CoLab Network

DRAFT Systematic Review

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

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This systematic review was conducted through the Post Market Drug Evaluation Program.

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 non-cancer 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 impacted** in patients with chronic non-cancer pain, prescribed opioid analgesics and diagnosed with opioid use disorder compared to those not diagnosed with opioid use disorder;
- **the risk of fatal and non-fatal opioid-related toxicity** as a combined outcome is impacted by long-term opioid analgesic therapy in chronic pain patients with opioid use disorder;
- **having 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;
- t**he dose of opioid analgesics or frequency of use** is impacted among patients with chronic non-cancer pain and opioid use disorder undergoing methadone maintenance therapy and prescribed opioid analgesics.

Further research is needed to increase the knowledge of Indigenous people and equity-deserving populations, and to improve certainty of evidence.

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Abbreviations

AMED	Allied and Complementary Medicine Database
AOR	Adjusted Odds Ratio
ARI	Absolute Risk Increase
ARR	Absolute Risk Reduction
CI	Confidence Interval
CNCP	chronic non-cancer pain
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HR	Hazard Ratio
HRQoL	health-related quality of life
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
SMD	Standard Mean Difference

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 non-pharmaceutical opioid use.[1,2] OUD is a growing public health concern across North America, disproportionately impacting various sex and age groups.[3]

Reliable national estimates are not available, but in British Columbia, the prevalence of OUD 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] Likewise, rates of opioid-related harms vary nationally, with fatalities and hospitalization rates being highest in Canada's western jurisdictions.[6] OUD and opioid-related harms remain serious issues across the country, with opioid-related toxicity being among the leading causes of death in adults.[3] The national rate of apparent opioid toxicity deaths in 2022 was estimated to be ~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 Non-Cancer Pain and OUD Comorbidity

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

There is a complex interplay between these two 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 (roughly 3.7 million) aged ≥ 15 years reported using opioids for pain relief over the past 12 months; of these, according to one study, 9.7% (approximately 351,000) engaged in problematic use, which was defined in the study as taking opioids 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 non-fatal opioid-related toxicity relative to those without chronic pain (OR: 1.55, 95% 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 (HRQoL).[17] While 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 one 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 two times as high in those with co-occurring chronic pain relative to those without 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 (67-78%) compared to those without chronic pain (51-58%).[14,23]

Given 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] Though buprenorphine formulations are

widely used for analgesic purposes, research related to pain efficacy in the context of co-occurring OUD and chronic pain related to pain efficacy 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, though 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 non-opioid pharmacotherapies (e.g., NSAIDs, anticonvulsants, and tricyclic antidepressants)[2,27,29] and non-pharmacological therapies (e.g., cognitive behavioural therapy).[2,28,29]

Evidence supporting the use of interventions such as cognitive behavioural 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. Likewise, many medical professionals prescribe non-opioid medications for chronic pain. However, despite some positive findings, analgesic effects of non-opioid 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, non-pharmacological pain treatment, and psychiatric and/or sleep disturbance treatments.[36] Of note, with regards to efficacy, a meta-analysis of 94 randomized controlled trials (RCTs) with median follow up of 60 days (IQR: 30-84 days) found that opioid use among patients with chronic non-cancer pain (CNCP) was associated with statistically significant, but clinically modest, improvements in pain, sleep and physical functioning; however, patients with comorbid 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] While 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] Likewise, individuals with OUD who develop chronic pain could face stigma, be labelled as “addicts”, and may encounter challenges in finding a physician willing to prescribe analgesic therapy, including opioid analgesics. Moreover, people with OUD might themselves 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 thus one option for chronic pain management in patients with OUD. As it stands, 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 policymakers through evidence synthesis can support evidence-informed decision-making in this complex area. Accordingly, this project aims to summarize evidence on the efficacy, effectiveness, and safety of opioid analgesics in managing chronic pain in people with OUD, a history of OUD, receiving OAT, and/or a history of receiving OAT.

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 the CADTH website for stakeholder feedback. The protocol was developed by the Subject Matter Health Research Lab based out of Humber River Health, in collaboration with CADTH as well as content and methodological experts (Refer to Authorship). 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 non-cancer 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 pain who are currently receiving OAT?
2. How can opioid analgesics be used safely and effectively in patients with chronic pain who are not receiving OAT and have OUD or a history of OUD?
3. Are the above-named patients at a higher risk of opioid-related toxicity or relapse? Is there an interval following OUD remission where 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 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, HRQoL, 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 the research question pertaining to safety, due to the limited number of eligible studies, we modified the protocol by expanding our search strategy, as explained below, and included prolonged opioid analgesic use as an additional outcome. This report captures findings from sub-analyses of RCTs and observational studies reporting on safety outcomes identified from systematic reviews which were previously registered in PROSPERO.

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

For the effectiveness research question, 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 when these terms were used in the original reports, and we followed the instructions from the National Institute on Drug Abuse for substitute terms.[43]

Literature Search Methods

In our protocol, we planned to search for two 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 list 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: Selection of Included Studies,

Figure 2).

Real-World Evidence from Observational Studies — Safety

The same evidence synthesis team conducted two systematic reviews and meta-analyses exploring predictors of fatal and nonfatal overdose[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 two reviews and also reviewed the bibliographic references of the included studies and related reviews for additional potentially eligible citations (Appendix 1: Selection of Included Studies Figure 3).

As the guideline evidence synthesis team only included observational studies that adjusted for confounding factors, we decided to broaden our search and screen the observational studies that enrolled 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 enrolled patients with CNCP using opioids for chronic pain. We screened these 3,504 titles and abstracts, and 49 full texts resulted from title abstract screening (Appendix 1: Selection of Included Studies, 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 1st, 2023, without language restrictions. We reviewed reference lists of eligible studies and related reviews for additional potentially eligible articles (Appendix 2: Search Strategy for).

Study Selection

Pairs of reviewers independently screened all 114 full texts of included RCTs, and 62 observational studies deemed eligible by the guideline evidence synthesis team against the eligibility 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, four 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. Available at www.covidence.org.

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 study selection process is presented in PRISMA flow charts (Appendix 1: Selection of Included Studies).

