	100.00	
Overestimate OUD					
Chabal	1997	Author's definition	0.618 (0.506, 0.719)	33.28	47/76
Hylan	2015	NIDA Prescription misuse or abuse	0.009 (0.006, 0.013)	33.61	25/2752
McHugh	2016	Opioid misuse: combination of COMM and ABC	0.608 (0.471, 0.730)	33.11	31/51
Subtotal (I^2 = .%, p = .)			0.344 (0.000, 0.915)	100.00	

Figure 9. Subgroup analysis of prevalence of opioid use disorder: Underestimate vs. similar as DSM-5 vs. overestimate instruments (interaction p=0.34).
*Used DSM-5 criteria without conditional exclusions (with tolerance and withdrawal criteria) for Degenhardt 2015 and Von Korff 2017

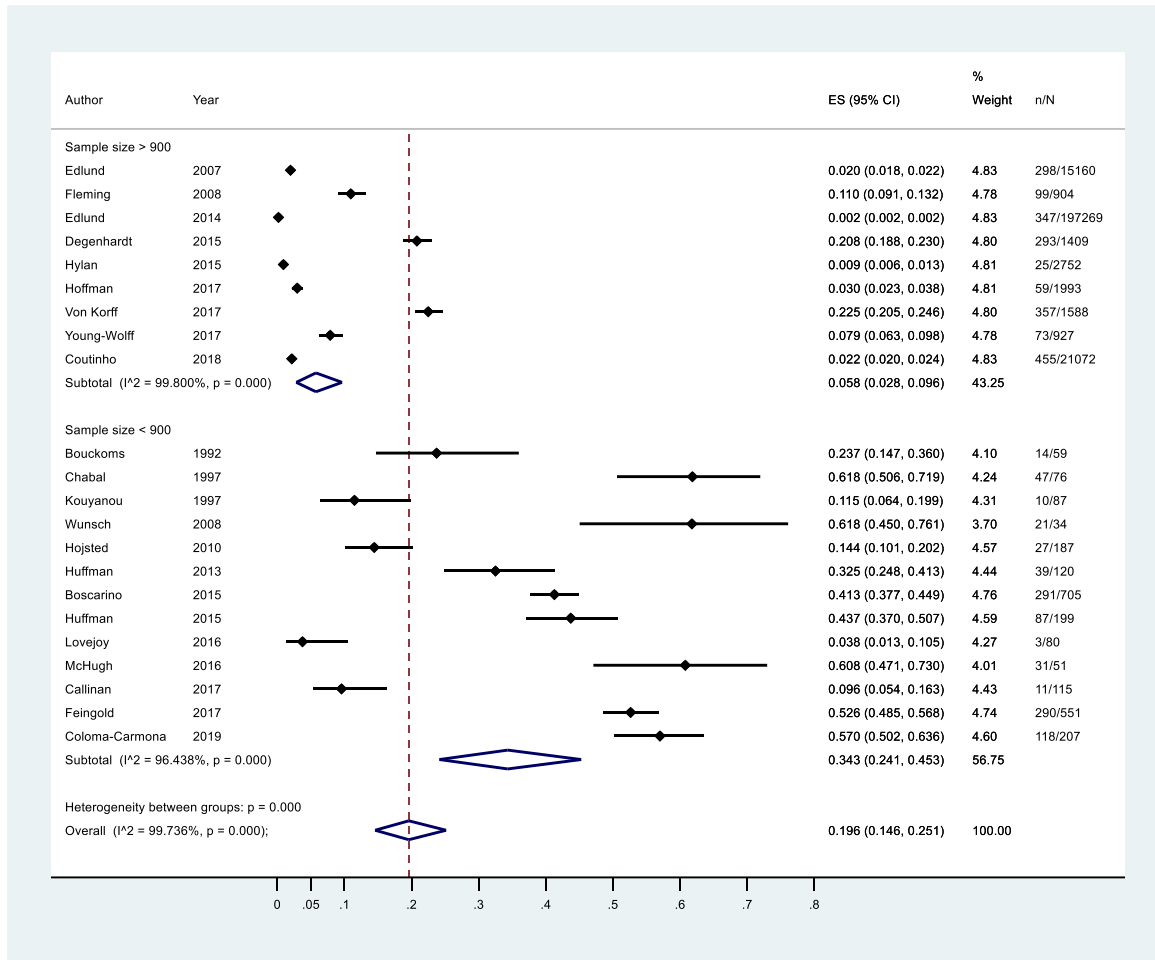| | | | | % | |
Author	Year		ES (95% CI)	Weight	n/N
Mild					
Chabal	1997		0.342 (0.245, 0.454)	9.04	26/76
Fleming	2008		0.011 (0.006, 0.020)	10.35	10/904
Boscarino	2015		0.281 (0.249, 0.315)	10.31	198/705
Degenhardt	2015		0.118 (0.102, 0.136)	10.40	166/1409
Coloma-Carmona	2019		0.304 (0.246, 0.370)	9.90	63/207
Subtotal (I^2 = 99.012%, p = 0.000)			0.182 (0.063, 0.345)	50.00	
Moderate to severe					
Chabal	1997		0.276 (0.188, 0.386)	9.04	21/76
Fleming	2008		0.098 (0.081, 0.120)	10.35	89/904
Boscarino	2015		0.132 (0.109, 0.159)	10.31	93/705
Degenhardt	2015		0.090 (0.076, 0.106)	10.40	127/1409
Coloma-Carmona	2019		0.266 (0.210, 0.330)	9.90	55/207
Subtotal (I^2 = 93.269%, p = 0.000)			0.155 (0.105, 0.211)	50.00	
Heterogeneity between groups: p = 0.717					
Overall (I^2 = 98.062%, p = 0.000);			0.170 (0.107, 0.244)	100.00	

