CoLab Network

Systematic Review

Opioid Analgesics to Treat Chronic Noncancer Pain in Patients Prescribed Opioid Agonist Therapy or With Opioid Use Disorder

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Key Messages

This systematic review included 5 observational studies primarily exploring the safety of opioid analgesics alone or in combination with opioid agonist therapy for the management of chronic pain for patients with opioid use disorder or with a history of opioid use disorder.

The evidence synthesis team did not find any evidence to inform the efficacy or effectiveness of opioid analgesics for the management of chronic pain in the context of opioid use disorder and/or use of opioid agonist therapy.

The risk of fatal opioid-related toxicity may decrease in patients with chronic noncancer pain and opioid use disorder receiving both opioid analgesics and opioid agonist treatment compared to those receiving opioid analgesics only (low-certainty evidence).

It is uncertain whether:

- **the risk of fatal opioid-related toxicity is affected** in patients with chronic noncancer pain who are prescribed opioid analgesics and are diagnosed with opioid use disorder compared to those who are not diagnosed with opioid use disorder
- **the risk of fatal and nonfatal opioid-related toxicity** as a combined outcome is affected by long-term opioid analgesic therapy in patients with chronic noncancer pain and opioid use disorder
- **a history of opioid use disorder** in the past 2 years increases the prevalence and incidence of prolonged opioid analgesic use in patients with chronic noncancer pain
- **the dosage of prescribed opioid analgesics** is affected in patients with chronic noncancer pain and opioid use disorder receiving methadone maintenance treatment.

Further research is needed to better understand the safety and effectiveness of opioid analgesics in First Nations, Inuit, and Métis Peoples as well as other equity-deserving populations with chronic noncancer pain and opioid use disorder, and to improve certainty of evidence.

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Abbreviations

AMED	Allied and Complementary Medicine Database
AOR	adjusted odds ratio
CI	confidence interval
CNCP	chronic noncancer pain
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HR	hazard ratio
LTOT	long-term opioid therapy
MMT	methadone maintenance treatment
OAT	opioid agonist therapy
OR	odds ratio
OUD	opioid use disorder
PRISMA-P	Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Protocols
RCT	randomized controlled trial
ROR	ratio of odds ratios
RR	relative risk

Introduction and Rationale

Opioid use disorder (OUD) is a chronic and relapsing pattern of opioid use associated with significant impairment. It may occur in the context of prescription opioid use (i.e., for analgesia) or nonpharmaceutical opioid use.[1,2] OUD is a growing public health concern across North America, disproportionately impacting various sex and gender and age groups.[3]

Reliable national estimates are not available, but the prevalence of OUD in British Columbia is estimated to be 1.92%.[3,4] The number of individuals seeking treatment for OUD in Ontario increased more than six-fold between 2000 to 2016.[5] Rates of opioid-related harms vary nationally, with fatalities and hospitalization rates being highest in Canada's western regions.[6] OUD and opioid-related harms remain serious issues across the country, with opioid-related toxicity among the leading causes of death in adults.[3] The national rate of apparent opioid toxicity deaths in 2022 was estimated to be approximately 19 per 100,000 people,[6] and harms accelerated during the COVID-19 pandemic. From the onset of the pandemic in March 2020 to September 2021, opioid-related life-threatening emergency department visits in Ontario increased by 57% and opioid-related deaths increased by 60%.[7,8]

Chronic Noncancer Pain and OUD Comorbidity

Chronic pain, defined as pain lasting 3 months or longer, is a major clinical and population health issue, with approximately 1 in 5 people in Canada (nearly 8 million people) living with this condition.[9] People living with OUD are more likely to live with chronic pain; a systematic review reported comorbid prevalence rates as high as 45%.[10] More than 8% of people living with chronic pain are estimated to have a history of OUD.[11]

There is a complex interplay between these 2 conditions. Chronic pain may precede or follow a diagnosis of OUD.[12,13] Prolonged use of opioid analgesics for the management of chronic pain can increase the risk of developing OUD, while using opioid analgesics in the context of OUD may exacerbate OUD symptoms and consequences.[14]

People living with chronic pain often take opioid analgesics for pain management, and with regular use, will develop physical dependence to these medications. In 2018, 12.7% of people living in Canada (approximately 3.7 million people) aged 15 years or older reported using opioids for pain relief over the past 12 months. According to 1 study, 9.7% of people using opioids (approximately 351,000 people) engaged in problematic use, which was defined in the study as taking opioid analgesics in greater amounts or more often than directed, intentionally using opioid analgesics for the experience or to get high, using opioid analgesics meant for reasons other than pain relief, or tampering with a product before taking it.[15]

The co-occurrence of chronic pain and OUD is associated with a self-reported 55% increased likelihood of nonfatal opioid-related toxicity relative to those without chronic pain (odds ratio [OR] = 1.55, 95% confidence interval [CI], 1.16 to 2.08).[16] Furthermore, increased severity of chronic pain in individuals with OUD is associated with worse health-related quality of life.[17] Although chronic pain is already linked to poor psychosocial functioning, reduced quality of life, and poor self-rated health, the impact is likely worse in individuals living with OUD.[18]

The majority of people living with OUD also have at least 1 coexisting psychiatric disorder.[12,19,20,21] This is of heightened concern among individuals with co-occurring OUD and chronic pain: a meta-analysis showed that the likelihood of self-reported psychiatric comorbidity in individuals with OUD was more than 2 times as high in those with co-occurring chronic pain relative to those who did not have co-occurring chronic pain (OR = 2.18; 95% CI, 1.6 to 2.9).[22] Other studies have similarly suggested that the prevalence of mental health concerns is significantly higher in people with OUD who have chronic pain (67% to 78%) compared to those without chronic pain (51% to 58%).[14,23]

Because of the possible increased risks of opioid analgesic use among people living with OUD, evidence-based guidance for the management of chronic pain is critical for ensuring that benefits are likely to exceed harms in this population.[12]

Challenges With Available Treatments for Co-Occurring OUD and Chronic Pain

Managing chronic pain in individuals with OUD presents unique challenges.[12] In many jurisdictions, opioid agonist therapy (OAT), commonly using methadone, buprenorphine, and/or slow-release oral morphine,[2,11,24,25] is considered as first-line therapy for OUD. OAT alone may be insufficient to effectively manage chronic pain in people with OUD.[11] Although buprenorphine formulations are widely used for analgesic purposes, research related to pain efficacy in the context of co-occurring OUD and chronic pain is primarily limited to transdermal formulations rather than buccal, sublingual, or injectable formulations commonly used as OAT.[26]

Clinical practice guidelines for the management of OUD[2,27–31] frequently include recommendations for treating chronic pain in people with OUD, although the evidence supporting these guidance statements for chronic pain management is limited. Most guidelines recommend that patients with co-occurring OUD and chronic pain should be supported in exploring alternative pain treatments that are both accessible and culturally appropriate, such as nonopioid pharmacotherapies (e.g., nonsteroidal anti-inflammatory drugs, anticonvulsants, and tricyclic antidepressants)[2,27,29] and nonpharmacological therapies (e.g., cognitive behaviour therapy).[2,28,29]

Evidence supporting the use of interventions such as cognitive behaviour therapy[32,33] and mindfulness-oriented recovery[34] for treating chronic pain in patients living with OUD is growing, but further study is needed to establish their effectiveness in this context. Many medical professionals prescribe nonopioid medications for chronic pain. However, despite some positive findings, analgesic effects of nonopioid medications for people living with OUD appear modest at best.[35]

These therapeutic limitations highlight the need to consider appropriate analgesic options in this comorbid context. One algorithm for managing chronic pain in patients living with substance use disorders advises using opioid analgesics when patients do not adequately benefit from other treatments, namely agonist therapy, nonpharmacological pain treatment, and psychiatric and/or sleep disturbance treatments.[36] Regarding efficacy, a meta-analysis of 94 randomized controlled trials (RCTs) with a median follow-up of 60 days (interquartile range, 30 to 84 days) found that opioid use among patients with chronic noncancer pain (CNCP) was associated with statistically significant, but clinically modest, improvements in pain, sleep,

and physical functioning; however, patients who are also living with OUD have typically been excluded from eligible trials.[37]

Not all patients are the same nor will they experience treatments the same. Rather, decision-making around therapy is informed by patient values and preferences, cost, accessibility, and other concerns.[38] Although risks and adverse effects of opioids are significant, some individuals may still prefer opioids if they feel their pain relief benefits outweigh side effects and concerns.[39] Individuals with OUD who develop chronic pain may experience stigma and be labelled as "drug-seeking," which can make it challenging to find a physician willing to prescribe analgesic therapy, including opioid analgesics. People with OUD might also be hesitant to use opioid analgesics due to their OUD diagnosis and history of opioid use. This can result in the undertreatment of pain, especially when there are financial and other accessibility barriers to other analgesic options.[40]

Opioid analgesics are 1 option for chronic pain management in patients with OUD. However, guidance for supporting this population is limited.[22] As concerns around poorly treated pain, opioid-related harms, health service utilization, accessibility, and cost grow, developing evidence-informed strategies for managing chronic pain in individuals with OUD and/or a history of OAT is critical.[12] Making relevant evidence readily available to patients, clinicians, health administrators, and policy-makers through evidence synthesis can support evidence-informed decision-making in this complex area. Accordingly, this project aims to summarize the evidence on the efficacy, effectiveness, and safety of opioid analgesics in managing chronic pain in people with OUD, with a history of OUD, receiving OAT, and/or with a history of receiving OAT.

Main Take-Aways

OUD is a significant public health concern in North America, with increasing prevalence and associated harms. Chronic pain and OUD often coexist, with individuals living with both conditions facing greater challenges in managing their health. The available treatments for co-occurring OUD and chronic pain presents unique challenges, and evidence-based guidance for their management is critical. This project aims to summarize the evidence on the efficacy, effectiveness, and safety of opioid analgesics alone or in combination with OAT to manage chronic pain for patients with OUD or a history of OUD.

Project Scope and Protocol Development

The methodology employed for this review follows the guidelines outlined in the Cochrane Handbook.[41] Reporting of the protocol adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Protocols (PRISMA-P).[42] The protocol was posted on our website for feedback. The protocol was developed in collaboration with the Subject Matter Health Research Lab based out of Humber River Health as well as content and methodological experts. This evidence synthesis follows the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 reporting guidelines.[39]

Objective

To explore the safety, efficacy, and effectiveness of opioid analgesics alone or in combination with OAT for the management of chronic noncancer pain in people with OUD or with a history of OUD.

Policy Questions

1. How can opioid analgesics be used safely and effectively in patients with chronic noncancer pain who are currently receiving OAT?
2. How can opioid analgesics be used safely and effectively in patients with chronic noncancer pain who are not receiving OAT and have OUD or a history of OUD?
3. Are these patients at a higher risk of opioid-related toxicity or relapse? Is there an interval following OUD remission during which risk of relapse is minimal?

Research Questions

This report addresses the following research questions. Details on the specific interventions and outcomes are included in Table 1.

1. In people with chronic noncancer pain who have OUD or a history of OUD, what is the effect of solitary use of opioid analgesics or concurrent use of opioid analgesics with OAT versus any comparison or no comparison on any effectiveness outcomes, including pain intensity, health-related quality of life, physical functioning, emotional functioning (anxiety, depression), and global rating of improvement?
2. In people with chronic pain who have OUD or a history of OUD, what is the effect of solitary use of opioid analgesics or concurrent use of opioid analgesics with OAT versus any comparison or no comparison on any safety outcomes, including relapse, increased substance use, extramedical use, opioid-related toxicity, hospitalization, and death?

Methods

A protocol was written a priori using appropriate reporting guidelines (PRISMA-P) for guidance on clarity and completeness, and it was followed throughout the study process.

For research question 1 pertaining to the efficacy of opioid analgesics in patients with chronic pain and OUD, we aimed to synthesize findings from a subanalysis of RCTs reporting on efficacy outcomes identified from systematic reviews that were previously registered in PROSPERO.

For research question 2 pertaining to safety, due to the limited number of eligible studies, we modified the protocol by expanding our search strategy, as explained subsequently, and included prolonged opioid analgesic use as an additional outcome. This report captures findings from subanalyses of RCTs and observational studies reporting on safety outcomes identified from systematic reviews that were previously registered in PROSPERO.

For the effectiveness research question 1, we registered and followed a novel protocol to capture real-world evidence in PROSPERO (identifier: CRD42023475381).

In this report, we avoided using the terms “opioid misuse,” “abuse,” and “overdose” even if these terms were used in the original reports; we followed the inclusive language instructions of the National Institute on Drug Abuse for substitute terms.[43]

Literature Search Methods

In our protocol, we planned to search for 2 bodies of evidence: RCTs and well-designed observational studies as a source of real-world evidence.

RCT Data — Safety and Efficacy

The Canadian Opioid Prescribing Guideline[44] evidence synthesis team conducted a systematic review to explore the efficacy of opioids for CNCP. They searched for RCTs on MEDLINE, Embase, PsycINFO, CINAHL, the Allied and Complementary Medicine Database (AMED), and Cochrane Central from inception to July 2023. They also reviewed the reference lists of all included studies and relevant reviews.[45] We reviewed the full text of all 114 trials that the guideline evidence synthesis team included against our eligibility criteria for the safety and efficacy research questions (Appendix 1, Figure 2).