Inclusion Criteria

The evidence synthesis team included RCTs of any design, ensuring a minimum of 10 subjects in each arm. Additionally, observational studies, both comparative and single arm, were included that had at least 20 participants that met eligibility criteria. The team included studies that enrolled adults ≥18 years old with chronic pain (defined as pain lasting ≥ 3 months) who have OUD or a history of OUD and compared opioid analgesics either alone or in combination with OAT versus any comparator including no treatment. For studies that enrolled a mixed population, the evidence synthesis team included those that reported results for participants with CNCP and OUD separately or those where at least 85% of the enrolled 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] Since the evidence synthesis team utilized 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
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, non-fatal 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 will also be 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 they were duplicate publications, case reports, case series, or conference abstracts. The evidence synthesis team also excluded studies that enrolled 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 ROBINS-I or the QUIPS tool to assess risk of bias in nonrandomized studies. ROBINS-I covers seven 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), odds ratio (OR), hazard ratio (HR)), and a corresponding 95% confidence interval (CI). We complemented relative measures of association (RR) with the absolute risk change for each outcome. In cases where 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)]) and upper/lower limits of 95% CI (95% CI = Exp (ln (RR) ± 1.96×SE)). An example for calculating RR and corresponding 95% CIs is provided in Appendix 3: Example for Calculating Relative Risk and Corresponding Confidence Interval. We used the Ratio of Odds Ratios (ROR) to compare the strength of association between two different groups or conditions, calculated using the formula provided in Appendix 4: Ratio of Odds Ratios (ROR).

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 one 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 less 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

For the safety report, no RCTs met eligibility criteria. Of the 3,504 unique records collecting observational data, 4 reports met the eligibility criteria (Appendix 1: Selection of Included Studies Figure 4).

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

We screened the reference list of all included studies, one 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 and one author[58] responded by providing crude data for fatal and non-fatal opioid-related toxicity separately.

Study Characteristics

The remainder of these results will focus on the five 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 (2009) reported the mean age and sex proportion data for only 38,843 participants (Table 2). The range of mean for age across the studies was 45.8 - 58.2 years and the duration of follow-up was between 1- 44.4 months. The studies enrolled female participants ranging from 6.3% to 64.6%, with 93.7% of participants in one study[56] being male (Table 2).

One study[58] reported data from Canada and the remaining four studies[54,56,59,60] reported data from the United States. Two studies[58,59] recruited subjects from outpatient settings, one study[60] utilized data from two health plan databases, one study[56] used a Veterans Health Administration database, and one study[54] examined the records from New York State Medicaid recipients (Table 2).

Table 2: Study characteristics

Study, Country	Sample size	Age Mean (SD)	Female N (%)	Length of follow up	Study setting	Population	Race and ethnicity	Intervention/ comparison	Outcome
Ward 2022, US	1,125	54.1 (12.6)	71 (6.3%)	12 months	Veterans' health administration	Patients with chronic pain and opioid use living with OUD	Non-Hispanic White 536 (34.4%); Non-Hispanic Black 949 (60.9%); Hispanic 25 (1.6%); Other 23(1.5%); Missing 25 (1.6%)	Treated with medications for OUD and psychosocial treatment vs untreated with MOUD	Non-fatal opioid-related toxicity, fatal opioid-related toxicity
Kennedy 2022, Canada	710	49.4 (12.6)	322 (45.4%)	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	Non-fatal opioid-related toxicity or fatal opioid-related toxicity
Mannes 2023, US	236,391	45.8 (12.3)	152,619 (64.6%)	12 months	New York State Medicaid claims	Patents with CNCP	Asian 33,751 (14.3%); Black/African American 41,159 (17.4%); Hispanic 30,776 (13.0%); White 70,215 (29.7%); Other 12,816 (5.4%); Unknown 47,674 (20.2%)	OUD and LTOT vs no OUD and LTOT before and during COVID pandemic	Non-fatal or fatal opioid-related toxicity (combined outcome)
Glenn 2016, US	611	51.5 (8.6)	235 (38.5%)	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 2009, US	38,843	58.2 (14.7)	25,062 (64.5%)	12 months	Health care plan registry	Patents with CNCP with opioid use episode	NR	With history of OUD in last 2 years	Prevalence and incidence of

								vs without history of OUD in last 2 years	long-term opioid use

OUD: opioid use disorder, MOUD: medication for opioid use disorder, CNCP: chronic non-cancer pain, OAT: opioid agonist therapy, LTOT: long-term opioid therapy, NR: Not reported

Critical Appraisal

Mannes et al. (2023) investigated the association between OUD, long-term opioid therapy (LTOT), and other risk factors with fatal and non-fatal opioid toxicity through adjusted analysis and was deemed to be of low risk of bias. Ward et al. (2022) was rated as low risk of bias for the propensity score-based analysis and calculating the relative risk of fatal and non-fatal opioid-related toxicity, which matched treated and untreated patients and incorporated potentially confounding variables. However, for the Cox proportional hazard analysis, Ward (2022) was considered to have a high risk of bias due to invalid measurement of OUD as one 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 ICD codes were reported in the study.

The three remaining studies[58–60] were at high risk of bias in at least one domain. While Kennedy et al. (2022) adjusted the data for confounders in the main analysis, the crude data provided by the author for the safety report was not adjusted for confounders. Glenn et al. (2016) 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) did not adjust analyses for confounding factors (

Appendix 5: Risk of Bias Assessment,

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

First author (year)	Risk of bias domain[a]							Overall risk of bias[b]
	Confounding	Participant selection	Classification	Deviation	Missing data	Measurement	Results selection	
Ward (2022)[56c]	Low	Low	Low	Low	Low	Low	Low	Low
Kennedy (2022)[58]	Serious	Low	Low	Low	Low	Low	Low	Serious
Glenn (2016)[59]	Serious	Low	Serious	Serious	Low	Serious	Low	Serious
Weisner (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] Judgement scale: Low, moderate, serious, critical, unclear.

[c] Ward (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]						Overall risk of bias[b]
	Participant selection	Missing data	Prognostic factor measurements	Outcome assessments	Optimal adjustment	Statistical analysis and reporting	
Ward (2022)[56c]	Low	Low	Serious	Low	Low	Low	Serious
Mannes (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] Judgement scale: Low, moderate, serious, critical, unclear.