0   .05   .1   .2   .3   .4   .5

Figure 10. Subgroup analysis of prevalence of opioid use disorder: Moderate to severe vs. mild opioid use disorder (interaction p=0.65) from within-study comparisons.
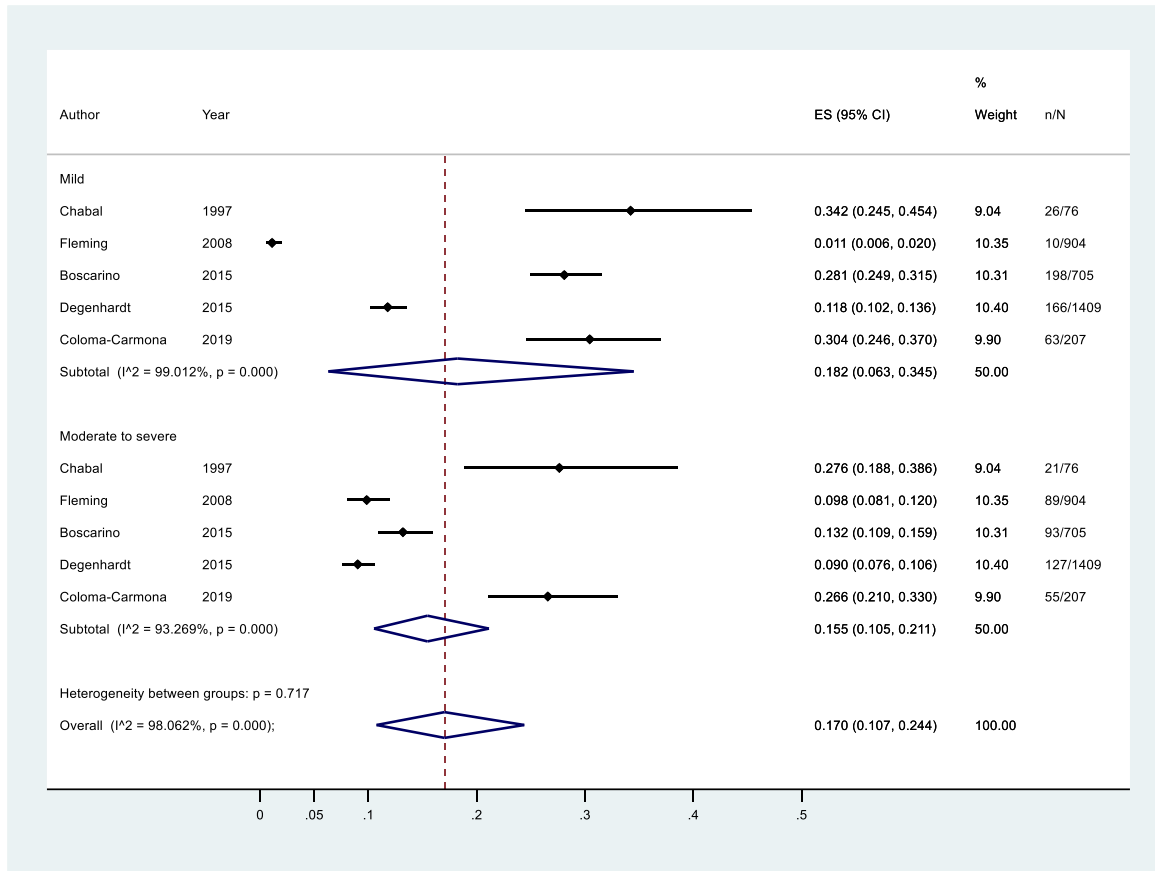***Used DSM-5 criteria with conditional exclusions (without tolerance and withdrawal criteria) for Degenhardt 2015 and Von Korff 2017**

Figure 11. Subgroup analysis of prevalence of opioid use disorder: Male vs. female (interaction p=0.86) from within-study comparisons.

Figure 12. Subgroup analysis of prevalence of opioid use disorder: High vs. low risk of bias (interaction p=0.92) for valid outcome measures.
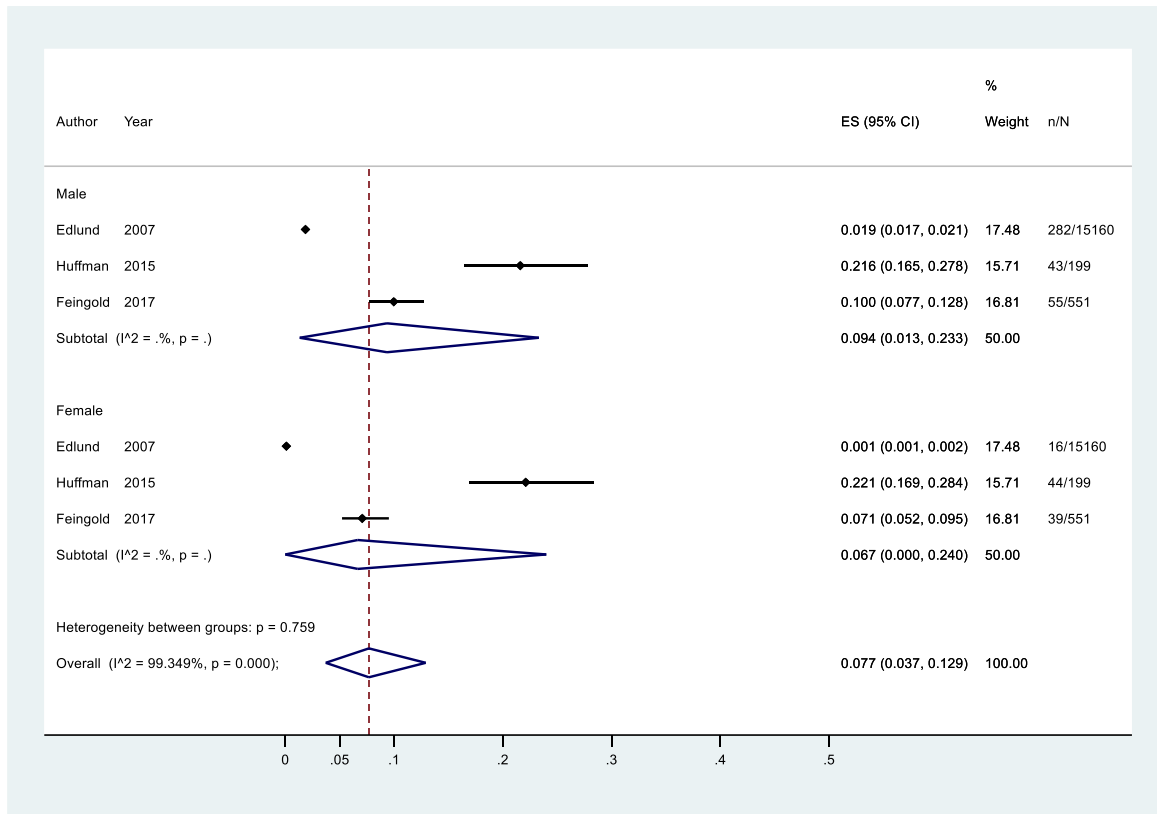***Used DSM-5 criteria with conditional exclusions (without tolerance and withdrawal criteria) for Degenhardt 2015 and Von Korff 2017**