Real-World Evidence From Observational Studies — Safety

The same evidence synthesis team conducted 2 systematic reviews and meta-analyses exploring predictors of fatal and nonfatal opioid poisoning[46] and of OUD (PROSPERO registration numbers CRD42017050972 and CRD42019119184) following prescription of opioid analgesics for chronic pain. These reviews used observational studies to evaluate risk factors associated with opioid-related toxicity, opioid addiction, and death from opioid use, as well as OUD following the prescription of opioid analgesics for treating chronic pain, through adjusted analysis. For both reviews, a health sciences librarian developed a search strategy and systematically searched MEDLINE, Embase, CINAHL, PsycINFO, and AMED from inception to July 2023.

The current evidence synthesis team screened the full text of 62 eligible studies from these 2 reviews and reviewed the bibliographic references of the included studies and related reviews for additional potentially eligible citations (Appendix 1, Figure 3).

Because the guideline evidence synthesis team only included observational studies that adjusted for confounding factors, we broadened our search and screened the observational studies that included patients with CNCP using opioids for chronic pain regardless of analyses performed. The guideline evidence synthesis team screened 19,785 titles and abstracts, of which 3,504 were identified as observational studies that included patients with CNCP using opioids for chronic pain. We screened these 3,504 titles and abstracts; 49 full texts resulted from title abstract screening (Appendix 1, Figure 4).

Real-World Evidence From Observational Studies — Effectiveness

We utilized a search strategy designed by an experienced medical librarian, which is available in the Supplementary File. We conducted searches in MEDLINE, Embase, PsycINFO, CINAHL, and AMED from inception to December 1, 2023, without language restrictions. We reviewed reference lists of eligible studies and related reviews for additional potentially eligible articles (Appendix 2).

Study Selection

Pairs of reviewers independently screened all 114 full texts of included RCTs, and 62 observational studies were deemed eligible by the guideline evidence synthesis team using the inclusion criteria outlined in Table 1. After broadening our search, the same pairs of reviewers independently screened 3,504 titles and abstracts, and 49 full texts resulted from title abstract screening. Finally, for the effectiveness review, 4 teams of paired reviewers screened 11,264 titles and abstracts, of which 278 full-text records were reviewed for eligibility.

Screening was conducted using the web-based systematic review software Covidence, developed by Veritas Health Innovation in Melbourne, Australia.

Before the formal screening process, we performed multiple rounds of pilot screening to achieve agreement. For each round, 50 titles and abstracts and 10 full texts were used for pilot screening. All conflicts were resolved through discussion to reach a consensus and, if needed, a senior reviewer (AS) was involved. The PRISMA flow charts of the study selection process are presented in Appendix 1.

Inclusion Criteria

The evidence synthesis team included RCTs of any design, ensuring a minimum of 10 subjects in each arm. In addition, observational studies, both comparative and single arm, were included that had at least 20 participants that met eligibility criteria. The team included studies that included adults aged 18 years and older with chronic pain (defined as pain lasting ≥ 3 months) who have OUD or a history of OUD and that compared opioid analgesics either alone or in combination with OAT versus any comparator including no treatment. For studies that included a mixed population, the evidence synthesis team included those that reported results for participants with CNCP and OUD separately or those in which at least 85% of the included patients (in the entire trial or in a separately reported subsample) had CNCP and OUD or a history of OUD (refer to Table 1). The 85% threshold is a conventional value that was also used for a similar purpose with the Canadian Opioid Prescribing Guidelines.[44] Because the evidence synthesis team used studies included by the opioid guideline team, the same threshold was applied for consistency. We considered long-term opioid use as an outcome of interest because long-term opioid use is associated with adverse outcomes, including opioid-related toxicity, major trauma, opioid addiction, attempted suicide, and self-harm.[47,48]

Table 1: Selection Criteria

Criteria	Description
Population	Adults with CNCP who have a diagnosis of OUD or a history of OUD
Intervention	Solitary use of opioid analgesics or concurrent use of opioid analgesics and OAT (i.e., buprenorphine with or without naloxone, methadone, and slow-release morphine)
Comparator	Any comparator or no comparator

Criteria	Description
Outcomes	Efficacy and effectiveness: pain intensity, HRQoL, physical functioning, emotional functioning (anxiety, depression), and global rating of improvement[49] Safety: relapse, opioid used other than prescribed, extramedical use, hospitalization, nonfatal opioid-related toxicity, and fatal opioid-related toxicity
Study designs	Randomized controlled trials, open-label trials, clinical practice guidelines, systematic reviews, observational (prospective or retrospective) studies including cohort, case-control, and cross-sectional studies. Primary research studies informing clinical practice guidelines were also included.

CNCP = chronic noncancer pain; HRQoL = health-related quality of life; OAT = opioid agonist therapy; OUD = opioid use disorder.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1 or if they were duplicate publications, case reports, case series, or conference abstracts. The evidence synthesis team also excluded studies that included patients presenting with acute pain (including acute postoperative pain), those with chronic pain related to cancer, those with end-of-life pain, and those receiving palliative or hospice care.

Critical Appraisal of Individual Studies

The evidence synthesis team used the Risk of Bias in Non-randomised Studies – Interventions (ROBINS-I) or the Quality in Prognostic Studies (QUIPS) tool to assess risk of bias in nonrandomized studies. ROBINS-I covers 7 domains: bias due to confounding, bias in the selection of participants into the study, bias in classification of interventions, bias due to deviations from the intended interventions, bias due to missing data, bias in the measurement of the outcome, and bias in selection of the reported result.[50] The QUIPS tool[51] is specifically designed for assessing the risk of bias in prognostic studies. QUIPS covers the following domains: the representativeness of the study population, the proportion of missing data (where ≥ 20% was considered indicative of high risk of bias), the validity of prognostic factor measurements, the validity of outcome assessments, whether predictive models were optimally adjusted, and the utilization of proper statistical analysis and reporting.

Data Analysis and Synthesis

The evidence synthesis team narratively summarized and reported effect estimates. For binary outcomes, the evidence synthesis team aimed to report baseline probability for the outcome, a measure of association (e.g., relative risk [RR], OR, hazard ratio [HR]), and a corresponding 95% CI. We complemented relative measures of association (RR) with the absolute risk change for each outcome. In cases in which a study presented raw or crude data without explicitly reporting effect sizes, we calculated the effect sizes by using the following formulas to calculate RR: RR = (A / [A + B]) / (C / [C + D]), where A = events in experimental arm; B = nonevents in experimental arm, C = events in control arm, and D = nonevents in control arm. The upper and lower limits of the 95% CI were calculated using the following formula: 95% CI = exp(ln [RR] ± 1.96 × SE), where SE = standard error. We used the ratio of odds ratios (ROR) to compare the strength of association between 2 different groups or conditions, calculated using the formula provided in Appendix 3.

The evidence synthesis team aimed to synthesize findings narratively across study types and outcome types. We did not conduct quantitative meta-synthesis for any outcomes.

Certainty (Quality) of Evidence

We assessed the certainty of evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. With GRADE, evidence from observational studies begins as low certainty but can be rated down for risk of bias, indirectness, imprecision, or publication bias.[52] We rated up 1 level when the effect in observational studies was sufficiently large (i.e., direct evidence, RR between 2 and 5 or 0.5 and 0.2 with no plausible confounders and very large with RR more than 5, or RR less than 0.2 and no serious problems with risk of bias or precision [sufficiently narrow CIs]).[53]

Results

Quantity of Research Available

Main Take-Aways

Five observational studies exploring the safety of opioid analgesics alone or in combination with OAT for the management of chronic pain for patients with OUD or with a history of OUD met the inclusion criteria. No studies exploring efficacy or effectiveness met the inclusion criteria.

For safety outcomes, no RCTs met the eligibility criteria. Of the 3,504 unique records collecting observational data, 4 reports met the eligibility criteria (Appendix 1, Figure 4).

For efficacy, no RCTs met the eligibility criteria. For effectiveness, 11,264 unique records were identified; however, none were deemed eligible for assessing the effectiveness of opioid analgesics in patients with CNCP with OUD. Only 1 study met all population, intervention, control, and outcome criteria. However, this was a case study of a single patient, so it was not eligible for this review. Through this search of effectiveness data, we identified 1 additional study[54] that addressed the safety of opioid analgesics in patients with CNCP with OUD (Appendix 1, Figure 5).

We screened the reference lists of all included studies and 1 clinical practice guideline,[55] and included studies from relevant systematic reviews but did not identify any additional relevant studies. We reached out to multiple authors[56,57] for more details from eligible studies; 1 author[58] responded by providing crude data for fatal and nonfatal opioid-related toxicity separately.

Study Characteristics

Main Take-Aways

The results focus on 5 observational studies that assessed the safety of opioid analgesics in the context of OUD and chronic pain. The studies varied in participant numbers, age range, sex and gender proportions, and geographic locations.

The remainder of these results will focus on the 5 observational studies regarding the safety of opioid analgesics in the context of OUD and chronic pain that did meet eligibility criteria. These studies had a wide range of participants, ranging from 611 to 1,662,336. Weisner et al. (2009)[60] reported detailed data, including the mean age and sex proportion data, for 38,843 participants with an OUD history, so this subset of data was used for this analysis (Table 2). The range of mean age across the studies was 45.8 to 58.2 years, and the duration of follow-up was between 1 to 44.4 months. Female participants included in the studies ranged from 6.3% to 64.6% and male participants ranged from 35.4% to 93.7% (Table 2).

One study[58] reported data from Canada and the remaining 4 studies[54,56,59,60] reported data from the US. Two studies[58,59] recruited subjects from outpatient settings, 1 study[60] utilized data from 2 health plan databases, 1 study[56] used a Veterans Health Administration database, and 1 study[54] examined the records of patients receiving New York State Medicaid (Table 2).

Critical Appraisal

Main Take-Aways

One study (Mannes et al. [2023])[54] was assessed at a low risk of bias, whereas the remaining 4 studies[56,58-60] were found to have high risk of bias in at least 1 domain. Caution is advised when interpreting this evidence.

The study by Mannes et al. (2023)[54] investigated the association between OUD, long-term opioid therapy (LTOT), and other risk factors with fatal and nonfatal opioid toxicity through adjusted analysis and was deemed to be of low risk of bias. The study by Ward et al. (2022)[56] was rated as low risk of bias for the propensity score-based analysis and calculating the RR of fatal and nonfatal opioid-related toxicity, which matched treated and untreated patients and incorporated potentially confounding variables. However, for the Cox proportional hazard analysis, this study was considered to have a high risk of bias due to invalid measurement of OUD as 1 of the prognostic factors. It was not clear what definition of OUD was used for the comparison of OUD as a prognostic factor given that both clinical diagnoses as well as International Classification of Diseases (ICD) codes were reported in the study (Table 3 and Table 4).

The 3 remaining studies[58–60] were at high risk of bias in at least 1 domain. Although Kennedy et al. (2022)[58] adjusted the data for confounders in the main analysis, the crude data provided by the author for the primary purpose of this review was not adjusted for confounders. The study by Glenn et al. (2016)[59] was judged to be at high risk of bias due to unadjusted analysis, bias in intervention measurement through self-reported data collection and retrospective determination, co-interventions involving illegal substances, and subjective outcome measurement. Weisner et al. (2009)[60] did not adjust analyses for confounding factors (Table 3).