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Findings

The research questions of two 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) explored the effect of the Substance Abuse Treatment Program (SATP-MOUD) for US military veterans with chronic pain, current opioid analgesic use and OUD. SATP-MOUD primarily included opioid agonist or antagonist medications for OUD (such as oral methadone, sublingual buprenorphine/naloxone, and injectable naltrexone), along with counseling and monitoring of substance use and psychosocial treatments. The study employed propensity score matching methods to compare the risk of fatal and non-fatal opioid-related toxicity for veterans in SATP-MOUD and not in SATP-MOUD with chronic pain and concurrent opioid analgesic use. 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 evidence synthesis team used the matched data to calculate the relative and absolute effect, along with their corresponding CIs, of fatal opioid-related toxicity and non-fatal opioid-related toxicity in veterans who received 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 [ARR]: 60 fewer deaths [95% CI: 18 to 94

fewer deaths in 1000 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. Though the hazard ratio is statistically significant, it is uncertain whether OUD diagnosis versus no OUD diagnosis is associated with a higher risk of fatal opioid-related toxicity [HR: 1.40 (95% CI: 1.02 to 1.92)] (very low certainty evidence) (c Ward (2022): The risk of bias assessment for evidence derived from Cox regression analysis

Appendix 6: Summary of Findings for Safety of Using Opioid Analgesics in CNCP Patients with OUD,

Table).

Likewise, based on measures of association calculated by the evidence synthesis team using data presented by Ward (2022), it is uncertain whether prescribing OAT along with psychosocial treatments in patients with CNCP and OUD who are using opioid analgesics impacts the risk of non-fatal opioid-related toxicity events (RR: 1.61 [95% CI: 0.97, 2.68]; absolute risk increase [ARI]: 24 more non-fatal opioid-related toxicity events [95% CI: 1 fewer to 67 more non-fatal opioid-related toxicity events in 1000 patients]) over 12 months (very low certainty evidence, Figure 1, c Ward (2022): The risk of bias assessment for evidence derived from Cox regression analysis

Appendix 6: Summary of Findings for Safety of Using Opioid Analgesics in CNCP Patients with OUD,

Table). 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 (2022) collected data on the number of fatal and non-fatal opioid-related toxicities in untreated participants 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 suggested that prescribed opioids for 90 days or more may increase the hazard of fatal opioid-related toxicity compared to those prescribed opioids for less than 90 days by nearly two-fold (HR: 1.87 [95% CI: 1.56 to 2.24]). Additionally, 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]), in patients with chronic pain receiving opioid analgesics (very low certainty evidence). Conversely, non-white versus white race/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) explored the association between opioid discontinuation and tapering (as predictors) and risk of fatal and non-fatal opioid-related toxicity (as a single outcome) in CNCP patients 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 non-fatal 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 non-fatal 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 of these data, as they applied to the objectives of the current synthesis, was the absence of separate results for fatal and non-fatal 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 (

Appendix 3: Example for Calculating Relative Risk and Corresponding Confidence Interval). While the study employed 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 non-fatal opioid-related toxicity.

Based on the data from Kennedy 2022, it is uncertain whether either fatal opioid-related toxicity or non-fatal opioid-related toxicity were impacted in patients receiving LTOT for pain and with a history of OUD. There was a four-fold increase in fatal opioid-related toxicity if patients were prescribed OAT (RR: 3.9 (95% CI: 2 to 7.6); ARI: 79 more deaths [95% CI: 28 to 177 more deaths in 1000 patients]) compared to not being prescribed OAT, but this

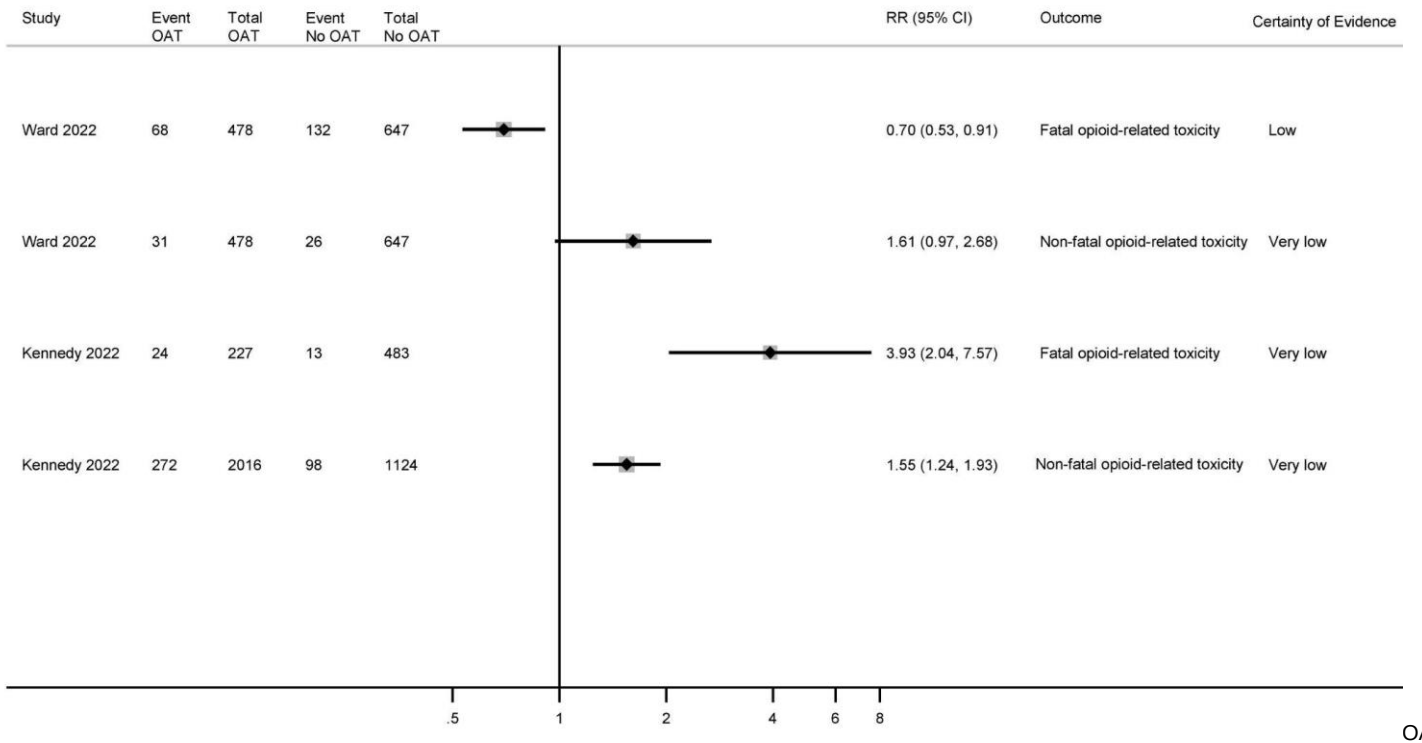
estimate was based on very low certainty evidence. Non-fatal opioid-related toxicity was 55% greater among those who received OAT compared to the group that did not receive OAT, but this estimate was based on very low certainty evidence (RR: 1.55 [95% CI: 1.24 to 1.93]; in terms of ARI, 48 more non-fatal opioid-related toxicity events were observed (95% CI: 21 to 81 more in 1000 patient-years observation over four years]) (Figure 1, c Ward (2022): The risk of bias assessment for evidence derived from Cox regression analysis