Figure 13. Subgroup analysis of prevalence of opioid use disorder: High (>20%) vs. low risk of bias (interaction p=0.88) for loss to follow-up.
*Used DSM-5 criteria with conditional exclusions (without tolerance and withdrawal criteria) for Degenhardt 2015 and Von Korff 2017
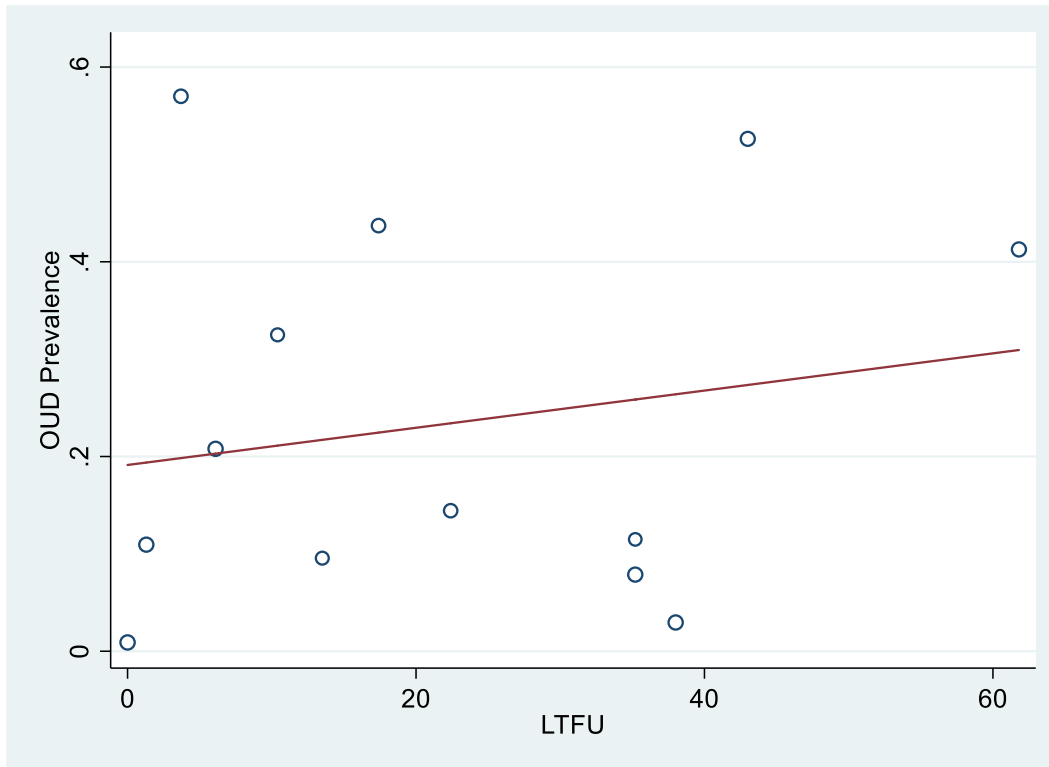
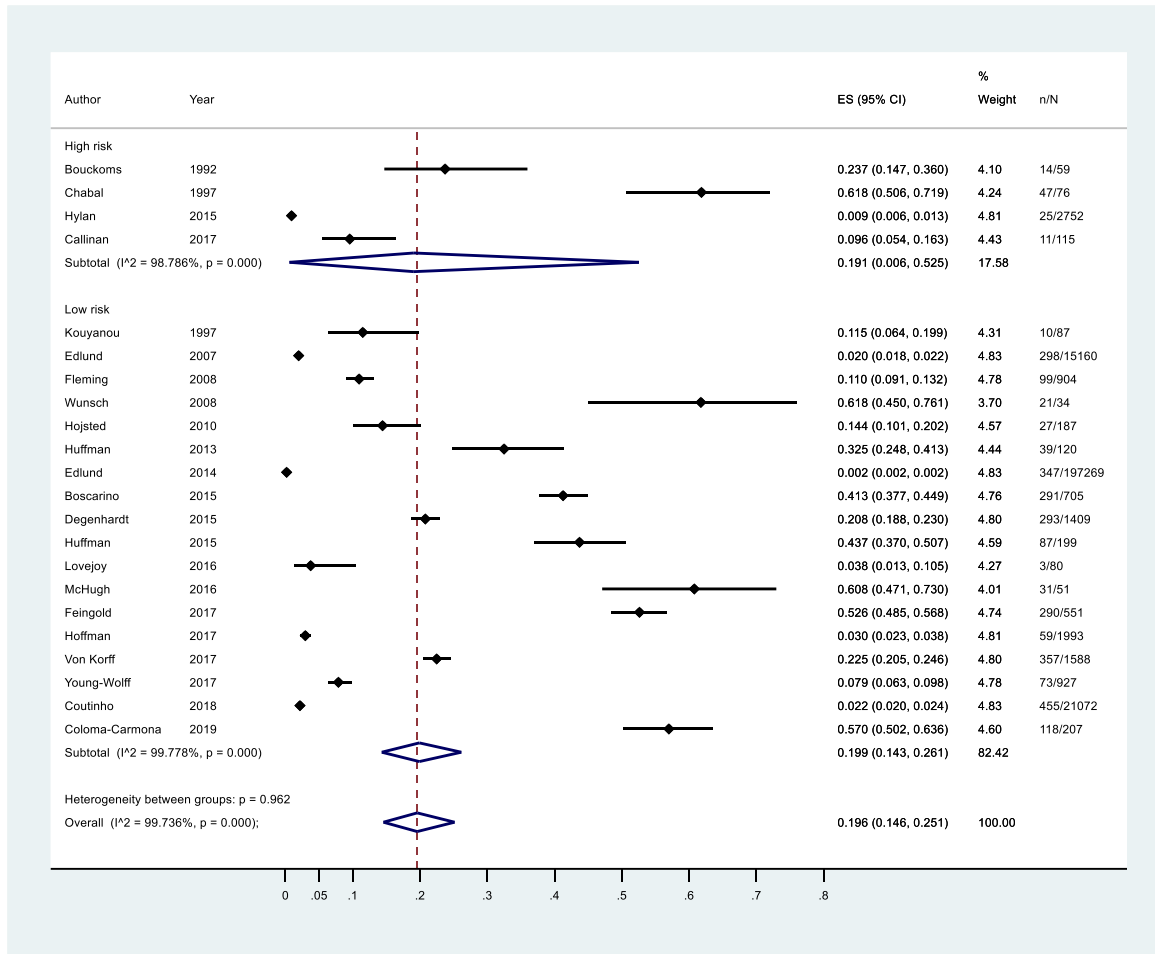**Figure 14. Meta-regression for prevalence of opioid use disorder and proportion of loss to follow-up (interaction p=0.46).**
*Used DSM-5 criteria with conditional exclusions (without tolerance and withdrawal criteria) for Degenhardt 2015 and Von Korff 2017
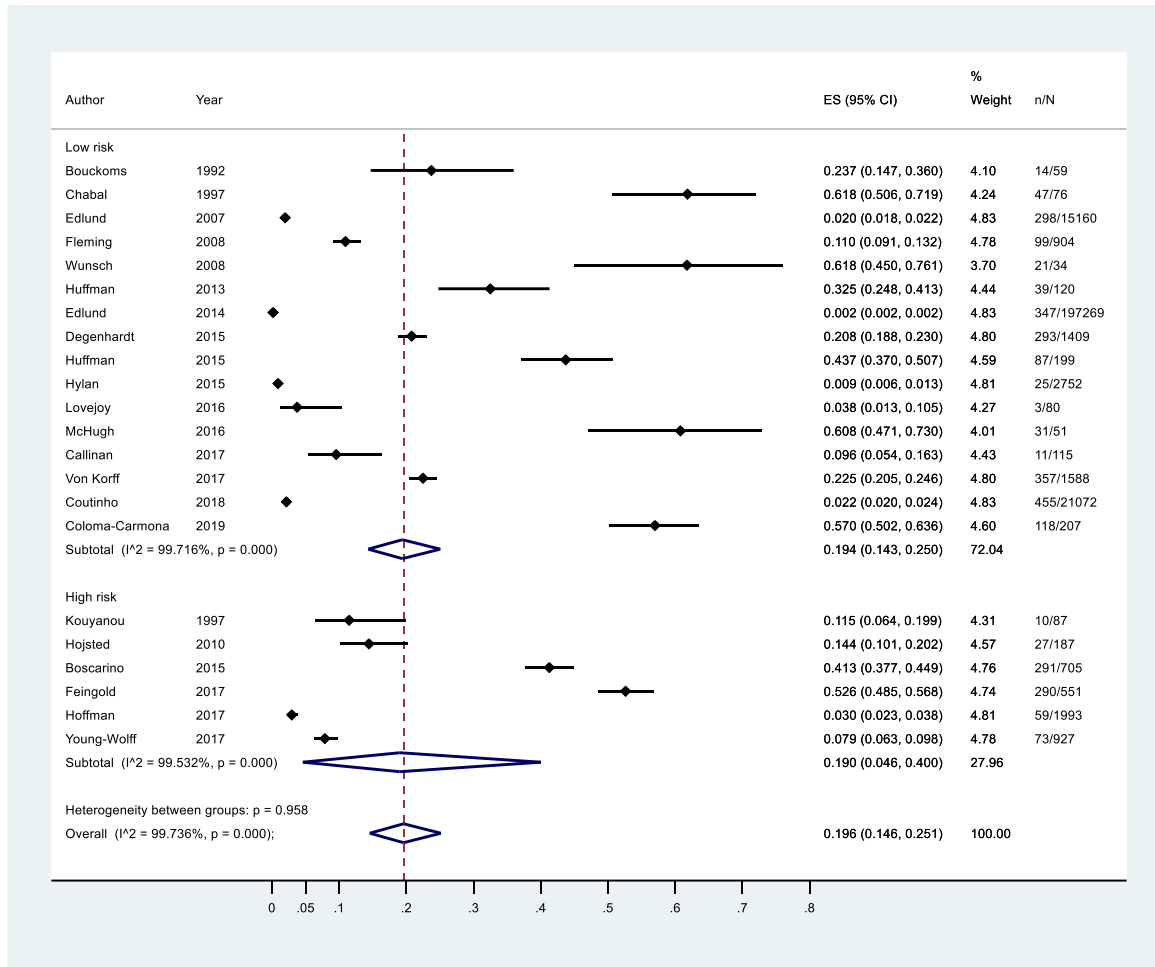
Appendix 15: Meta-Analysis of the Association of Significant Predictors for Opioid Use Disorder