Table 2: Study Characteristics

Study, design, country	Sample size	Age (years), mean (SD)	Sex or gender, n (%)	Length of follow-up	Study setting	Population	Race and ethnicity, n (%)	Intervention or comparison	Outcome
Ward et al. (2022)[56] Retrospective cohort US	1,125	54.1 (12.6)	Female: 71 (6.3%) Male: 1,054 (93.7%)	12 months	Veterans Health Administration	Patients with chronic pain and opioid use (all participants in intervention group were diagnosed with OUD but not all participants in control group had OUD)	Hispanic: 25 (1.6%) Non-Hispanic Black: 949 (60.9%) Non-Hispanic white: 536 (34.4%) Other: 23 (1.5%) Missing: 25 (1.6%)	Treated with medications for OUD and psychosocial treatment vs. untreated with MOUD	Nonfatal opioid-related toxicity, fatal opioid-related toxicity
Kennedy et al. (2022)[58] Retrospective cohort Canada	710	49.4 (12.6)	Female: 322 (45.4%) Male: 388 (54.6%)	44.4 months	Outpatient	Patients on LTOT (≥ 90 days with ≥ 90% of days on therapy with history of OUD in past 3 years) for pain	NR	Prescribed OAT in past 90 days vs. not prescribed OAT	Nonfatal opioid-related toxicity or fatal opioid-related toxicity
Mannes et al. (2023)[54] Retrospective cohort US	236,391	45.8 (12.3)	Female: 152,619 (64.6%) Male: 83,772 (35.4%)	12 months	New York State Medicaid claims	Patents with CNCP	Asian: 33,751 (14.3%) Black or African American: 41,159 (17.4%) Hispanic: 30,776 (13.0%)	OUD and LTOT vs. no OUD and LTOT before and during COVID-19 pandemic	Nonfatal or fatal opioid-related toxicity (combined outcome)

Study, design, country	Sample size	Age (years), mean (SD)	Sex or gender, n (%)	Length of follow-up	Study setting	Population	Race and ethnicity, n (%)	Intervention or comparison	Outcome
							White: 70,215 (29.7%) Other: 12,816 (5.4%) Unknown: 47,674 (20.2%)		
Glenn et al. (2016)[59] Cross-sectional US	611	51.5 (8.6)	Female: 235 (38.5%) Male: 376 (61.5%)	1 month	Outpatient	Patients with chronic pain on methadone maintenance treatment	Hispanic: 376 (61.5%) Non-Hispanic Black: 156 (25.5%) Non-Hispanic white: 60 (9.8%) Non-Hispanic other: 19 (3.1%)	Prescribed opioid analgesics vs. not prescribed opioid analgesics	Taking opioid analgesics in higher dose, taking opioid analgesics more frequently, taking higher dose or more frequently
Weisner et al. (2009)[60] Cross-sectional US	38,843	58.2 (14.7)	Female: 25,062 (64.5%) Male: 13,781 (35.5%)	12 months	Health care plan registry	Patents with CNCP with opioid use episode	NR	With history of OUD in past 2 years vs. without history of OUD in past 2 years	Prevalence and incidence of long-term opioid use

CNCP = chronic noncancer pain; LTOT = long-term opioid therapy; MOUD = medication for opioid use disorder; NR = not reported; OAT = opioid agonist therapy; OUD = opioid use disorder; vs. = versus.

Table 3: Risk of Bias Assessment Using the ROBINS-I

First author (year)	Risk of bias domain[a]							
	Confounding	Participant selection	Classification	Deviation	Missing data	Measurement	Results selection	Overall risk of bias[b]
Ward et al. (2022)[c56]	Low	Low	Low	Low	Low	Low	Low	Low
Kennedy et al. (2022)[58]	Serious	Low	Low	Low	Low	Low	Low	Serious
Glenn et al. (2016)[59]	Serious	Low	Serious	Serious	Low	Serious	Low	Serious
Weisner et al. (2009)[60]	Serious	Low	Low	Low	Low	Low	Low	Serious

[a]**Confounding:** bias due to confounding; **Participant selection:** bias in selection of participants; **Classification:** bias in classification of interventions; **Deviation:** bias due to deviations from intended interventions; **Missing data:** bias due to missing data; **Measurement:** bias in measurement of outcomes; **Results selection:** bias in selection of reported results.

[b]Judgment scale: low, moderate, serious, critical, unclear.

[c]Ward et al. (2022): The risk of bias assessment for evidence derived from propensity score–matched data.

Table 4: Risk of Bias Assessment Using the QUIPS Tool

First author (year)	Risk of bias domain[a]						
	Participant selection	Missing data	Prognostic factor measurements	Outcome assessments	Optimal adjustment	Statistical analysis and reporting	Overall risk of bias[b]
Ward et al. (2022)[c56]	Low	Low	Serious	Low	Low	Low	Serious
Mannes et al. (2023)[54]	Low	Low	Low	Low	Low	Low	Low

[a]**Participant selection:** bias in selection of participants; **Missing data:** bias due to missing data; **Prognostic factor measurements:** bias in validity of prognostic factor measurements; **Outcome assessments:** bias due to validity of outcome assessments; **Optimal adjustment:** Bias due optimal adjustment of predictive model; **Statistical analysis and reporting:** Bias in utilization of proper statistical analysis and reporting.

[b]Judgment scale: low, moderate, serious, critical, unclear.

[c]Ward et al. (2022): The risk of bias assessment for evidence derived from Cox regression.

Findings

Main Take-Aways

The risk of fatal opioid-related harm may decrease in patients with chronic pain and OUD who receive both opioid analgesics and OAT treatment compared to those who only receive opioid analgesics. However, the evidence supporting this is not very strong.

It is uncertain whether the risk of fatal opioid-related harm is affected in patients with chronic pain who are prescribed opioid analgesics and have OUD compared to those who do not have OUD.

It is uncertain whether long-term opioid analgesic therapy in patients with chronic pain and OUD affects the combined outcome of fatal and nonfatal opioid-related harm.

It is uncertain whether having a history of OUD in the past 2 years increases the likelihood of prolonged opioid analgesic use in patients with chronic pain.

It is uncertain whether the dosage of opioid analgesic use is affected in patients with chronic pain and OUD who are undergoing methadone maintenance treatment and are prescribed opioid analgesics.

The research questions of 2 studies[56,58] were similar, with both exploring the effect of receiving OAT in patients with OUD who use opioid analgesics for CNCP.

Ward et al. (2022)[56] explored the effect of the substance abuse treatment program including medication for OUD (SATP-MOUD) for US military veterans with chronic pain and current opioid analgesic use on fatal and nonfatal opioid-related toxicity. SATP-MOUD primarily included opioid agonist or antagonist medications for OUD (e.g., oral methadone, sublingual buprenorphine or naloxone, and injectable naltrexone), along with counselling and monitoring of substance use and psychosocial treatments. The study employed propensity score matching methods to compare the risk of fatal and nonfatal opioid-related toxicity for veterans with chronic pain and concurrent opioid analgesic use who were in SATP-MOUD versus not in SATP-MOUD. Subsequently, Cox proportional hazard models were used to identify the associations between each predictor and fatal opioid-related toxicity in the matched comparison groups. The authors used the ICD codes in the records of the participants, which revealed that 31% of individuals in the SATP-MOUD group and 14% in the group were not in SATP-MOUD were diagnosed with OUD. However, the authors considered all patients enrolled in SATP-MOUD as having OUD based on the nature of their treatment with medications for OUD.

The evidence synthesis team used the matched data from Ward et al. (2022)[56] to calculate the relative and absolute effect, along with their corresponding CIs, of fatal opioid-related toxicity and nonfatal opioid-related toxicity in veterans who received SATP-MOUD versus those who did not receive the SATP-MOUD. Low-certainty evidence suggests that prescribing OAT along with psychosocial treatments in veterans with CNCP and OUD who are using opioid analgesics may reduce fatal opioid-related toxicity risk by 30% over 12 months (RR = 0.70 [95% CI, 0.53 to 0.91]; absolute risk reduction = 60 fewer deaths [95% CI, 18 to 94 fewer deaths in 1,000 patients]). The RR estimate aligned with the HR estimate (HR = 0.62; 95% CI, 0.47 to 0.82) for the same comparison, indicating a 38% lower fatal opioid-related toxicity hazard at any time point for individuals treated with OAT. Although the HR is statistically significant, it is uncertain whether an OUD diagnosis versus

no OUD diagnosis is associated with a higher risk of fatal opioid-related toxicity because it is not clear whether the author considered all participants in SATP-MOUD to have OUD or used participants' ICD code records to associate OUD diagnosis with time to death in a proportional hazard model (HR = 1.40; 95% CI, 1.02 to 1.92) (very low–certainty evidence).

Based on measures of association calculated by the evidence synthesis team using data presented by Ward et al. (2022),[56] it is uncertain whether prescribing OAT along with psychosocial treatments in patients with CNCP and OUD who are using opioid analgesics affects the risk of nonfatal opioid-related toxicity events (RR = 1.61 [95% CI, 0.97 to 2.68]; absolute risk increase: 24 more nonfatal opioid-related toxicity events [95% CI, 1 fewer to 67 more nonfatal opioid-related toxicity events in 1,000 patients]) over 12 months (very low–certainty evidence; Figure 1 and Appendix 4). This evidence was of lower certainty compared to evidence for the fatal opioid-related toxicity due to serious imprecision.

The evidence synthesis team understood that Ward et al. (2022)[56] collected data on the number of fatal and nonfatal opioid-related toxicities in participants not treated with SATP-MOUD, stratified based on history of OUD. These crude data were requested from the authors for further analysis but were not received by the evidence synthesis team.

This regression analysis conducted by Ward (2022)[56] suggested that opioids prescribed for 90 days or more may increase the hazard of fatal opioid-related toxicity compared to opioids prescribed for less than 90 days by nearly two-fold (HR = 1.87; 95% CI, 1.56 to 2.24). In addition, the results showed that some factors may slightly increase the hazard of fatal opioid-related toxicity, including increasing age (HR = 1.06; 95% CI, 1.05 to 1.07 for each year increase), number of comorbidities (HR = 1.05; 95% CI, 1.02 to 1.07 for each comorbidity), each inpatient service utilization (HR = 1.40; 95% CI, 1.29 to 1.52), and each outpatient service utilization (HR = 1.02; 95% CI, 1.01 to 1.02), and in patients with chronic pain receiving opioid analgesics (very low–certainty evidence). Conversely, "minority race" [from the original source] and ethnicity (HR = 0.75; 95% CI, 0.63 to 0.88) and a severe depression diagnosis (HR = 0.73; 95% CI, 0.60 to 0.88) may have a protective effect on fatal opioid-related toxicity for CNCP patients receiving opioid analgesics, according to the adjusted model.

Kennedy et al. (2022)[58] explored the association between opioid discontinuation and tapering (as predictors) and risk of fatal and nonfatal opioid-related toxicity (as a single outcome) in patients with CNCP on LTOT (≥ 90 days; ≥ 90% of days treated), including those with a history of OUD in the past 3 years. They stratified patients based on their use of OAT and employed Cox regression analysis. The results of the main adjusted analysis showed that discontinuing opioids (≥ 7 days gap in therapy), compared to continuing opioid treatment, was associated with increased fatal and nonfatal opioid-related toxicity hazards among all groups of patients, including those with no diagnosis of OUD (HR = 1.44; 95% CI, 1.12 to 1.83), patients diagnosed with OUD but not prescribed OAT (HR = 3.18; 95% CI, 1.87 to 5.40), and patients with OUD prescribed OAT (HR = 2.52; 95% CI, 1.68 to 3.78).

The results of the main adjusted analysis showed that tapering opioids (≥ 2 sequential decreases of ≥ 5% in average daily morphine), compared to continuing opioid treatment, was associated with decreased fatal and

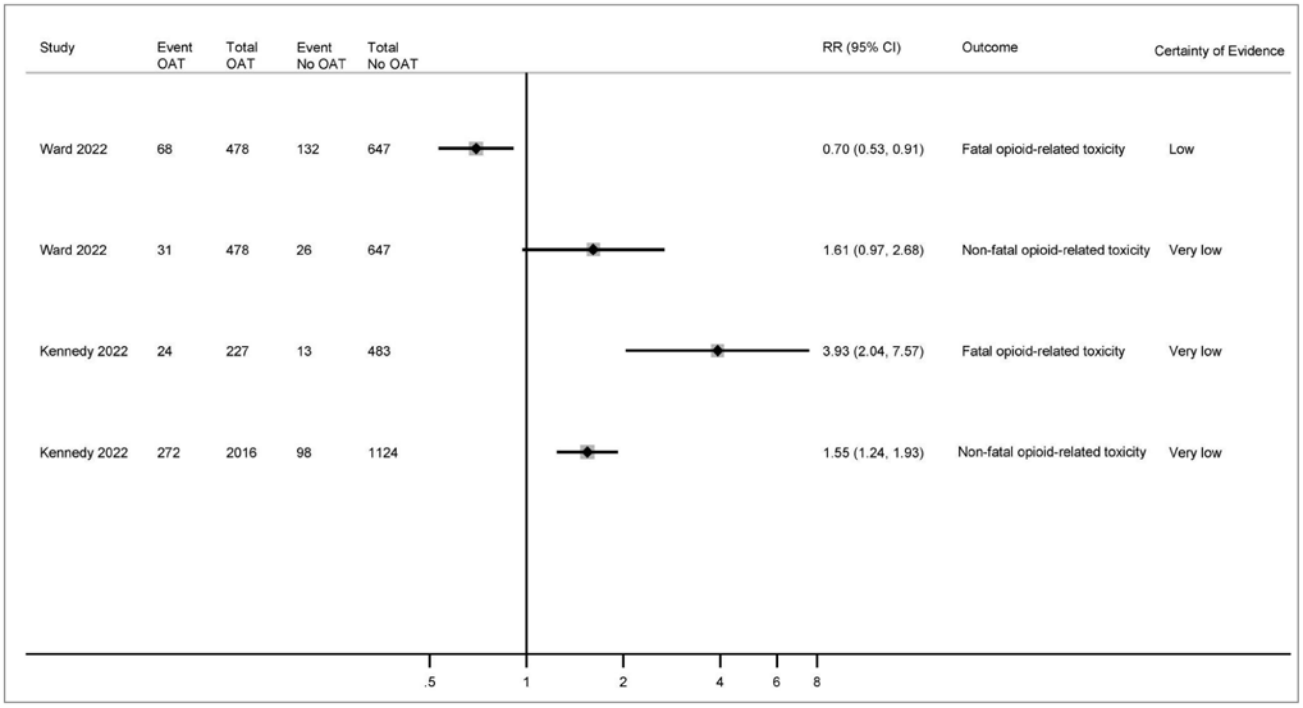
nonfatal opioid-related toxicity hazard among patients diagnosed with OUD but not prescribed OAT (HR = 0.31; 95% CI, 0.14 to 0.67). Furthermore, Cox regression analysis indicated that tapering opioids, compared to continuing opioid treatment, did not significantly reduce the hazard of opioid-related toxicity in OUD patients receiving OAT (HR = 0.61; 95% CI, 0.30 to 1.22).