Appendix 6: Summary of Findings for Safety of Using Opioid Analgesics in CNCP Patients with OUD,

Table)**.** Stratified data, comparing outcomes between those with and without OUD and prescribed opioid analgesics but no OAT, have been requested from the authors but were not made available to the evidence synthesis team.

It was noted by the evidence synthesis team that the data in Kennedy et al. (2022) 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 fatal opioid-related toxicity and non-fatal opioid-related toxicity for patients with chronic pain and OUD on long-term opioid analgesic therapy



OAT = opioid agonist therapy; RR = relative risk; RR > 1 indicates increased risk of outcome

Mannes et al. (2023) utilized adjusted analysis to investigate the association between LTOT[a], OUD, and the COVID-19 pandemic on fatal and non-fatal 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, medical, and mental illness comorbidities, with fatal and non-fatal opioid-related toxicity as a combined outcome in patients with chronic pain.

[a] ≥ 3 consecutive months with ≥ 30 days of use of any prescription opioids, inclusive of forms of mOUD (i.e., buprenorphine and methadone).

The results of the adjusted analysis before the pandemic showed an association between LTOT and OUD with fatal and non-fatal opioid-related toxicity versus the reference standard of no LTOT and no OUD, indicated by an adjusted odds ratio (AOR) of 5.82 (95% CI: 3.58 to 9.44). Additionally, an association was found between only OUD versus the reference standard of no LTOT and no OUD and fatal and non-fatal opioid-related toxicity, with an AOR of 5.65 (95% CI: 4.73 to 6.75). For the primary concern of this review, the evidence synthesis team compared the likelihood of combined fatal and non-fatal 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 chronic pain patients with OUD impacted the likelihood of fatal and non-fatal opioid-related toxicity before the pandemic (ROR: 1.03 [95% CI: 0.61 to 1.73], very low certainty evidence) (Appendix 4: Ratio of Odds Ratios (ROR), c Ward (2022): The risk of bias assessment for evidence derived from Cox regression analysis

Appendix 6: Summary of Findings for Safety of Using Opioid Analgesics in CNCP Patients with OUD,

Table).

Similarly, during the pandemic, Mannes (2023) 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). For the primary concern of this review, the evidence synthesis team compared the likelihood of combined fatal and non-fatal 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 impacted the likelihood of fatal and non-fatal opioid-related toxicity during the pandemic (ROR: 0.72 [95% CI: 0.40 to 1.29], very low certainty evidence) (Appendix 4: Ratio of Odds Ratios (ROR), c Ward (2022): The risk of bias assessment for evidence derived from Cox regression analysis

Appendix 6: Summary of Findings for Safety of Using Opioid Analgesics in CNCP Patients with OUD,

Table).

In a study with a different focus, Glenn et al. (2016) investigated the pattern of opioid analgesic use in patients receiving methadone maintenance treatment (MMT) and prescribed opioid analgesics. 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 on MMT had chronic pain. We used the data from 182 patients on MMT and prescribed opioid analgesics, 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.

It is uncertain whether dose and frequency of opioid analgesic use is impacted for people with chronic pain on MMT who are also prescribed opioid analgesics. Among patients with chronic pain on MMT who were prescribed opioid analgesics, 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[b] (very low certainty evidence) (c Ward (2022): The risk of bias assessment for evidence derived from Cox regression analysis

[b] We used the raw numbers in Table 1 to calculate the percentages. As reported in Table 1, 48% 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.

Appendix 6: Summary of Findings for Safety of Using Opioid Analgesics in CNCP Patients with OUD,

Table). Weisner et al. (2009) 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 history of substance use disorders, including alcohol, opioids, and other drugs using data from two 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 utilized data from a subgroup of patients with OUD to compare the prevalence and incidence of prolonged opioid analgesic use in people with and without 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 (95% CI: 10 to 13.4) times higher in CNCP patients with a history of OUD compared to those with no history of OUD (absolute increase of individuals with long-term opioid use was 454 [95% CI: 386 to 532] more in 1000, very low certainty evidence). At KPNC, the relative incidence of long-term opioid use for people with a history of OUD versus those without OUD in 2005 was 7.4 (95% CI: 6.3 to 8.7) (absolute increase of new cases with long-term opioid use was 51 more [95% CI: 42 to 62 more], very low certainty evidence). At GH, incidence of long-term opioid use for the population with OUD in 1997 was reported 6.96% and the corresponding incidence for people without OUD was reported 8.8%[c] (c Ward (2022): The risk of bias assessment for evidence derived from Cox regression analysis

[c] Based on the crude numbers reported in the manuscript, the evidence synthesis team calculated the incidence of long-term opioid use in 1997 at GH for the population with OUD to be 8/122= 7.14% and the corresponding incidence for people without OUD as 1,703/193,103= 0.88%. The numbers reported above in the main text reflect what was reported in the manuscript.

Appendix 6: Summary of Findings for Safety of Using Opioid Analgesics in CNCP Patients with OUD,

Table).

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 five observational studies with safety outcomes, and while 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 employing statistical methods like multivariate analysis or matching, e.g., using propensity scores, researchers attempt 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 (2022) 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. Although Ward (2022) was assessed as having low risk of bias for the comparison of SATP-MOUD versus no SATP-MOUD, since 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 invalid measurement of OUD as a prognostic factor (

Appendix 5: Risk of Bias Assessment). Additionally, when assessing the association between the length of opioid use (≥ 90 days versus < 90) and the hazard of fatal opioid-related toxicity, a caveat should be raised. The duration of opioid use may exhibit collinearity with opioid dosage, potentially affecting the likelihood of opioid-related toxicity.