Author	Year	Sample size	Adjusted OR (95% CI)	% Weight
Edlund	2007	15160	2.33 (1.92, 2.82)	33.15
Campbell	2015	1417	1.36 (1.10, 1.67)	32.64
Hylan	2015	2752	1.30 (1.12, 1.52)	34.21
Overall			1.60 (1.11, 2.30)	100.00

NOTE: Weights are from random effects analysis
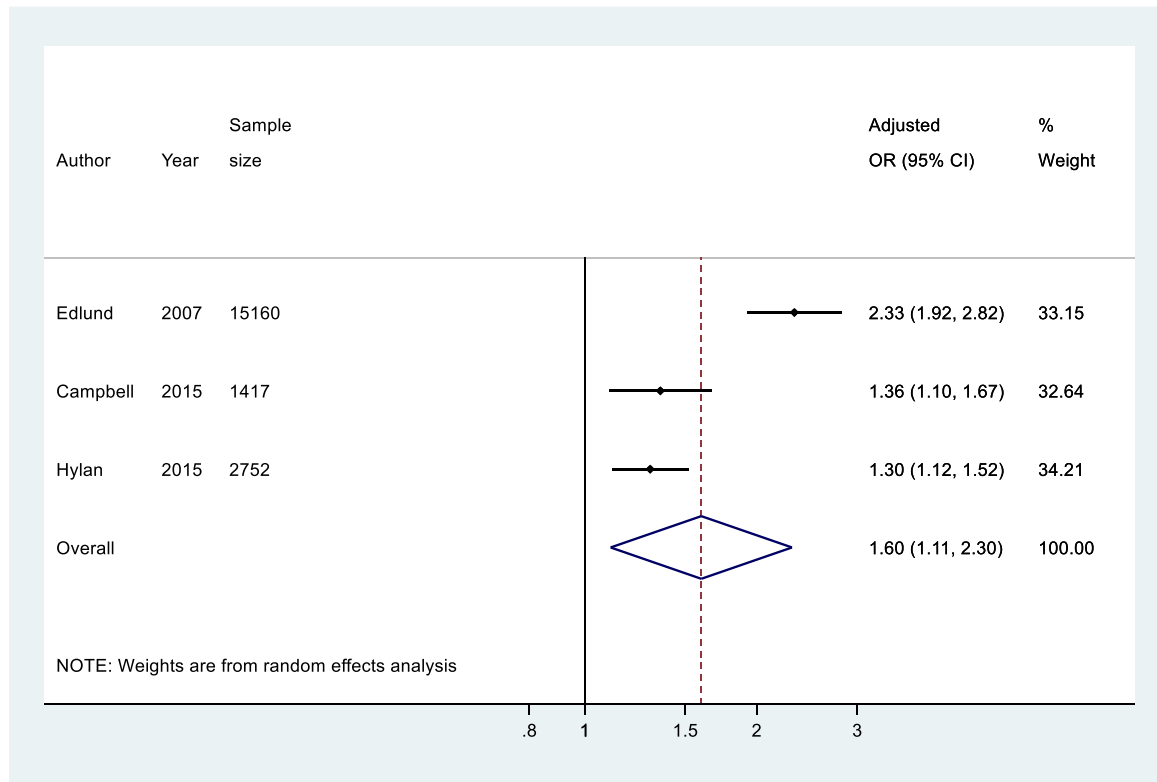
Figure 15. Predictor of opioid use disorder: Age (every 10-year decrease).