One limitation with the data from Kennedy (2022)[58] in relation to the objectives of the current synthesis was the absence of separate results for fatal and nonfatal opioid-related toxicity. On request, the author provided these crude data, which the evidence synthesis team used to calculate RR and absolute risk change for these outcomes independently. Although the study used adjusted analysis to investigate the association between changes in opioid dose (tapering and discontinuation) and opioid-related toxicity, we identified this analysis as having a high risk of bias for the purposes of this synthesis due to a lack of adjustment for confounding factors in the data that we used to calculate relative and absolute risks of fatal and nonfatal opioid-related toxicity.

Based on the crude data we obtained from the Kennedy et al. (2022)[58] study for the primary purpose of this review, it is uncertain whether either the risk of fatal opioid-related toxicity or nonfatal opioid-related toxicity were impacted in patients receiving LTOT for pain and with a history of OUD. There was a 4-fold increase in risk of fatal opioid-related toxicity if patients were prescribed OAT (RR = 3.9 [95% CI, 2.0 to 7.6]; absolute risk increase: 79 more deaths [95% CI, 28 to 177 more deaths in 1,000 patients]) compared to not being prescribed OAT, but this estimate was based on very low–certainty evidence. Nonfatal opioid-related toxicity was 55% greater among those who received OAT compared to the group that did not receive OAT, but this estimate was based on very low–certainty evidence (RR = 1.55 [95% CI, 1.24 to 1.93]; in terms of absolute risk increase, 48 more nonfatal opioid-related toxicity events were observed [95% CI, 21 to 81 more in 1,000 patient-years observation over 4 years]) (Figure 1 and Appendix 4). Stratified data comparing outcomes of those patients with and without OUD prescribed opioid analgesics but not OAT have been requested from the authors but were not made available to the evidence synthesis team.

The evidence synthesis team noted that the data in the study by Kennedy et al. (2022)[58] were stratified based on OUD and treatment with OAT to investigate the association between opioid analgesic use and opioid-related toxicity using a Cox regression model. These data were requested from the author but were not made available to the evidence synthesis team.

Figure 1: Comparison of the Effect of Opioid Agonist Therapy on Relative Risk of Fatal and Nonfatal Opioid-Related Toxicity in Patients With Chronic Pain and OUD on Long-Term Opioid Analgesic Therapy



OAT = opioid agonist therapy; RR = relative risk.

Notes: RR > 1 indicates increased risk of outcome.

Ward et al. (2022)[56] — **Population**: patients with chronic pain who use opioid analgesics; **Intervention**: SATP-MOUD for all patients, **Comparison:** no SATP-MOUD and not all patients had OUD; Propensity score–matched data.

Kennedy et al. (2022)[58] — **Population:** Patients with chronic pain on long-term opioid use and OUD, **Intervention:** OAT, **Comparison:** No OAT; crude data

Mannes et al. (2023)[54] utilized adjusted analysis to investigate the association between LTOT (≥ 3 consecutive months with ≥ 30 days of use of any prescription opioids, inclusive of forms of mOUD [i.e., buprenorphine and methadone], OUD, and the COVID-19 pandemic on fatal and nonfatal opioid-related toxicity [as a combined outcome]) in patients with chronic pain using data from New York State Medicaid claims spanning from 2019 to 2020. They also examined the association between other risk factors, including demographic variables and medical and mental illness comorbidities, with fatal and nonfatal opioid-related toxicity as a combined outcome in patients with chronic pain. These results should be interpreted cautiously considering that not all participants used long-term opioid analgesics; some cases involved the use of buprenorphine or methadone as LTOT.

The results of the adjusted analysis by Mannes et al. (2023),[54] based on data collected before the pandemic, showed an association between LTOT and OUD with fatal and nonfatal opioid-related toxicity versus the reference standard of no LTOT and no OUD, indicated by an adjusted OR (AOR) of 5.82 (95% CI, 3.58 to 9.44). In addition, a large association was found between having only OUD and fatal and nonfatal opioid-related toxicity when compared to the reference standard of no LTOT and no OUD, with an AOR of 5.65 (95% CI,

4.73 to 6.75). For the primary objective of this review, which was exploring the association between using LTOT and fatal and nonfatal opioid toxicity in the context of OUD, the evidence synthesis team compared the likelihood of combined fatal and nonfatal opioid-related toxicity between those with OUD and on LTOT to those with OUD and not on LTOT before the pandemic. It is uncertain whether LTOT in patients with chronic pain and OUD affected the likelihood of fatal and nonfatal opioid-related toxicity before the pandemic (ROR = 1.03; 95% CI, 0.61 to 1.73; very low–certainty evidence) (Appendix 3 and Appendix 4).

Similarly, based on data collected during the pandemic, Mannes et al. (2023)[54] reported an association between LTOT and OUD versus the reference standard of no LTOT and no OUD on opioid-related toxicity, with an AOR of 3.70 (95% CI, 2.11 to 6.50). An association was also observed between only OUD versus the reference standard of no LTOT and no OUD on opioid-related toxicity, with an AOR of 5.16 (95% CI, 4.33 to 6.14). As part of the primary objective of this review, the evidence synthesis team compared the likelihood of combined fatal and nonfatal opioid-related toxicity between those with OUD and on LTOT to those with OUD and not on LTOT during the pandemic. It is uncertain whether LTOT in chronic pain patients with OUD affected the likelihood of fatal and nonfatal opioid-related toxicity during the pandemic (ROR = 0.72; 95% CI, 0.40 to 1.29; very low–certainty evidence) (Appendix 3 and Appendix 4).

In a study with a different focus, Glenn et al. (2016)[59] investigated the pattern of opioid analgesic use in patients receiving methadone maintenance treatment (MMT) and prescribed opioid analgesic therapy. This study involved a secondary analysis of screening interview data derived from a parent study conducted between 2012 and 2015. Participants in the parent study provided self-reported information on opioid analgesic use and substance use. In this study, only 62% of patients receiving MMT had chronic pain. We used the data from 182 patients receiving MMT and prescribed opioid analgesic therapy, of whom 162 (89%) had chronic pain conditions. This study was determined to have a high risk of bias due to unadjusted analysis, bias in intervention measurement through self-reported data collection and retrospective determination, co-interventions involving illegal substances, and subjective outcome measurement.

Based on the study by Glenn et al. (2016),[59] it is uncertain whether dose and frequency of opioid analgesic use were impacted for people with chronic pain receiving MMT who were also prescribed opioid analgesics. Among patients with chronic pain receiving MMT who were prescribed opioid analgesic therapy, 47.2% took opioid analgesics at a higher dose than prescribed, 44.5% took opioid analgesics more frequently than prescribed, and 56.6% took opioid analgesics either at higher doses or more frequently than prescribed. We used the raw numbers presented in Table 1 in the study by Glenn (2016)[59] to calculate the percentages. As reported by Glenn (2016),[59] 48% of patients took opioids in higher doses than prescribed, 45.3% took opioids more frequently than prescribed, and 57.5% took opioids in higher doses or more frequently than prescribed. The percentages reported in the footnote reflect what was reported in the manuscript (very low–certainty evidence) (Appendix 4).

Weisner et al. (2009)[60] conducted a longitudinal study to report the trend of LTOT in patients with CNCP and substance use disorders from 1997 to 2005. The main objective of the study was to compare the prevalence and incidence of long-term opioid use in populations with and without a history of substance use disorders, including alcohol, opioids, and other drugs, using data from 2 health plans of Kaiser Permanente of Northern

California (KPNC) and Group Health Cooperative (GH) of Seattle, Washington. The study adjusted data for age and sex, calculating percent change annually to illustrate how the prevalence and incidence of long-term opioid use changed among individuals with and without a history of alcohol, opioid, and other substance use disorders.

We used data from a subgroup of patients with OUD the Weisner (2009)[60] study to compare the prevalence and incidence of prolonged opioid analgesic use in people with and without a history of OUD. This study was determined to have a high risk of bias due to unadjusted data for confounders. It is uncertain whether there is a higher risk of prolonged opioid analgesic use in people with a history of OUD compared to people without OUD. In 2005, the prevalence of long-term opioid use was 11.6 times (95% CI, 10 to 13.4 times) higher in patients with CNCP and a history of OUD compared to those with no history of OUD (absolute increase of individuals with long-term opioid use was 454 more per 1,000 [95% CI, 386 to 532 more per 1,000], very low–certainty evidence). At KPNC, in 2005 the relative incidence of long-term opioid use for people with a history of OUD versus those without OUD was 7.4 (95% CI, 6.3 to 8.7) (absolute increase of new cases with long-term opioid use was 51 more per 1,000 [95% CI, 42 to 62 more per 1,000]; very low–certainty evidence) (Appendix 4). At GH, the incidence of long-term opioid use in 1997 for the patient population with OUD was reported as 6.96% and the corresponding incidence for people without OUD was reported as 8.8%. Based on the crude numbers reported by Weisner (2009),[60] the evidence synthesis team calculated the incidence rate of long-term opioid use at GH in 1997 for those with OUD to be 8 of 122 (6.56%) and the corresponding incidence for those without OUD as 1,703 of 193,103 (0.88%) indicating that the numbers reported in the article were miscalculated.

Limitations

We did not identify any data to inform understanding of the efficacy or real-world effectiveness of opioid analgesic therapy for the management of chronic pain in the context of OUD or OAT. We found 5 observational studies with safety outcomes, and although none of them directly corresponded to our primary populations, interventions, and outcomes of interest, we identified pertinent data within them that could begin to help inform decision-making in this area of opioid analgesic use for pain management in people with OUD and chronic pain.

In observational studies, unlike RCTs, prognostic factors and confounders are not balanced between the intervention and control groups. By using statistical methods such as multivariate analysis or matching (e.g., using propensity scores), researchers attempted to control for confounding variables, making the comparison more reliable.

Three[58–60] of the included studies were deemed to be at high risk of bias due to unadjusted analysis for confounders. Two studies conducted adjusted analysis;[54,56] however, caution is advised when interpreting this evidence.

Ward et al. (2022)[56] used propensity scores to match population characteristics with all participants in the SATP-MOUD group who were considered to have OUD. However, the assessment of OUD status using ICD-10 codes in the participants' records showed that only 31.1% of participants in the SATP-MOUD program

were diagnosed with OUD. The Ward et al. (2022) study was assessed as having low risk of bias for the comparison of SATP-MOUD versus no SATP-MOUD; however, because it is not clear whether the author considered all participants in SATP-MOUD to have OUD or used participants' ICD code records to associate OUD diagnosis with time to death in a proportional hazard model, we assessed the evidence from the Cox model comparing OUD to no OUD status as having a high risk of bias due to an invalid measurement of OUD as a prognostic factor (Table 4). In addition, when assessing the association between the length of opioid use (≥ 90 days versus < 90 days) and the hazard of fatal opioid-related toxicity, the duration of opioid use may exhibit collinearity with opioid dosage, potentially affecting the likelihood of opioid-related toxicity.

Mannes et al. (2023)[54] included LTOT only, OUD only, and the interaction between LTOT, OUD, and prepandemic versus during pandemic periods variables all simultaneously in the adjusted model. There is a potential for collinearity among LTOT, OUD, and their interaction terms, which include both LTOT and OUD, but this possibility has not been explored. Furthermore, fatal and nonfatal opioid-related toxicities were combined as outcomes. Given the differing incidence rates of fatal and nonfatal opioid toxicity, along with the possibility of multiple nonfatal toxicity events occurring for a single patient, we cannot discern the specific associations of OUD, LTOT, and OUD plus LTOT with each type of opioid-related toxicity. Furthermore, the authors included both buprenorphine and methadone as types of LTOT. Among participants on LTOT, 33% were using buprenorphine and methadone; this notable prevalence contributed to a reduction in the quality of evidence due to indirectness. The high rate of buprenorphine and methadone use in this population may have contributed to the lack of significant difference in the rates of opioid toxicity in the LTOT and OUD versus no LTOT and OUD populations given the possible relative protective effects of buprenorphine and methadone against opioid toxicity. Data for the population on opioid analgesic therapy only, and not buprenorphine or methadone, were not available for separate analysis.