Mannes (2023) included LTOT only, OUD only, and the interaction between LTOT, OUD and pre-pandemic 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 non-fatal opioid-related toxicities were combined as outcomes. Given the differing incidence rates of fatal and non-fatal opioid toxicity, along with the possibility of multiple non-fatal 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 "long-term opioid therapy". 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 (2016) were affected by the use of subjective methods to measure the intervention, use of non-pharmaceutical drugs as co-intervention, and non-blinded 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 non-fatal opioid-related toxicity[54,56,58], we were not sure if the toxicity was caused by pharmaceutical or non-pharmaceutical sources, and this poses a major limitation on the interpretation of results. Additionally, possibly relevant data collected by two studies[56,58], but not reported in the published manuscripts, 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, four studies[54,56,59,60] were conducted in the United States, and one of these studies used data from the Veterans Health Administration of USA. 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. Given Canada's unique demographic composition and the potential disparities in OUD prevalence among different populations, including Indigenous People who live with higher rates of both chronic pain[62] and opioid-related harms[63], the absence of data on equity-deserving populations and Indigenous People in our review underscores a critical gap.

Considering the types of opioid analgesics, non-pharmaceutical drugs, and OAT practices, it is worth noting that two 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, analgesic approaches, non-pharmaceutical interventions, and OAT practices. Thus, caution is required in applying these data to the contemporary Canadian context.

Conclusions and Implications for Decision- or Policy-Making

This review gathers evidence from five 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. While we did not find studies with objectives directly aligned with our research question, we found data within them that can be utilized to begin to address the research and policy questions.

Low certainty evidence from one study[56] which matched OAT-treated and non-treated patients using propensity scores, showed that fatal opioid-related toxicity may be reduced amongst those treated with OAT. Conversely, uncertain evidence based on unpublished crude data supplied by the authors of another study[58] suggested a nearly fourfold *increase* in fatal opioid-related toxicity in patients with LTOT for pain with a history of OUD and on OAT. Furthermore, based on data from two studies,[56,58],given the very low certainty

of evidence, it is uncertain whether the risk of non-fatal opioid-related toxicity could be *increased* in the context of OAT for patients with chronic pain and OUD who use opioid analgesics. Likewise, it is uncertain whether a diagnosis of OUD impacts the hazard of fatal opioid-related toxicity in chronic pain patients who use opioids.[56]

Based on data from another study, it is uncertain whether LTOT in chronic pain patients with OUD impacts the likelihood of fatal and non-fatal opioid-related toxicity compared to those with OUD not on LTOT.[54] Additionally, while one study identified that over half of the patients with chronic pain undergoing MMT and prescribed opioid analgesics either increased their dosage or used them more frequently than prescribed, the evidence was of very low certainty. It is also uncertain whether having a history of OUD in the past two years could increase the prevalence and incidence of prolonged opioid use in patients with CNCP.[60]

The possibly conflicting results on fatal opioid-related toxicity reported by Ward (2022) (reporting a mortality reduction, low certainty evidence) and Kennedy (2022) (reporting a mortality increase, very low certainty evidence) might be driven by contextual factors. Ward et al. used data from the Veterans Health Administration, which was predominantly composed of male military veterans, while Kennedy et al. utilized data from a provincial health insurance client list in British Columbia, Canada, consisting mostly of civilians with a fairly balanced representation of both sexes. Furthermore, Ward et al. used matched data employing propensity scores and deemed to have low risk of bias, whereas Kennedy et al. did not use matched data and it was at high risk of bias. Additionally, all demographic characteristic variables were significantly different at baseline in Kennedy et al., and 80-89% 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.

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. While moderate to low certainty evidence suggests that non-pharmacological interventions may be beneficial for chronic pain management,[64] 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, let alone for specific populations living with CNPC and OUD such as Indigenous Peoples.

The dearth of evidence poses significant obstacles to informed decision-making across multiple levels of healthcare. At the policymaking level, it can hinder regulatory processes, complicating the evaluation of intervention risks and benefits for approval or reimbursement. Healthcare 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 healthcare 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.[65,66] Though 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.

Likewise, other kinds of evidence, besides 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.[67] 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 last 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.[68] Synthesizing studies

of patients may help to broaden our understanding of the impacts of different kinds of decisions and the experiences of equity-deserving communities and Indigenous Peoples, as well as provide more context-specific information relevant to Canada.[69,70]

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,[71,72] although this evidence is generally considered to be of very low quality and is therefore not considered during typical systematic reviews or health technology assessments. During screening for the effectiveness synthesis for this review, the only study to meet all PICO criteria besides study design was a case report, suggesting the possibility of less indirectness compared to the observational studies included in this report. Overall, as has been 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.

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Appendix 1: Selection of Included Studies

Figure 2: PRISMA flowchart No. 1

114 RCTs were identified by guideline data synthesis team for effectiveness outcomes, 114 were excluded due to wrong patient population.