Author	Year	Sample size		Adjusted OR (95% CI)	% Weight
Campbell	2015	1417		1.61 (0.99, 2.63)	29.08
Hylan	2015	2752		1.47 (1.03, 2.09)	56.50
Young-Wolff	2017	184	Male	2.98 (0.85, 10.42)	4.45
Young-Wolff	2017	356	Female	2.30 (1.00, 5.31)	9.97
Overall				1.63 (1.25, 2.12)	100.00

NOTE: Weights are from random effects analysis

Current smokers vs. not
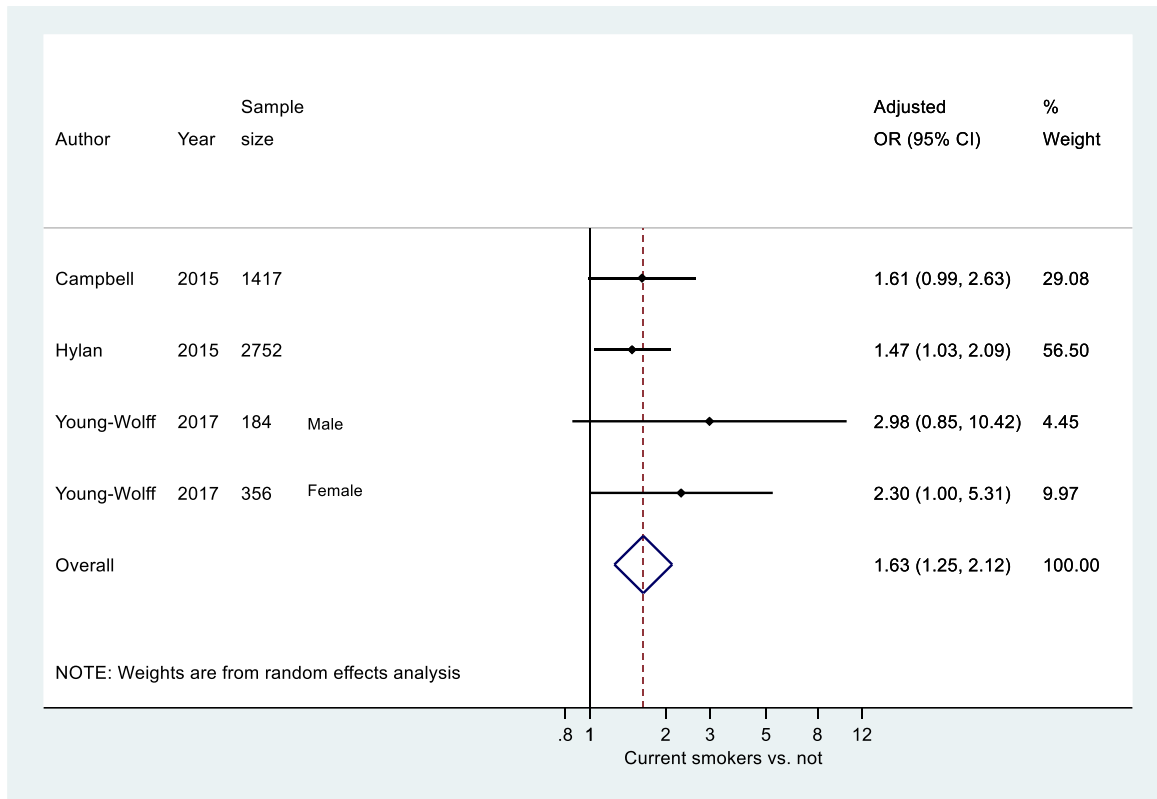
Figure 16. Predictor of opioid use disorder: Current smoker (yes vs. no).

Figure 17. Predictor of opioid use disorder: Male vs. female.

Author	Year	Sample size		Adjusted OR (95% CI)	% Weight
Edlund	2007	15160		1.46 (1.12, 1.91)	44.89
Campbell	2015	1417		1.02 (0.61, 1.70)	18.26
Hylan	2015	2752		1.73 (1.22, 2.45)	32.45
Gardner	2019	89		2.77 (0.90, 8.57)	4.41
Overall				1.49 (1.17, 1.89)	100.00

NOTE: Weights are from random effects analysis

History of mental health disorder: yes vs. no

Figure 18. Predictor of opioid use disorder: History of mental health disorders (yes vs. no).