Furthermore, the results of Glenn et al. (2016)[59] were affected by the use of subjective methods to measure the intervention, use of nonpharmaceutical drugs as a co-intervention, and nonblinded subjective outcome measurements. Studies with a high risk of bias due to limitations in design and execution can introduce bias to treatment effect estimates and reduce confidence in those estimates. The severity of limitations correlates with the likelihood of downgrading the quality of evidence.[61]

For studies that reported fatal and nonfatal opioid-related toxicity,[54,56,58] we were not sure if the toxicity was caused by pharmaceutical or nonpharmaceutical sources, and this poses a major limitation on the interpretation of results. In addition, possibly relevant data collected by 2 studies,[56,58] but not reported in the published articles, were unavailable to the evidence synthesis team at the time of writing this report. Given the high uncertainty and conflicting outcomes in the available data, the inclusion of these additional data could potentially change the interpretation and relevance of the findings.

In terms of the generalizability of evidence, 4 studies[54,56,59,60] were conducted in the US, and 1 of these studies used data from the Veterans Health Administration in the US. This limitation poses challenges in translating findings to the Canadian context, considering differences in health systems, health and clinical policies, and cultural factors. Regarding racial and ethnic minority groups, there was insufficient representation in the identified studies and a lack of stratification of outcomes by these factors. Furthermore, no studies included

adolescents, and thus we have no evidence for this important population that lives with a similar prevalence of chronic pain as adults and lower but increasing rates of OUD and opioid-related harms.[62]

Canada has a unique demographic composition and there are potential disparities in OUD prevalence among different populations, including Indigenous Peoples who experience higher rates of chronic pain[63] and opioid-related harms[64] compared to other populations in Canada. The absence of data for equity-deserving populations and First Nations, Inuit, and Métis Peoples in our review underscores a critical knowledge gap in this area.

Considering the types of opioid analgesics, nonpharmaceutical drugs, and OAT practices, it is worth noting that 2 studies[59,60] were conducted up to a decade ago. Since then, there have been substantial changes in toxicity risk due to the drug supply, opioid tolerance among patients, analgesic approaches, nonpharmaceutical interventions, and OAT practices. Thus, caution is required in applying these data to the contemporary Canadian context.

Involving patient partners can be an important means for improving relevance, responsiveness, and trustworthiness in research. However, this was not part of the process for this review. Canada's Drug Agency is considering involving patient partners in future projects.

Conclusions and Implications for Decision- or Policy-Making

Main Take-Aways

This report sheds light on a significant gap in the existing literature, revealing a lack of evidence on the safety of, and especially the efficacy and effectiveness of, opioid analgesics in the specific context of patients with chronic pain and coexisting OUD. It highlights the impact of this scarcity of evidence on health care decision-making at various levels. Rapid and diverse evidence generation of real-world data, and synthesis of available qualitative data and case reports, can help to inform and optimize decision-making in this complex area.

This review gathers evidence from 5 observational studies that report safety outcomes of opioid analgesic use in the context of CNCP and OUD. We have no evidence to inform important concerns of efficacy and effectiveness. Although we did not find studies with objectives directly aligned with our research question, we found data within them that can be used to begin to address the research and policy questions.

Fatal and Nonfatal Opioid-Related Toxicity in Patients With Chronic Pain and OUD Receiving Opioid Analgesics

Low-certainty evidence from 1 study[56] that matched patients who were treated with OAT and patients who were not treated using propensity scores showed that risk of fatal opioid-related toxicity may be reduced among patients with chronic pain and OUD treated with OAT compared to those who are not treated. Conversely, uncertain evidence based on unpublished crude data supplied by the authors of another study[58] suggested a nearly 4-fold increase in fatal opioid-related toxicity among patients with a history of OUD receiving OAT while using LTOT for pain compared to a control group that did not receive OAT. It is

also uncertain whether a diagnosis of OUD affects the hazard of fatal opioid-related toxicity in patients with chronic pain who use opioid analgesics.[56] Finally, based on further data from these 2 studies and the very low certainty of evidence, it is uncertain whether the risk of nonfatal opioid-related toxicity could be increased in the context of OAT for patients with chronic pain and OUD who use opioid analgesics.

Considering the conflicting results on fatal opioid-related toxicity reported by these 2 studies, Ward et al. (2022)[56] showed a reduction in mortality with low-certainty evidence and Kennedy et al. (2022)[58] indicated a mortality increase with very low–certainty evidence. However, Ward et al. used a more advanced methodology by matching 2 groups using propensity scores, which suggests that the evidence from this study is of higher quality. Moreover, it is important to consider contextual factors when comparing the results of 2 studies. Ward et al. used data from the Veterans Health Administration, which was predominantly composed of male military veterans, whereas Kennedy et al. used data from a provincial health insurance client list in British Columbia, consisting mostly of civilians with a fairly balanced representation of both sexes and genders. In addition, all demographic characteristic variables were significantly different at baseline in the Kennedy et al.[58] study, and 80% to 89% of individuals had severe mental health conditions. None of these can conclusively explain the conflict in findings, suggesting that further studies are required to refine certainty.

Based on data from another study, it is uncertain whether LTOT in patients with chronic pain and OUD affects the likelihood of fatal and nonfatal opioid-related toxicity compared to those with OUD not on LTOT.[54]

Changes in Opioid Analgesic Use in the Context of OUD

Although 1 study identified that more than half of patients with chronic pain undergoing MMT and prescribed opioid analgesic therapy either increased their dosage or used the opioids more frequently than prescribed, the evidence was of very low–certainty. It is unclear whether such changes represent problematic or disordered opioid use or if they represent appropriate changes in medical therapy to better manage pain. It is also uncertain whether having a history of OUD in the past 2 years could increase the prevalence and incidence of prolonged opioid use in patients with CNCP.[60]

Implications

As highlighted in the introduction section, decision-making to support patients with CNCP within the context of OUD can be challenging for patients, clinicians, and health administrators. Although moderate- to low-certainty evidence suggests that nonpharmacological interventions may be beneficial for chronic pain management,[65] not all individuals have access to these interventions due to limited availability or lack of coverage. Such limitations to access contribute to the undertreatment of chronic pain.

Our report sheds light on a significant gap in the existing literature, revealing a paucity of evidence concerning the safety of, and especially the efficacy and effectiveness of, opioid analgesics in the specific context of patients with CNCP and coexisting OUD. This gap is even more pronounced for populations with higher rates of CNCP and OUD, such as Indigenous Peoples. Several studies are based on data from the 2000s and 2010s, and there have been substantial changes in factors such as toxicity risk associated with the drug supply, opioid tolerance in patients, pain relief methods, nonpharmaceutical interventions, and OAT practices since then. This highlights the need for studies that are more reflective of the contemporary context.

The dearth of evidence poses significant obstacles to informed decision-making across multiple levels of health care. At the policy-making level, it can hinder regulatory processes, complicating the evaluation of intervention risks and benefits for approval or reimbursement. Health care providers struggle with uncertainty in determining the best course of action for patients, resulting in variations in treatment approaches, and potentially inferior outcomes. Patients, in turn, confront uncertainty when navigating health care decisions, leading to diminished confidence in treatment options and possibly reduced adherence to prescribed regimens. Consequently, addressing this shortage of evidence is paramount for fostering effective decision-making and optimizing patient care.

Given the significant impact of opioid use across health systems in Canada and internationally, there is a need for rapid evidence generation in this area. To address this need, concerted efforts to conduct well-designed prospective or retrospective observational studies that collect real-world data on the safety and effectiveness of opioid analgesics for diverse patient populations in various clinical settings living with chronic pain and OUD are required.[66,67] Although there are known challenges in identifying people living with OUD and pain using administrative data, multiple administrative data systems in Canada, from primary care systems to province-wide data systems, may be well equipped to face this challenge.

Other kinds of evidence beyond trial and observational study data should be prioritized. Qualitative evidence synthesis, which involves interpreting the perspectives, experiences, and values of patients, clinicians, and health administrators, is increasingly being used to support decision-making, especially in complex areas, including being used to inform clinical practice guideline development.[68] There has been important growth in both exploratory and explanatory qualitative studies regarding opioid analgesic use in the context of chronic pain as well as OUD over the past decade, and these studies may be helpful in better understanding and contextualizing the role of these medications within this context. Synthesizing studies of clinicians can deepen our understanding of clinical practices and decision-making processes in this area in which there is a lack of quantitative evidence.[69] Synthesizing studies of patients may help to broaden our understanding of the effects of different kinds of decisions and the experiences of equity-deserving communities and First Nations, Inuit, and Métis Peoples, as well as provide more context-specific information relevant to Canada.[70,71]

Finally, in clinical areas where there is a paucity of trial or observational evidence, the synthesis of individual case reports or case series may provide some useful information to support decision-making,[72,73] although this evidence is generally considered to be of very low quality and therefore not considered during typical systematic reviews or health technology assessments. Indeed, during screening for the effectiveness synthesis for this review, the only study that met all PICO (population, intervention, comparison, outcome) criteria besides study design was a case report. Thus, despite the poor quality of evidence from case reports, in this instance they may provide more direct evidence with respect to the population, intervention, comparators, and outcomes compared to the otherwise higher-quality observational studies included in this report. As was identified in response to the complex and emergent need and use of evidence to respond to the COVID-19 pandemic, flexibility and pragmatism regarding evidence may be needed to inform this complex area of opioid analgesic use for chronic pain management in the context of OUD or OAT.

References

1. Egan D, Fraifeld B, Trainum B. Opioid use disorder. Washington (DC): American Psychiatric Association; 2022; https://www.psychiatry.org/patients-families/opioid-use-disorder#:~:text=Opioid%20Use%20Disorder%20Symptoms&text=Taking%20larger%20amounts%20or%20taking,or%20recovering%20from%20its%20effects%20.%20%20A. Accessed 2023 Jun 17.
2. *Opioid agonist therapy: a synthesis of Canadian guidelines for treating opioid use disorder.* Toronto (ON): Centre for Addiction and Mental Health; 2021.
3. Min JE, Pearce LA, Homayra F, et al. Estimates of opioid use disorder prevalence from a regression-based multi-sample stratified capture-recapture analysis. *Drug Alcohol Depend*. 2020;217:108337. PubMed
4. Belzak L, Halverson J. The opioid crisis in Canada: a national perspective. *Health Promot Chronic Dis Prev Can*. 2018;38(6):224-233. PubMed
5. Morin KA, Eibl JK, Franklyn AM, Marsh DC. The opioid crisis: past, present and future policy climate in Ontario, Canada. *Subst Abuse Treat Prev Policy*. 2017;12(1):45. PubMed
6. Government of Canada. Opioid- and stimulant-related harms. 2023; https://health-infobase.canada.ca/substance-related-harms/opioids-stimulants/graphs. Accessed 2023 Jul 12.
7. The Ontario Drug Policy Research Network, *Public Health Ontario, The Office of the Chief Coroner for Ontario / Ontario Forensic Pathology Service. Opioid toxicity and access to treatment among adolescents and young adults in Ontario.* Toronto (ON): ODPRN; 2023.
8. Friesen EL, Kurdyak PA, Gomes T, et al. The impact of the COVID-19 pandemic on opioid-related harm in Ontario. Toronto (ON): Ontario COVID-19 Science Advisory Table; 2021.
9. Public Health Agency Canada. Chronic pain. 2023; https://www.canada.ca/en/public-health/services/diseases/chronic-pain.html Accessed 2023 Jun 20.
10. Delorme J, Kerckhove N, Authier N, Pereira B, Bertin C, Chenaf C. Systematic review and meta-analysis of the prevalence of chronic pain among patients with opioid use disorder and receiving opioid substitution therapy. *J Pain*. 2023;24(2):192-203. PubMed
11. Edwards KA, Vowles KE, McHugh RK, Venner KL, Witkiewitz K. Changes in pain during buprenorphine maintenance treatment among patients with opioid use disorder and chronic pain. *J Consult Clin Psychol*. 2022;90(4):314-325. PubMed
12. Speed TJ, Parekh V, Coe W, Antoine D. Comorbid chronic pain and opioid use disorder: literature review and potential treatment innovations. *Int Rev Psychiatry*. 2018;30(5):136-146. PubMed
13. Dhingra L, Perlman DC, Masson C, et al. Longitudinal analysis of pain and illicit drug use behaviors in outpatients on methadone maintenance. *Drug Alcohol Depend*. 2015;149:285-289. PubMed
14. Hser YI, Mooney LJ, Saxon AJ, Miotto K, Bell DS, Huang D. Chronic pain among patients with opioid use disorder: Results from electronic health records data. *J Subst Abuse Treat*. 2017;77:26-30. PubMed
15. Carrière G, Garner R, Sanmartin C. Significant factors associated with problematic use of opioid pain relief medications among the household population, Canada, 2018. *Health Rep*. 2021;32(12):13-26. PubMed
16. Hartz SM, Culverhouse RC, Mintz CM, et al. Association between recent overdose and chronic pain among individuals in treatment for opioid use disorder. *PLoS One*. 2022;17(11):e0271379. PubMed
17. Jones JD, Vogelman JS, Luba R, Mumtaz M, Comer SD. Chronic pain and opioid abuse: factors associated with health-related quality of life. *Am J Addict*. 2017;26(8):815-821. PubMed
18. Clark MR, Stoller KB, Brooner RK. Assessment and management of chronic pain in individuals seeking treatment for opioid dependence disorder. *Can J Psychiatry*. 2008;53(8):496-508. PubMed
19. Dhingra L, Masson C, Perlman DC, et al. Epidemiology of pain among outpatients in methadone maintenance treatment programs. *Drug Alcohol Depend*. 2013;128(1):161-165. PubMed