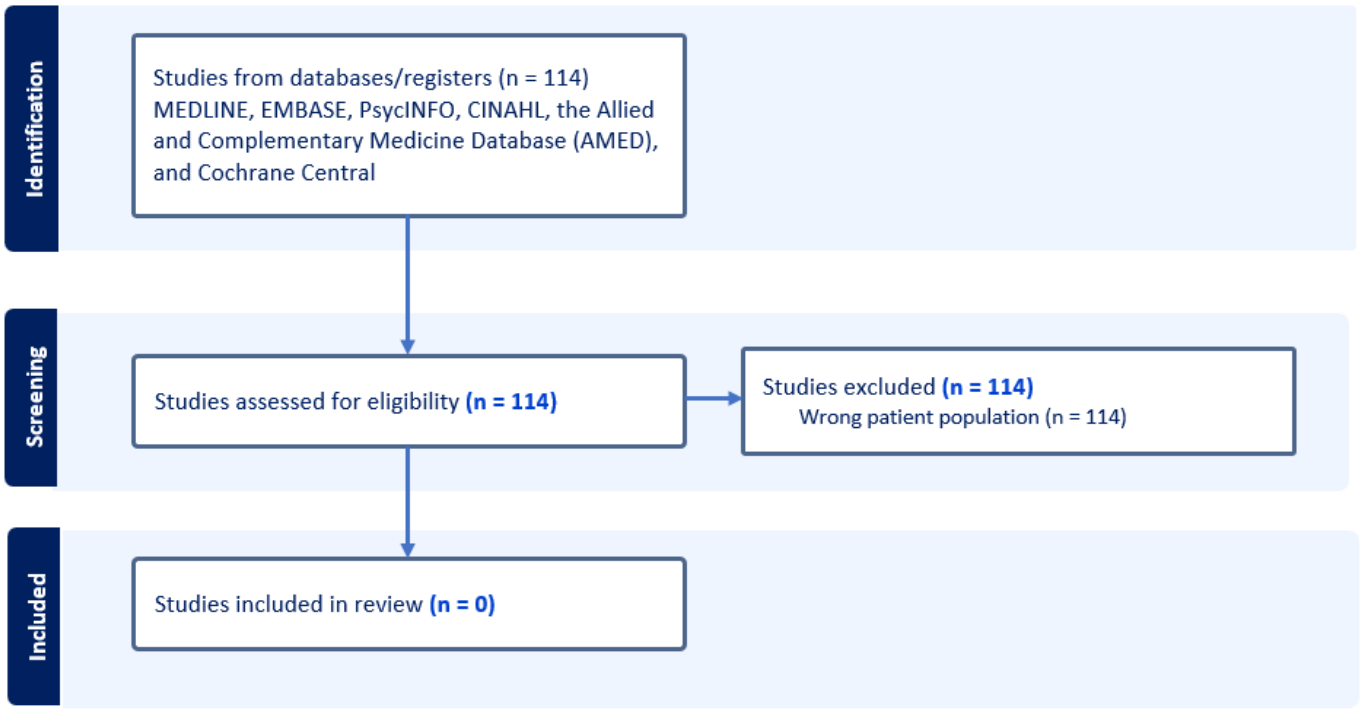


Figure 3: PRISMA flowchart No. 2

62 observational studies were identified by guideline data synthesis team for effectiveness and safety outcomes, 62 were excluded for different reasons

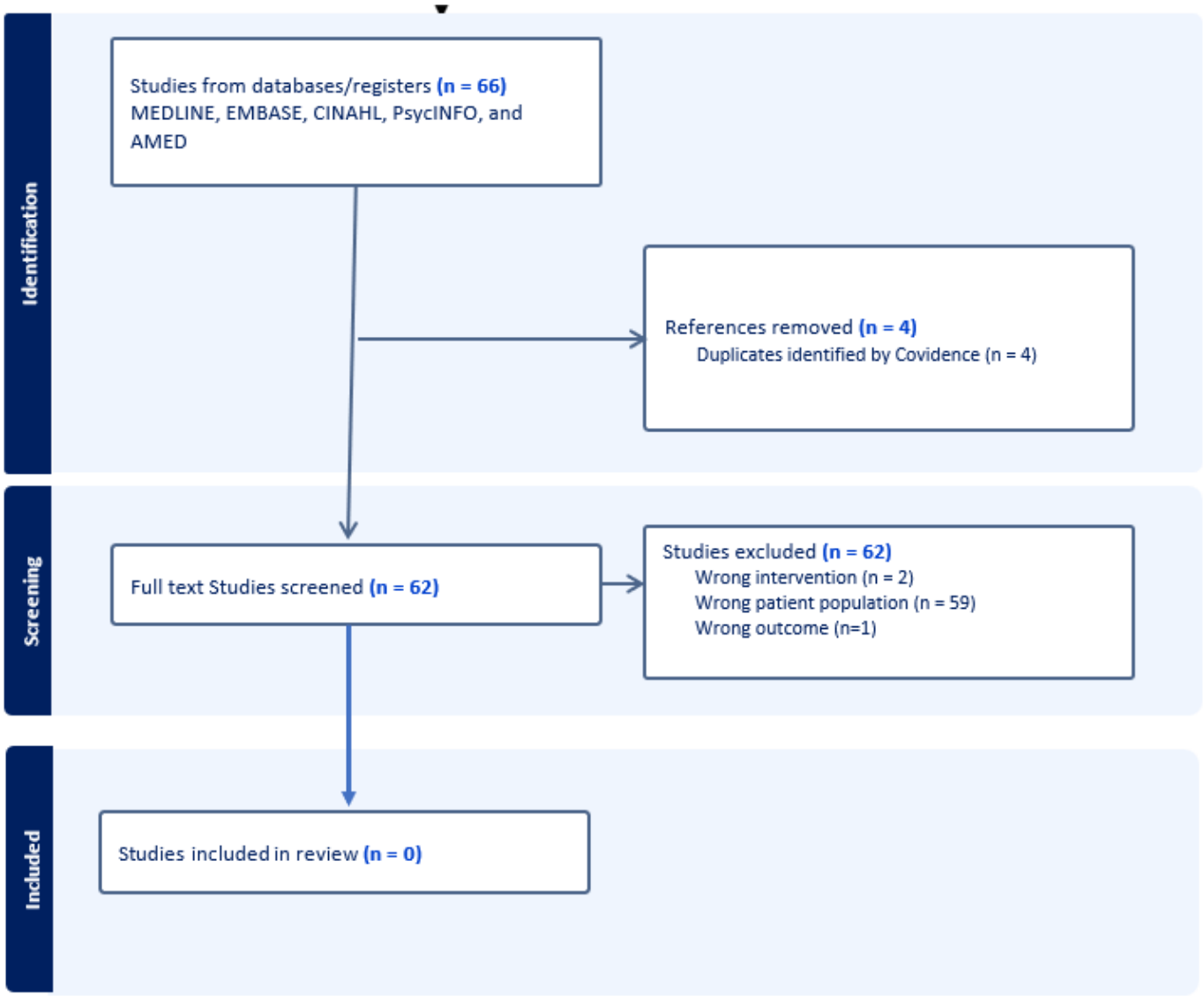


Figure 4: PRISMA flowchart No. 3

3504 citations were identified, 3455 were excluded, while 49 potentially relevant full-text reports were retrieved for scrutiny. In total 4 studies were included in the safety review.