Appendix 16: Subgroup Analyses of Pre-Defined Factors for Opioid Use Disorder

Author	Year	Sample size		Adjusted OR (95% CI)	% Weight
Low risk					
Edlund	2007	15160		1.46 (1.12, 1.91)	44.89
Campbell	2015	1417		1.02 (0.61, 1.70)	18.26
Subtotal				1.31 (0.95, 1.81)	63.14
High risk					
Hylan	2015	2752		1.73 (1.22, 2.45)	32.45
Gardner	2019	89		2.77 (0.90, 8.57)	4.41
Subtotal				1.80 (1.29, 2.51)	36.86
Overall				1.49 (1.17, 1.89)	100.00

NOTE: Weights are from random effects analysis

History of mental health disorder: yes vs. no
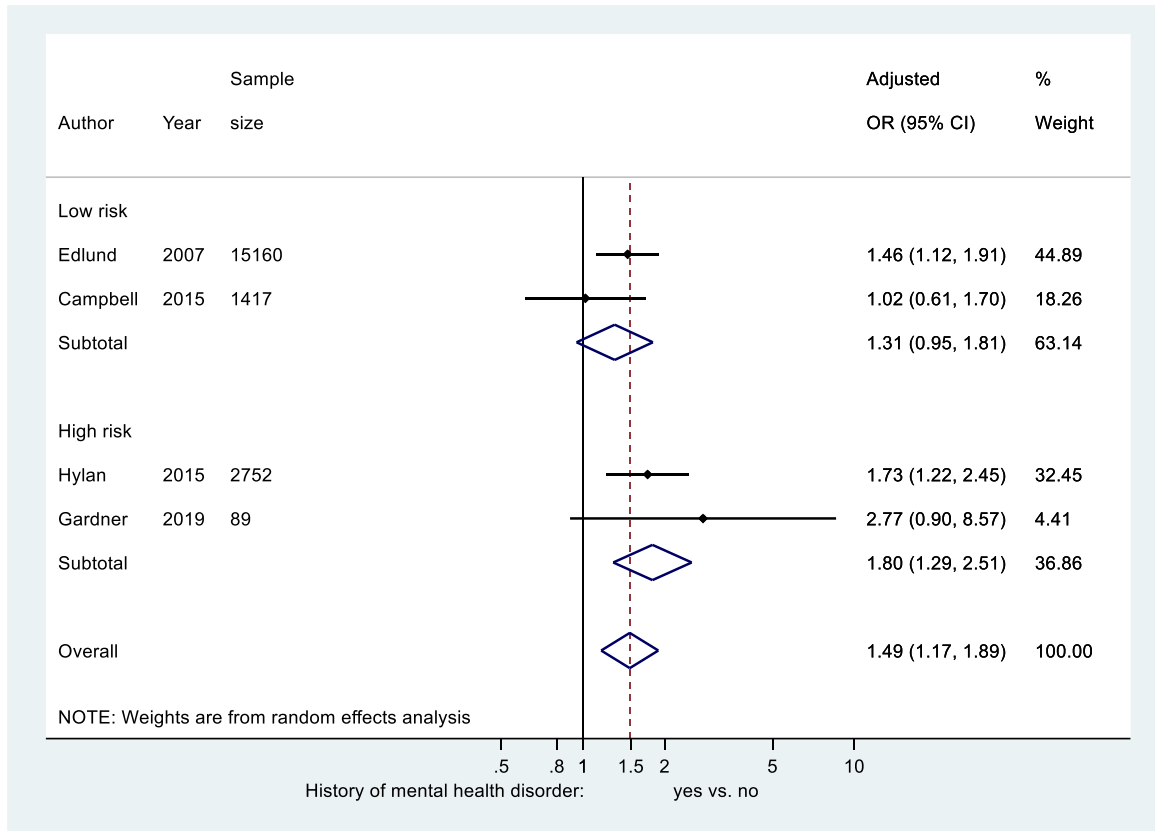
Figure 19. Subgroup analysis of history of mental health disorders - appropriately adjusted vs. not (interaction p=0.91).
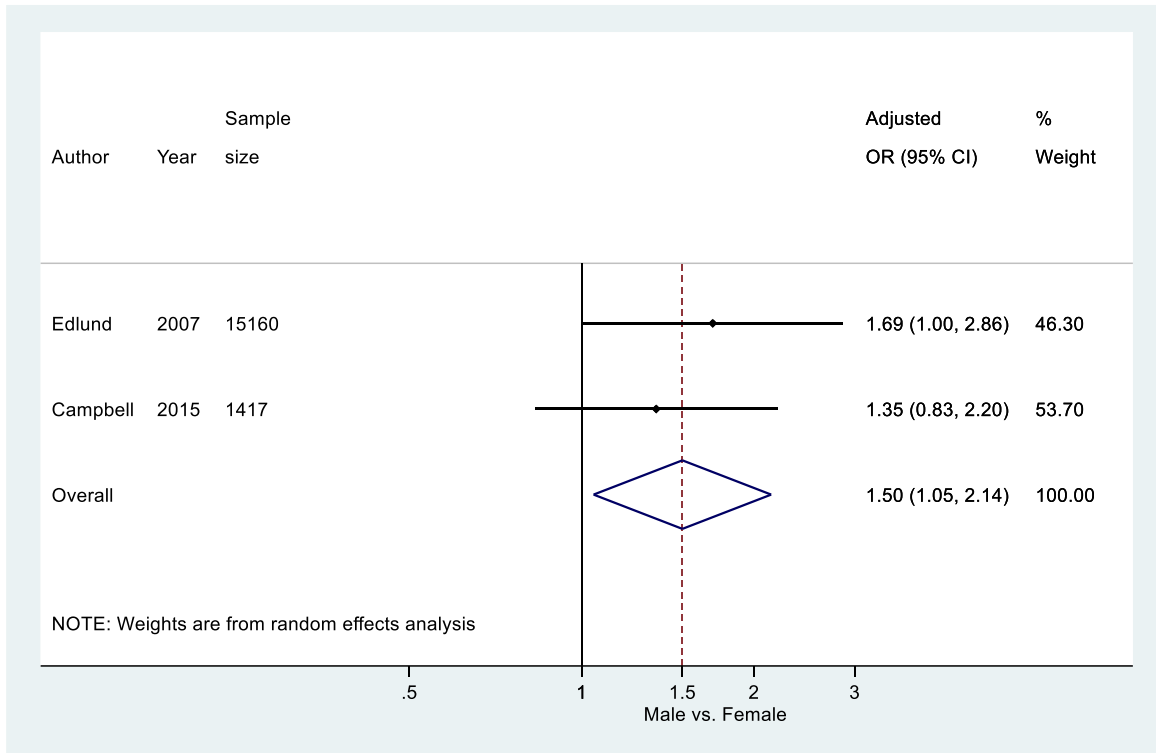
Appendix 17: Meta-Analysis of the Association of Non-Significant Predictors for Opioid Use Disorder