20. Barry DT, Cutter CJ, Beitel M, Kerns RD, Liong C, Schottenfeld RS. Psychiatric disorders among patients seeking treatment for co-occurring chronic pain and opioid use disorder. *J Clin Psychiatry*. 2016;77(10):13715. PubMed
21. Zhu Y, Mooney LJ, Yoo C, et al. Psychiatric comorbidity and treatment outcomes in patients with opioid use disorder: results from a multisite trial of buprenorphine-naloxone and methadone. *Drug Alcohol Depend*. 2021;228:108996. PubMed
22. Dennis BB, Bawor M, Naji L, et al. Impact of chronic pain on treatment prognosis for patients with opioid use disorder: a systematic review and meta-analysis. Subst Abuse. 2015;9:SART-S30120.
23. Jamison RN, Kauffman J, Katz NP. Characteristics of methadone maintenance patients with chronic pain. *J Pain Symptom Manage*. 2000;19(1):53-62. PubMed
24. Blanco C, Volkow ND. Management of opioid use disorder in the USA: present status and future directions. *Lancet*. 2019;393(10182):1760-1772. PubMed
25. Eibl JK, Morin K, Leinonen E, Marsh DC. The State of opioid agonist therapy in Canada 20 years after federal oversight. *Can J Psychiatry*. 2017;62(7):444-450. PubMed
26. Lazaridou A, Paschali M, Edwards RR, Gilligan C. Is buprenorphine effective for chronic pain? A systematic review and meta-analysis. *Pain Med*. 2020;21(12):3691-3699. PubMed
27. *Methadone maintenance treatment program standards and clinical guidelines.* Toronto (ON); College of Physicians and Surgeons of Ontario; 2011.
28. VA/DoD clinical practice guideline for the management of substance use disorders. Patient guide. Washington (DC): U.S. Department of Veterans Affairs; 2015; https://www.healthquality.va.gov/guidelines/MH/sud/VADoDSUDCPGPatientSummaryFinal.pdf Accessed 2024 May 29.
29. Handford C, Kahan M, Lester MD, Ordean A. *Buprenorphine/naloxone for opioid dependence: clinical practice guideline.* Toronto (ON): Centre for Addiction and Mental Health; 2012.
30. National Institute for Health and Care Excellence. Drug misuse: opioid detoxification Clinical guideline [CG52]. 2007.
31. *CRISM national guidelines for the clinical management of opioid use disorder.* Toronto (ON): Canadian Research Initiative in Substance Misuse. 2018.
32. DeBar L, Mayhew M, Benes L, et al. A Primary care-based cognitive behavioral therapy intervention for long-term opioid users with chronic pain : a randomized pragmatic trial. *Ann Intern Med*. 2021;175(1):46-55. PubMed
33. Barry DT, Beitel M, Cutter CJ, et al. An evaluation of the feasibility, acceptability, and preliminary efficacy of cognitive-behavioral therapy for opioid use disorder and chronic pain. *Drug Alcohol Depend*. 2018;194:460-467. PubMed
34. Garland EL, Hanley AW, Nakamura Y, et al. Mindfulness-oriented recovery enhancement vs supportive group therapy for co-occurring opioid misuse and chronic pain in primary care: a randomized clinical trial. *JAMA Intern Med*. 2022;182(4):407-417. PubMed
35. Nicol AL, Hurley RW, Benzon HT. Alternatives to opioids in the pharmacologic management of chronic pain syndromes: a narrative review of randomized, controlled, and blinded clinical trials. *Anesth Analg*. 2017;125(5):1682-1703. PubMed
36. *Managing chronic pain in adults with or in recovery from substance use disorders: Treatment Improvement Protocol Series (TIP 54).* Rockville (MD): U. S. Department of Health and Human Services; 2013.
37. Busse JW, Wang L, Kamaleldin M, et al. Opioids for Chronic noncancer pain: a systematic review and meta-analysis. *JAMA*. 2018;320(23):2448-2460. PubMed
38. Duensing L, Eksterowicz N, Macario A, Brown M, Stern L, Ogbonnaya A. Patient and physician perceptions of treatment of moderate-to-severe chronic pain with oral opioids. *Curr Med Res Opin*. 2010;26(7):1579-1585. PubMed
39. Goshua A, Craigie S, Guyatt GH, et al. Patient values and preferences regarding opioids for chronic noncancer pain: a systematic review. *Pain Med*. 2018;19(12):2469-2480. PubMed

40. Antoniou T, Ala-Leppilampi K, Shearer D, Parsons JA, Tadrous M, Gomes T. "Like being put on an ice floe and shoved away": a qualitative study of the impacts of opioid-related policy changes on people who take opioids. *International Journal of Drug Policy*. 2019;66:15-22. PubMed

41. Higgins JP, Thomas J, Chandler J, Cumpston M, Li T. *Cochrane handbook for systematic reviews of interventions: Chichester (GB)*: John Wiley & Sons; 2023.

42. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev*. 2015;4(1):1. PubMed

43. National Institute on Drug Abuse. Words matter-terms to use and avoid when talking about addiction. 2021; https://nida.nih.gov/nidamed-medical-health-professionals/health-professions-education/words-matter-terms-to-use-avoid-when-talking-about-addiction Accessed 2024 May 29.

44. Busse JW, Craigie S, Juurlink DN, et al. Guideline for opioid therapy and chronic noncancer pain. *CMAJ*. 2017;189(18):E659-E666. PubMed

45. Chou R, Hartung D, Turner J, *Others. Opioid treatments for chronic pain: comparative effectiveness review, no. 229. AHRQ comparative effectiveness reviews (report no.: 20-EHC011).* Rockville, (MD); Agency for Healthcare Research and Quality; 2020.

46. Wang L, Hong PJ, Jiang W, et al. Predictors of fatal and nonfatal overdose after prescription of opioids for chronic pain: a systematic review and meta-analysis of observational studies. *CMAJ*. 2023;195(41):E1399-E1411. PubMed

47. Bedson J, Chen Y, Ashworth J, Hayward RA, Dunn KM, Jordan KP. Risk of adverse events in patients prescribed long-term opioids: a cohort study in the UK Clinical Practice Research Datalink. *Eur J Pain*. 2019;23(5):908-922. PubMed

48. Paulozzi LJ, Zhang K, Jones CM, Mack KA. Risk of adverse health outcomes with increasing duration and regularity of opioid therapy. *J Am Board Fam Med*. 2014;27(3):329-338. PubMed

49. Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain*. 2008;9(2):105-121. PubMed

50. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016;355:i4919. PubMed

51. Grooten WJA, Tseli E, Äng BO, et al. Elaborating on the assessment of the risk of bias in prognostic studies in pain rehabilitation using QUIPS—aspects of interrater agreement. *Diagnostic and Prognostic Research*. 2019;3(1):5. PubMed

52. Santesso N, Glenton C, Dahm P, et al. GRADE guidelines 26: informative statements to communicate the findings of systematic reviews of interventions. *J Clin Epidemiol*. 2020;119:126-135. PubMed

53. Guyatt GH, Oxman AD, Sultan S, et al. GRADE guidelines: 9. Rating up the quality of evidence. *J Clin Epidemiol*. 2011;64(12):1311-1316. PubMed

54. Mannes ZL, Wheeler-Martin K, Terlizzi K, et al. Risks of opioid overdose among New York State Medicaid recipients with chronic pain before and during the COVID-19 pandemic. *Prev Med*. 2023;177:107789. PubMed

55. Manchikanti L, Abdi S, Atluri S, et al. American Society of Interventional Pain Physicians (ASIPP) guidelines for responsible opioid prescribing in chronic non-cancer pain: Part I--evidence assessment. *Pain Physician*. 2012;15(3 Suppl):S1-65. PubMed

56. Ward R, Tang YL, Axon RN, Casarella J, Whitfield N, Rauch SAM. Effectiveness of a substance use treatment program for veterans with chronic pain and opioid use disorder. *J Subst Abuse Treat*. 2022;132:108635. PubMed

57. Seal KH, Maguen S, Bertenthal D, et al. Observational evidence for buprenorphine's impact on posttraumatic stress symptoms in veterans with chronic pain and opioid use disorder. *J Clin Psychiatry*. 2016;77(9):1182-1188. PubMed

58. Kennedy MC, Crabtree A, Nolan S, et al. Discontinuation and tapering of prescribed opioids and risk of overdose among people on long-term opioid therapy for pain with and without opioid use disorder in British Columbia, Canada: a retrospective cohort study. *PLoS Med*. 2022;19(12):e1004123. PubMed

59. Glenn MC, Sohler NL, Starrels JL, et al. Characteristics of methadone maintenance treatment patients prescribed opioid analgesics. *Subst Abus*. 2016;37(3):387-391. PubMed

60. Weisner CM, Campbell CI, Ray GT, et al. Trends in prescribed opioid therapy for non-cancer pain for individuals with prior substance use disorders. *Pain*. 2009;145(3):287-293. PubMed

61. Schünemann H, Brożek J, Guyatt G, Oxman A. The GRADE handbook. 2013; https://gdt.gradepro.org/app/handbook/handbook.html Accessed 2024 May 29 .

62. Health Canada. Understanding a broader range of opioid-related hospitalizations in Canada. 2021 May 12; https://www.canada.ca/en/health-canada/services/opioids/data-surveillance-research/understanding-broader-range-opioid-related-hospitalizations.html. Accessed 2024 May 17.

63. Statistics Canada. Health indicators, by Aboriginal identity, four-year period estimates. 2016 Dec 9; https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1310045701. Accessed 2024 Apr 10.

64. First Nations Health Authority. First Nations opioid overdose deaths rise in 2018. 2019; https://www.fnha.ca/about/news-and-events/news/first-nations-opioid-overdose-deaths-rise-in-2018. Accessed 2024 May 29.

65. CADTH. Non-drug ways to manage chronic pain. 2020; https://www.cadth.ca/chronicpain. Accessed 2023 Nov 7.

66. Lacasse A, Cauvier Charest E, Dault R, et al. Validity of algorithms for identification of individuals suffering from chronic noncancer pain in administrative databases: a systematic review. *Pain Med*. 2020;21(9):1825-1839. PubMed

67. Scherrer JF, Sullivan MD, LaRochelle MR, Grucza R. Validating opioid use disorder diagnoses in administrative data: a commentary on existing evidence and future directions. *Addict Sci Clin Pract*. 2023;18(1):49. PubMed

68. Flemming K, Booth A, Garside R, Tunçalp Ö, Noyes J. Qualitative evidence synthesis for complex interventions and guideline development: clarification of the purpose, designs and relevant methods. *BMJ Glob Health*. 2019;4(Suppl 1):e000882. PubMed

69. Varley AL, Lappan S, Jackson J, et al. Understanding barriers and facilitators to the uptake of best practices for the treatment of co-occurring chronic pain and opioid use disorder. *J Dual Diagn*. 2020;16(2):239-249. PubMed

70. Calcaterra SL, Lockhart S, Callister C, Hoover K, Binswanger IA. Opioid use disorder treatment initiation and continuation: a qualitative study of patients who received addiction consultation and hospital-based providers. *J Gen Intern Med*. 2022;37(11):2786-2794. PubMed

71. Blake S, Ruel B, Seamark C, Seamark D. Experiences of patients requiring strong opioid drugs for chronic non-cancer pain: a patient-initiated study. *Br J Gen Pract*. 2007;57(535):101-108. PubMed

72. Murad MH, Sultan S, Haffar S, Bazerbachi F. Methodological quality and synthesis of case series and case reports. *BMJ Evid Based Med*. 2018;23(2):60-63. PubMed

73. Morgan RL, Ashoorion V, Cuker A, et al. Management of heparin-induced thrombocytopenia: systematic reviews and meta-analyses. *Blood Adv*. 2020;4(20):5184-5193. PubMed

Appendix 1: Selection of Included Studies

Note that this appendix has not been copy-edited.