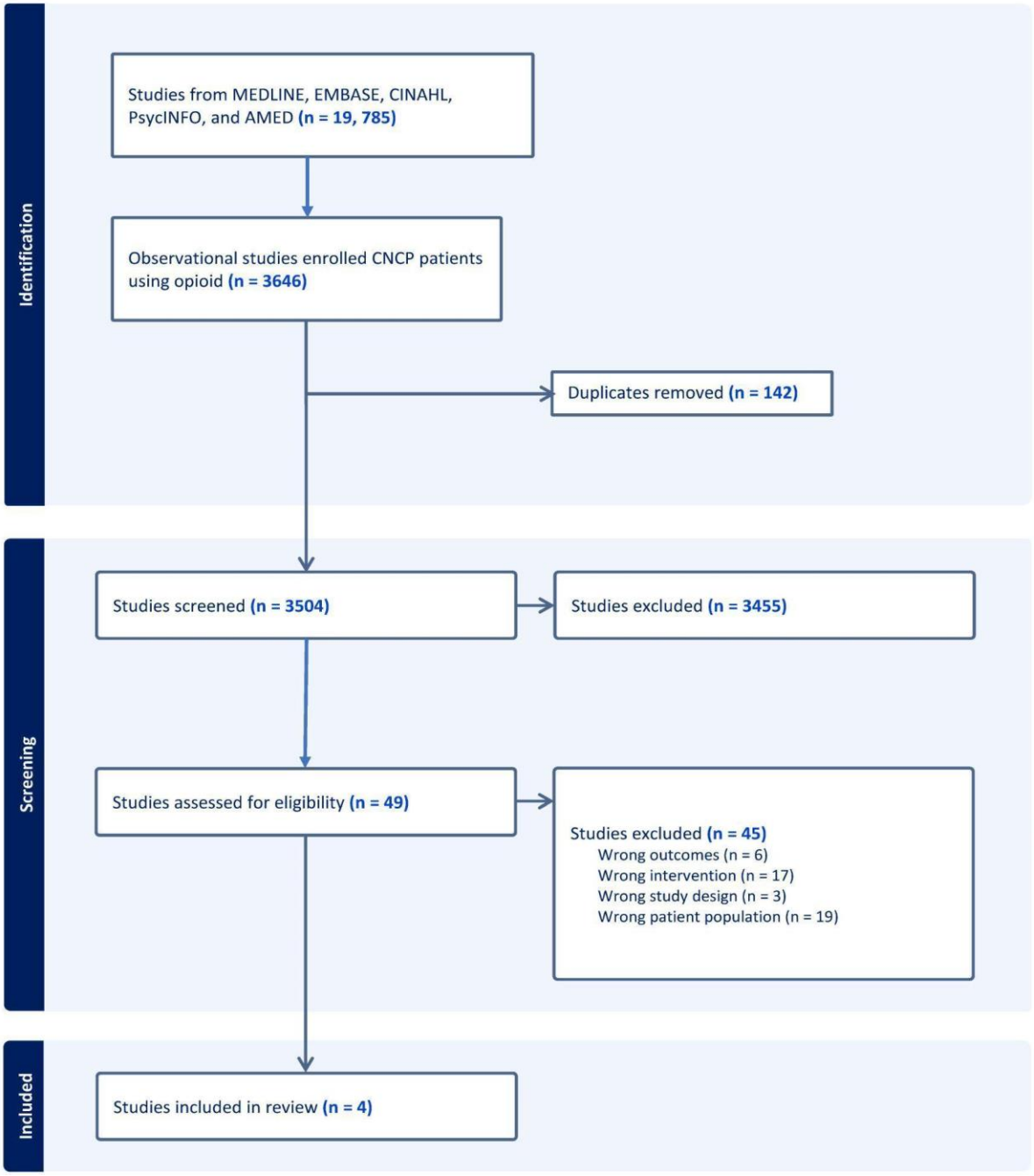
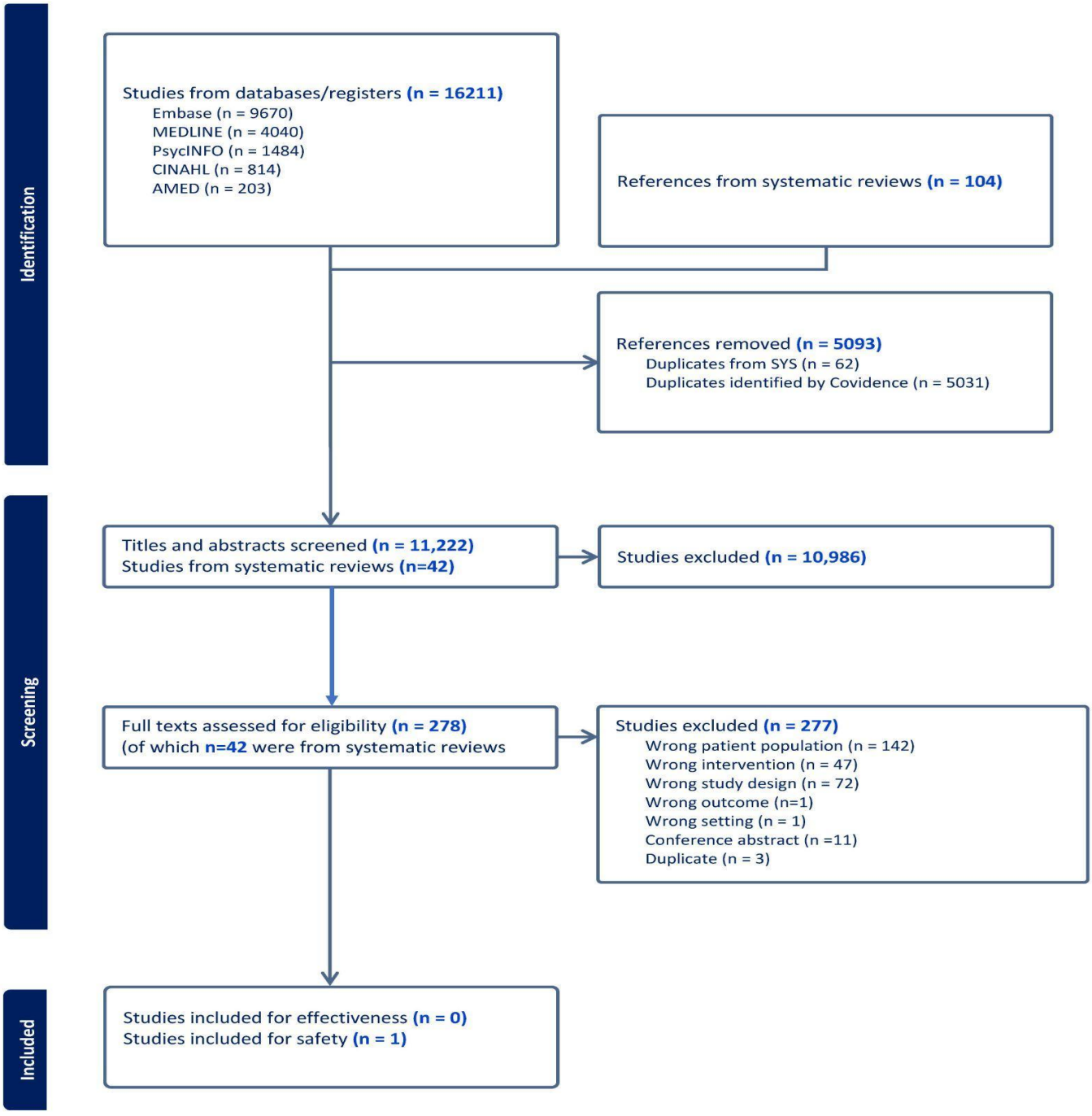