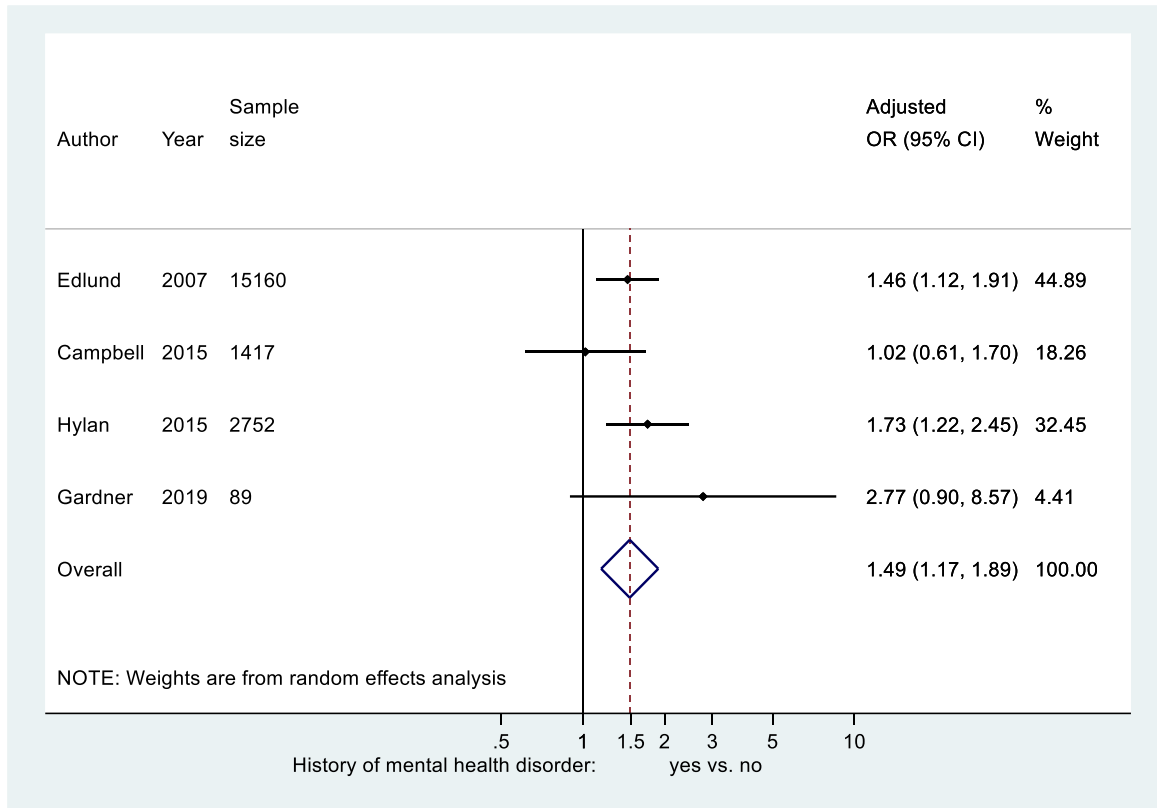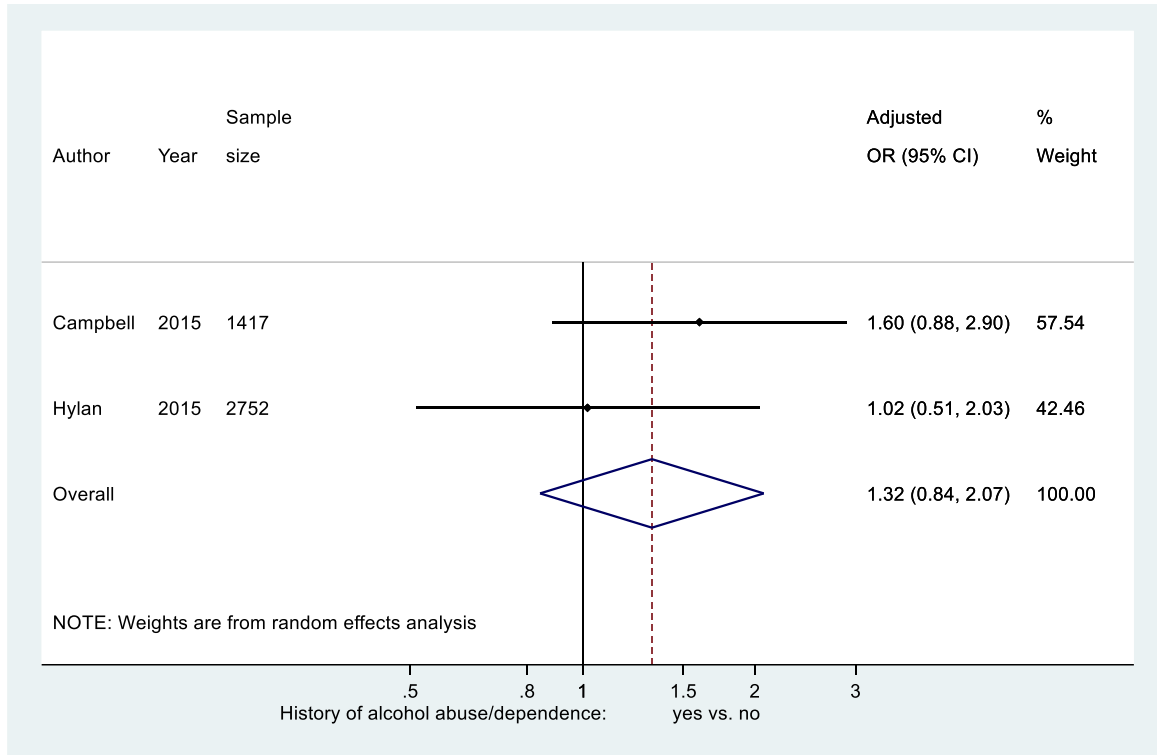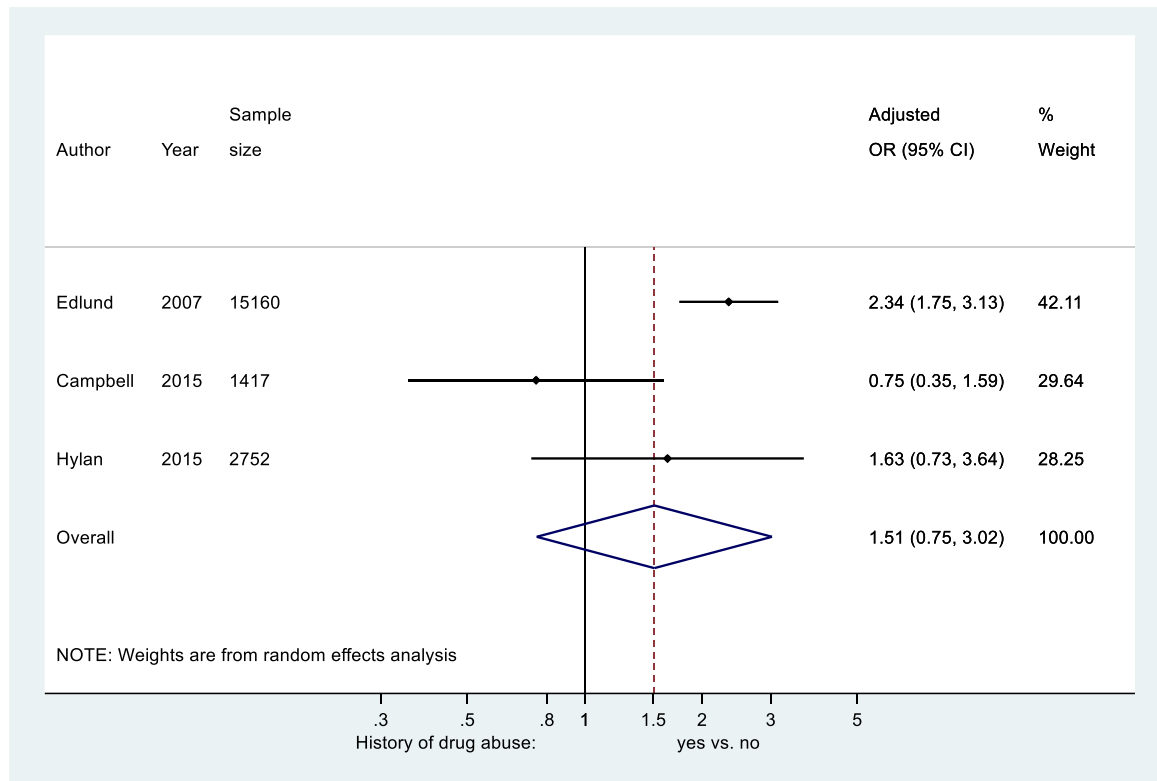**Figure 20. Predictor of opioid use disorder: History of alcohol abuse/dependence (yes vs. no).**