Figure 2: PRISMA Flow Chart for RCTs Screened for Efficacy Outcomes

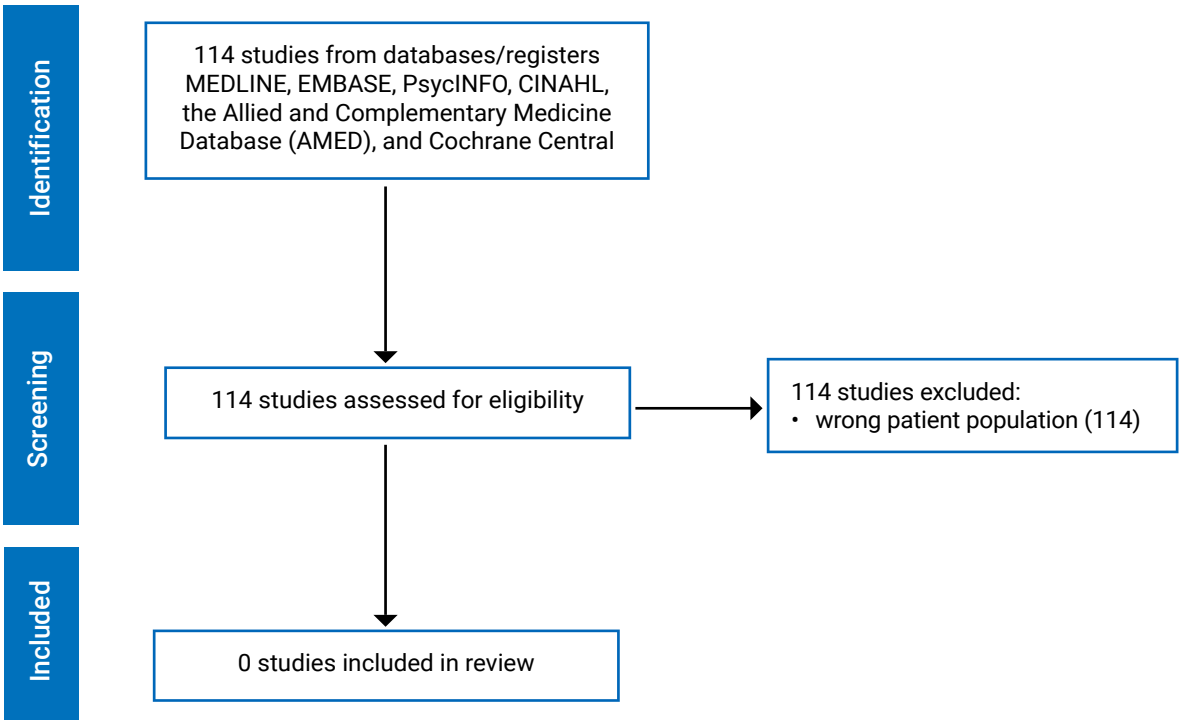


Figure 3: PRISMA Flow Chart for Observational Studies Identified by Guideline Data Synthesis Team for Effectiveness and Safety Outcomes

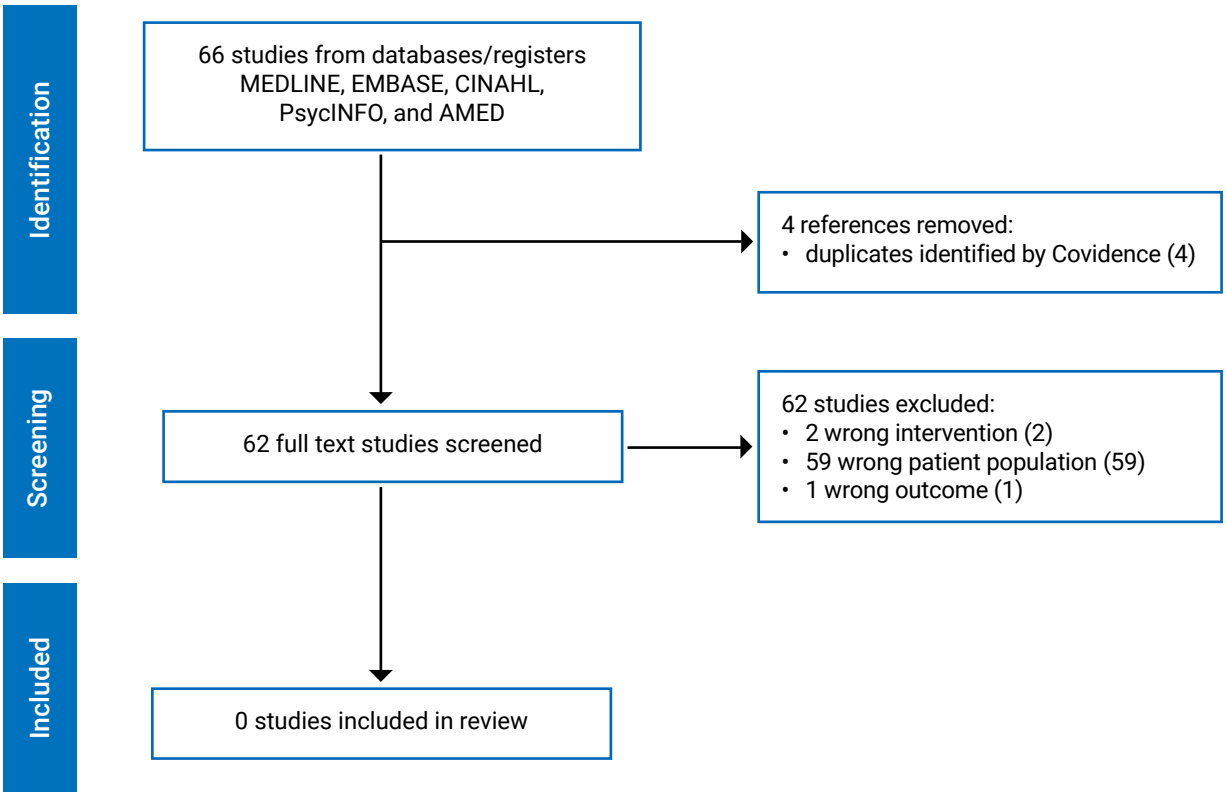


Figure 4: PRISMA Flow Chart for Observational Studies Screened for Safety Outcomes

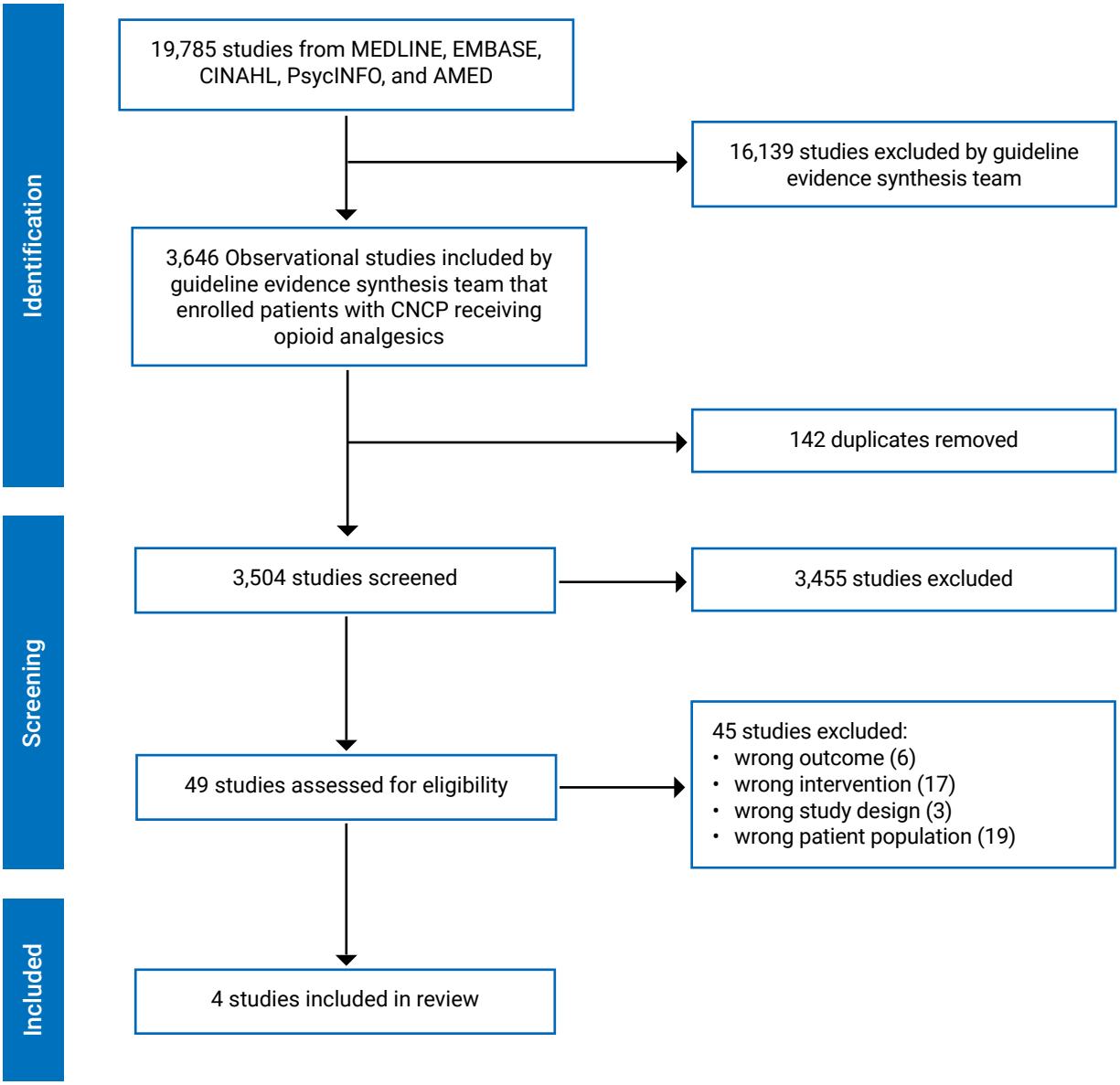
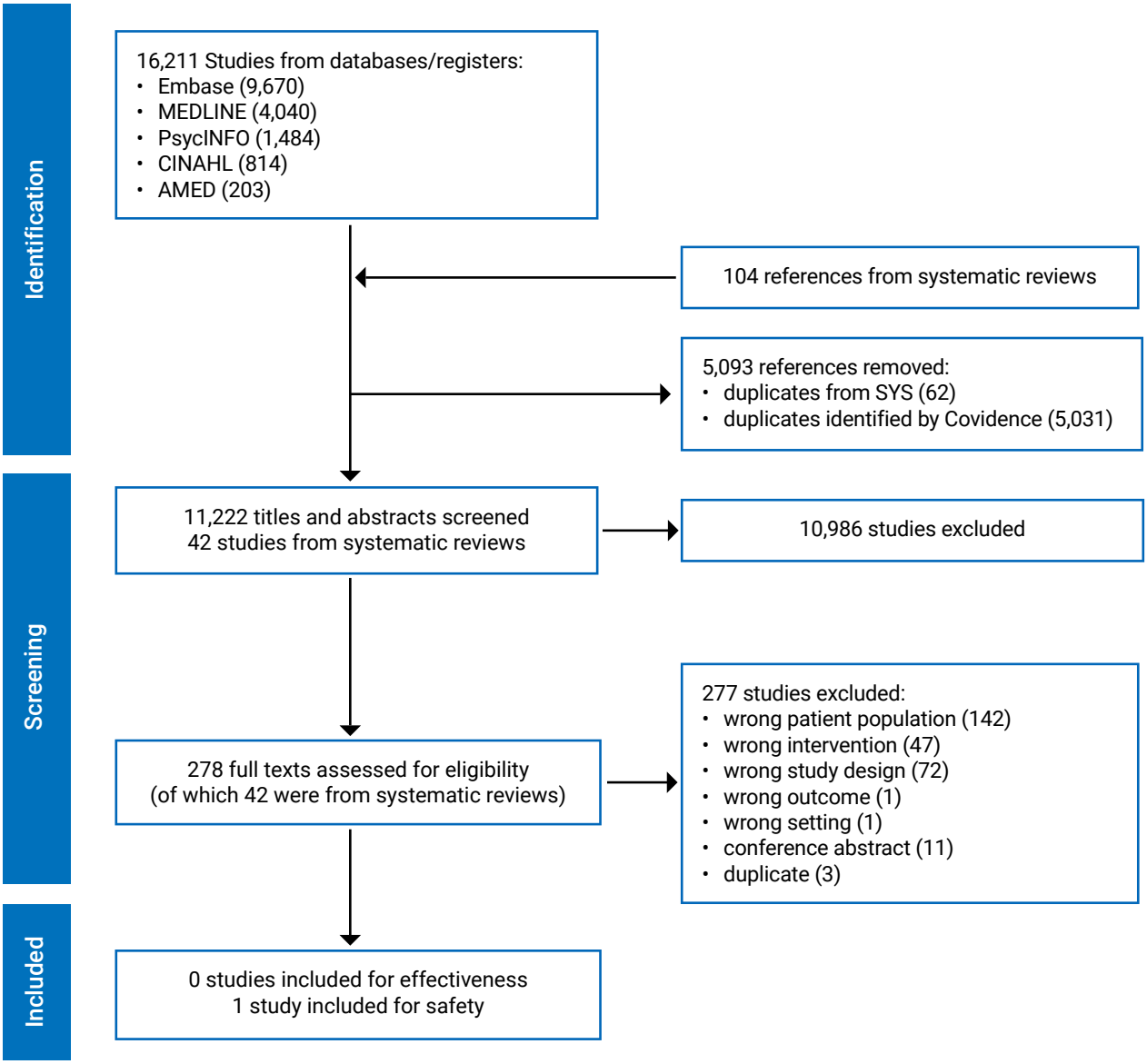


Figure 5: PRISMA Flow Chart for Observational Studies Screened for Effectiveness Outcomes



Appendix 2: Search Strategy for Effectiveness

Refer to supplemental materials with all database search strategies.