Author	Year	Sample size		Adjusted OR (95% CI)	% Weight
Edlund	2007	15160		2.34 (1.75, 3.13)	42.11
Campbell	2015	1417		0.75 (0.35, 1.59)	29.64
Hylan	2015	2752		1.63 (0.73, 3.64)	28.25
Overall				1.51 (0.75, 3.02)	100.00

NOTE: Weights are from random effects analysis

.3   .5   .8 1   1.5 2   3   5

History of drug abuse: yes vs. no

Figure 21. Predictor of opioid use disorder: History of drug abuse (yes vs. no).

Appendix 18: Significant associations of 7 unpooled predictors with opioid use disorder.

Table 5. Significant associations of 7 unpooled predictors with opioid use disorder.

Predictor	Significant associations with OUD		Non-significant association	Total	Notes for significant results
	No. studies (n)	**OR/HR/RR (95% CI) or beta-coefficient**	**No. studies (n)**	**No. studies (n)**	
Social-demographic factors					
Race	1 (15160)	Adjusted OR Black 0.6 (0.41 to 0.88); Other 1.49 (0.77 to 2.91); Unknown 0.47 (0.3 to 0.72)	1 (89)	2 (15249)	Black people and people of unknown race had a significantly decreased risk of OUD compared to white people
Marital status	1 (15160)	Adjusted OR Divorced 1.58 (1.22 to 2.06); Single 1.6 (1.02 to 2.51); Separated 1.84 (1.12 to 3.02); Widowed 1.21 (0.64 to 2.3)	2 (1506)	2 (16666)	Being divorced, single, or separated significantly increased risk of OUD compared to being married

Opioid-related factors

Days supplied of opioids	1 (15160)	Adjusted OR 1.84 (1.35 to 2.51)	1 (15160)	211+ days supplied of opioids significantly increased risk of OUD compared to 91-150 days
Non-authorized dose increase	1 (89)	Adjusted OR 6.12 (1.55 to 24.2)	1 (89)	Non-authorized dose increase significantly increased risk of OUD compared to no non-authorized dose increase
Borrow pain medicine	1 (89)	Adjusted OR 5.2 (1.24 to 21.9)	1 (89)	Borrowing pain medicine significantly increased risk of OUD compared to not borrowing pain medicine
Non-adherence, past 3 months	1 (1417)	Adjusted RR 2.47 (1.44 to 4.24)	1 (1417)	1 or more instances of nonadherence significantly increased risk of OUD compared to 0 instance of nonadherence
Health care utilization factors				
Days with physical health care visits	1 (15160)	Adjusted OR 7-11 days 1.07 (0.71 to 1.6); 12-19 days 1.24 (0.85 to 1.82); 20+ days 1.52 (1.03 to 2.25)	1 (15160)	20+ days of physical health care visits significantly increased risk of OUD compared to 0-6 days

OR: odds ratio; HR: hazard ratio; RR: relative risk; CI: confidence interval; OUD: opioid use disorder

Appendix 19: Non-significant associations of 23 unpooled predictors with opioid use disorder.

Table 6. Non-significant associations of 23 unpooled predictors with opioid use disorder.

	Predictor	Non-significant association No. studies (n)
Social-demographic factors	Mean past surgeries	1 (89)
	ED visits within 12 months	1 (89)
	Mean length of diagnosis	1 (89)
	Pain severity	1 (1417)
	Headache	2 (292561)
	Arthritis	2 (292561)
	Tertiary qualifications	1 (1417)
	Unemployed	1 (1417)
	Median number of pain conditions	1 (1417)
	Median years living with pain	1 (1417)
	Pain interference	1 (1417)
	Pain Self-Efficacy Questionnaire	1 (1417)
	Type of payment	1 (89)
	Back pain	1 (15160)
Opioid-related factors	Adequate pain control	1 (89)
	New user of chronic opioids	1 (15160)
	Current oxycodone prescription	1 (89)
	Mean opioid prescriptions	1 (89)
	Mean opioid pills	1 (89)
	Request early refill	1 (89)
	Pain contract	1 (89)
	Mean number of physicians prescribing	1 (89)
	Median daily opioid morphine equivalent (OME)	1 (1417)

ED: emergency department