Appendix 3: Calculation of Ratio of Odds Ratios

Note that this appendix has not been copy-edited.

Ln (OR1)
Ln (OR2)
SE = $(SE1^2 + SE2^2)^{0.5}$
SE1 and SE2 are log SE1 and log SE2 (Ln upper limit – Ln lower limit) / 3.92
Ln (ROR) = Ln (OR1) – Ln (OR2)
ROR = Exp (Ln (ROR))
Lower limit 95% CI = Ln (ROR) – (Z × SE)
Upper limit 95% CI = Ln (ROR) + (Z × SE)
Lower limit 95% CI = Exp (Ln (ROR) – (Z × SE))
Upper limit 95% CI = Exp (Ln (ROR) + (Z × SE))
Mannes (2023)[54]: Table 2, page 3 of 7

Comparing prepandemic adjusted odds ratios
LTOT and OUD, prepandemic-adjusted OR = **5.82 (95% CI, 3.58 to 9.44**)
Log lower limit of 95% CI = 1.275; Log upper limit of 95% CI = 2.245; **SE1** = (2.245 to 1.275) / 3.92 = **0.247**
Only OUD, prepandemic adjusted OR = **5.65 (95% CI, 4.73 to 6.75)**
Log lower limit of 95% CI = 1.554; Log upper limit of 95% CI = 1.910; **SE2** = (2.245 to 1.275) / 3.92 = **0.091**
Ln (ROR) = Ln (OR1) – Ln (OR2) 1.761 to 1.732 = 0.029; **ROR = 1.03**

SE of difference = $(SE1^2 + SE2^2)^{0.5}$ = **0.263**
Lower limit 95% CI = Ln (ROR) – (Z × SE of diff) = 0.029 – (1.96 × 0.263) = −0.486; **lower limit 95% CI = 0.615**
Upper limit 95% CI = Ln (ROR) + (Z × SE of diff) = 0.029 – (1.96 × 0.263) = 0.546; **upper limit 95% CI = 1.726**

Comparing during pandemic adjusted odds ratios
LTOT and OUD, during pandemic adjusted OR = **3.70 (95% CI, 2.11 to 6.50**)
Log lower limit of 95% CI = 0.747; Log upper limit of 95% CI = 1.872; **SE1** = (1.872 to 0.77) / 3.92 = **0.287**
Only OUD, during pandemic adjusted OR = **5.16 (95% CI, 4.33 to 6.14)**
Log lower limit of 95% CI = 1.466; Log upper limit of 95% CI = 1.815; **SE2** = (1.815 to 1.466) / 3.92 = **0.089**
Ln (ROR) = Ln (OR1) – Ln (OR2) 1.308 to 1.641 = −0.333; **ROR = 0.72**

SE of difference = $(SE1^2 + SE2^2)^{0.5}$ = **0.30**
Lower limit 95% CI = Ln (ROR) – (Z × SE of diff) = −0.333 – (1.96 × 0.30) = −0.922; **lower limit 95% CI = 0.40**
Upper limit 95% CI = Ln (ROR) + (Z × SE of diff) = −0.333 – (1.96 × 0.30) = 0.256; **upper limit 95% CI = 1.29**

Appendix 4: Summary of Findings for Safety of Using Opioid Analgesics in Patients With CNCP and Living With OUD

Table 5: Summary of Findings for Safety of Using Opioid Analgesics in Patients With CNCP and Living With OUD and Assessing Quality of Evidence Using GRADE Evidence Profile

Sample size, length of follow-up	Quality assessment						Effect size	Anticipated absolute effect: Baseline risk	Anticipated absolute effect: Risk difference (95% CI)
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall			
Ward 2022 **P: Patients with chronic pain and opioid use living with OUD** **I: Treated with medications for OUD (oral methadone, sublingual buprenorphine/naloxone, and injectable naltrexone) (OAT)** **C: Not treated with MOUD (OAT)** **O: Fatal opioid-related toxicity and nonfatal opioid-related toxicity**									
Fatal opioid-related toxicity									
1,125 patients, Length of follow-up 12 months	Low risk of bias[a]	NA	No Serious indirectness	No serious imprecision for death	NA	Low[b]	RR: 0.70 (95% CI, 0.53 to 0.91)	20%	60 (95% CI, 18 to 94) fewer deaths per 1,000 participants
Nonfatal opioid-related toxicity									
1,125 patients, Length of follow-up 12 months	Low risk of bias[a]	NA	No serious indirectness	Serious imprecision	NA	Very Low	RR: 1.61 (95% CI, 0.97 −2.68)	4%	24 more nonfatal toxicity (95% CI, 1 fewer, 67 more)

Sample size, length of follow-up	Quality assessment						Effect size	Anticipated absolute effect: Baseline risk	Anticipated absolute effect: Risk difference (95% CI)
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall			
Ward 2022 **P: Patients with chronic pain and opioid use** **I: Diagnosed with OUD** **C: Not diagnosed with OUD** **O: Fatal opioid-related toxicity and nonfatal opioid-related toxicity**									
Fatal opioid-related toxicity									
1,125 patients, Length of follow-up 12 months	High risk of bias[c]	NA	No serious indirectness	No serious imprecision for death	NA	Very Low	HR: 1.40 (95% CI, 1.02 to 1.92)	NA	NA
Kennedy 2022 **P: Patients with long-term opioid therapy for pain (> = 90 days with > = 90% of days on therapy with history of OUD in past 3 years** **I: Prescribed OAT in past 90 days** **C: Not prescribed OAT** **O: Fatal opioid-related toxicity and nonfatal opioid-related toxicity**									
Fatal opioid-related toxicity									
711 patients, Median follow-up median 44.4 months (IQR: 2.6 to 4)	High risk of bias[d]	NA	No serious indirectness	No serious imprecision	NA	Very Low[e]	RR: 3.93 (95% CI, 2.04 to 7.57)	2.7%	79 more (28 to 177 more per 1,000)
Nonfatal opioid-related toxicity									
711 patients, Median follow-up median 44.4	High risk of bias[d]	NA	No serious indirectness	No serious imprecision	NA	Very Low[f]	RR: 1.55 (95% CI, 1.24 to 1.93)	8.7% (87 nonfatal opioid-related toxicity in 1,000	48 more (95% CI, 21 to 81 more in 1,000 person- year observation)

Sample size, length of follow-up	Quality assessment						Effect size	Anticipated absolute effect: Baseline risk	Anticipated absolute effect: Risk difference (95% CI)
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall			
months (IQR: 2.6 to 4)								person-year observation)	
Mannes 2023 **P: Patients with CNCP** **I: With history of OUD and Long-term opioid therapy** **C: With history of OUD** **O: Fatal and nonfatal opioid-related toxicity**									
Predictor: LTOT and OUD vs OUD only, prepandemic									
236,391 patients, follow-up 12 months	Low risk of bias[g]	NA	Serious indirectness[h]	Serious imprecision	NA	Very Low	ROR = 1.03 (0.61 to 1.73)	NA	NA
Predictor: LTOT and OUD vs OUD only, during pandemic									
236,391 patients, follow-up 12 months	Low risk of bias[g]	NA	Serious indirectness[h]	Serious imprecision	NA	Very Low	ROR = 0.72 (0.40 to 1.29)	NA	NA
Glenn 2016 **P: Patients with chronic pain on methadone maintenance treatment** **I: Prescribed opioid analgesics** **C: Not prescribed opioid analgesics** **O: Taking opioid analgesics in higher dose, taking opioid analgesics more frequently, taking both (higher dose and more frequently)**									
Taking opioid analgesics in higher dose than prescribed									
1,125 patients, Length of follow-up 12 months	High risk of bias[i]	NA	No serious indirectness	NA	NA	Very Low[f]	NA	86 out of 182 (47.2%)	NA

Sample size, length of follow-up	Quality assessment						Effect size	Anticipated absolute effect: Baseline risk	Anticipated absolute effect: Risk difference (95% CI)
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall			
Taking opioid analgesics more frequently than prescribed									
1,125 patients, Length of follow-up 12 months	High risk of bias[i]	NA	No serious indirectness	NA	NA	Very Low[f]	NA	81 out of 182 (44.5%)	NA
Taking opioid analgesics in higher dose OR more frequently than prescribed									
1,125 patients, Length of follow-up 12 months	High risk of bias[i]	NA	No serious indirectness	NA	NA	Very Low[f]	NA	103 out of 182 (56.6%)	NA
Weisner 2009 **P: Patients with CNCP with opioid use episode (dispensing for an oral or transdermal opioid with none dispensed in the prior 6 months)** **I: With history of OUD in past 2 years** **C: Without history of OUD in past 2 years** **O: Prevalence of long-term opioid use, Incidence of long-term opioid use (opioid use episodes lasting longer than 90 days with at least 10 prescriptions and/or at least 120 days supply dispensed)**									
Prevalence of long-term opioid use in 2005									
1,662,336 patients, follow-up 12 months	High risk of bias[d]	NA	Serious indirectness[j]	No serious imprecision	NA	Very Low[e]	Prevalence:11.55 (95% CI, 9.98 to 13.37)	4.3%	454 more long-term opioid use (95% CI, 386 to 532 more) in 1,000 CNCP patients with OUD history
Incidence of long-term opioid use per year at Kaiser Permanente of Northern California Health plan in 2005									
1,461,494 patients,	High risk of bias[d]	NA	Serious indirectness[j]	No serious imprecision	NA	Very Low[e]	Incidence: 7.42 (95% CI, 6.31 to 8.73)	0.8%	51 more long-term opioid use (95% CI, 42 to 62 more)

Sample size, length of follow-up	Quality assessment						Effect size	Anticipated absolute effect: Baseline risk	Anticipated absolute effect: Risk difference (95% CI)
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall			
follow-up 12 months									in 1,000 CNCP patients with OUD history

C = comparator; CNCP = chronic noncancer pain; I = intervention; mOUD = buprenorphine and methadone; NA = not applicable; O = outcome; OAT = opioid agonist therapy; OUD = opioid use disorder; P = population; ROR = ratio of odds ratios.

[a]Utilized propensity score to match treated and untreated patients, incorporating potentially confounding variables.

[b]No serious imprecision despite the low number of events (200 deaths in 1,125 participants), considering the importance of the outcome (i.e., mortality). The lower end of the confidence interval for absolute risk reduction indicates that OAT plus opioid analgesics reduced deaths by 18 per 1,000 participants.

[c]High risk of bias due to unclear definition of OUD diagnosis as a prognostic factor.

[d]Serious risk of bias due to unadjusted analysis.

[e]The effect size indicates a large magnitude of effect; however, the certainty of the evidence was not rated up due to high risk of bias.

[f]Certainty was rated down on basis of high risk of bias.

[g]Low risk of bias as all risk factors included in adjusted analysis.

[h]Serious indirectness as 33% of participants used buprenorphine or methadone as long-term opioid therapy.

[i]High risk of bias due to issues in multiple domains, including bias in measuring the intervention, presence of co-interventions, and bias in the measurement of outcomes.

[j]Serious indirectness due to different intervention and outcome from PICO.

Note that this table has not been copy-edited.

Authorship

Authors

Vahid Ashoorion made substantial contributions to the conception and design of the protocol, executed the search, performed data extraction and synthesis, conducted critical revisions for important intellectual content, circulated the report among co-investigators, collected input, applied edits, and prepared the final report.

Tushar Sood was involved with collecting, screening, and synthesizing data, manuscript writing, and editing/ revision.

Shezel Muneer contributed to editing and writing of the protocol, manuscript, and designing figures.

Jason W. Busse contributed to the protocol design and reviewed and revised earlier drafts of the report.

Danielle Rice contributed to conception and design and interpretation of study results including key messages. Involved in report revising critically for important intellectual content. I agree to be accountable for all aspects of your contribution, and for ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Jaris Swidrovich assisted with the direction and revision(s) of this work.

Umair Majid reviewed the scope and project progress, the final reports, and provided additional support as needed throughout the project.

Abhimanyu Sud contributed to the conception and design of the project, supervised data acquisition and analysis, provided guidance for interpreting results and formulating key messages/conclusions, writing, reviewing, and editing earlier drafts and the final report.

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Louis de Léséleuc and **David Stock** reviewed the drafts and final report. **Emily Farrell** provided knowledge mobilization support. **Brandy Appleby** provided project management support.

Conflicts of Interest

Jason W. Busse disclosed the following:

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Umair Majid disclosed the following:

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For more information on CoLab and its work visit **colab.cadth.ca**

Canada's Drug and Health Technology Agency

CoLab Network

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About CADTH: CADTH is a not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs and medical devices in our health care system.

About CoLab: CoLab is a pan-Canadian network of experts in applied research, scientific methods, and data analysis. CoLab members work with CADTH's Post-Market Drug Evaluation Program to produce credible and timely evidence on post-market drug safety and effectiveness.