Figure 5: PRISMA flowchart No. 4

11,222 citations were identified, 10,986 were excluded, while 278 potentially relevant full-text reports were retrieved for scrutiny. In total no study was included for effectiveness and 1 study included for safety review.



Appendix 2: Search Strategy for Effectiveness

See Supplemental materials with all databases search strategies.

Appendix 3: Example for Calculating Relative Risk and Corresponding Confidence Interval

Fatal opioid-related toxicity from Kennedy 2022

	Event	Non Event	
Diagnosed OUD and prescribed OAT	a=24	b= 203	a+b=227
Diagnosed OUD but not prescribed OAT	c=13	d=470	c+d=483

RR = (A/A+B)/ (C/C+D) = (24/227)/(13/483) = **3.93**

SE = √ (1/a+1/c-1/b-1/d) = √ (1/24+1/13-1/203-1/470) = √0.112 = 0.335

95%CI = Exp (ln (RR)± Z×SE) = ln3.93 ± 1.96*0.335=1.37 ± 0.66 = Ln Upper CI = 2.02, Ln Lower CI = 0.71

Exp (2.02) = **7.57 = Upper CI**

Exp (0.71) = **2.04 = Lower CI**

RR = 3.93 (95%CI: 2.04 to 7.57)

Appendix 4: Ratio of Odds Ratios (ROR)

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))

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Comparing pre-pandemic adjusted odds ratios

LTOT and OUD, pre-pandemic 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** = (2.245-1.275)/3.92 = **0.247**

Only OUD, pre-pandemic 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** = (2.245-1.275)/3.92 = **0.091**

Ln (ROR) = Ln (OR1) – Ln (OR2) 1.761 – 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** = (1.872-0.77)/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** = (1.815-1.466)/3.92 = **0.089**

Ln (ROR) = Ln (OR1) – Ln (OR2) 1.308 –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 5: Risk of Bias Assessment

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

First author (year)	Risk of bias domain[a]							Overall risk of bias[b]
	Confounding	Participant selection	Classification	Deviation	Missing data	Measurement	Results selection	
Ward (2022)[56c]	Low	Low	Low	Low	Low	Low	Low	Low
Kennedy (2022)[58]	Serious	Low	Low	Low	Low	Low	Low	Serious
Glenn (2016)[59]	Serious	Low	Serious	Serious	Low	Serious	Low	Serious
Weisner (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] Judgement scale: Low, moderate, serious, critical, unclear.

[c] Ward (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]						Overall risk of bias[b]
	Participant selection	Missing data	Prognostic factor measurements	Outcome assessments	Optimal adjustment	Statistical analysis and reporting	
Ward (2022)[56c]	Low	Low	Serious	Low	Low	Low	Serious
Mannes (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] Judgement scale: Low, moderate, serious, critical, unclear.

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

Appendix 6: Summary of Findings for Safety of Using Opioid Analgesics in CNCP Patients with OUD

Table 5: Summary of Findings for Safety of Using Opioid Analgesics in CNCP Patients with OUD

GRADE evidence profile									
Sample size, Length of follow up	Quality assess-ment: Risk of bias	Quality assessment : Inconsistency	Quality assessment : Indirectness	Quality assessment : Imprecision	Quality assessment : Publication Bias	Quality assessment: Overall	Effect size	Anticipated absolute effect: Baseline Risk	Anticipated absolute effect: Risk Difference (95% CI)
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 non-fatal opioid-related toxicity									
Fatal opioid-related toxicity									
1,125 patients, Length of follow-up 12 mo	Low risk of bias[a]	NA	No Serious indirectness	No serious imprecision for death	NA	Low[b]	RR: 0.70 (95%CI: 0.53-0.91)	20%	60 (95% CI: 18-94) fewer deaths per 1000 participants
Non-fatal opioid-related toxicity									
1,125 patients, Length of follow-up 12 mo	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 non-fatal toxicity (95%CI: 1 fewer, 67 more)
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 non-fatal opioid-related toxicity									
Fatal opioid-related toxicity									
1,125 patients, Length of follow-up 12 mo	High risk of bias[c]	NA	No serious indirectness	No serious imprecision for death	NA	Very Low	HR: 1.40 (95%CI: 1.02-1.92)	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 non-fatal opioid-related toxicity									
Fatal opioid-related toxicity									

711 patients, Median follow-up median 44.4 mo (IQR: 2.6-4)	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 1000
Non-fatal opioid-related toxicity									
711 patients, Median follow-up median 44.4 mo (IQR: 2.6-4)	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 1000 person-year observation)	48 more (95%CI: 21 to 81 more in 1000 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 non-fatal opioid-related toxicity									
Predictor: LTOT and OUD vs OUD only, pre-pandemic									
236,391 patients, follow-up 12 mo	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 mo	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 mo	High risk of bias[i]	NA	No serious indirectness	NA	NA	Very Low[f]	NA	86 out of 182 (47.2%)	NA
Taking opioid analgesics more frequently than prescribed									
1,125 patients, Length of follow-up 12 mo	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	High risk of bias[i]	NA	No serious indirectness	NA	NA	Very Low[f]	NA	103 out of 182 (56.6%)	NA

follow-up 12 mo									
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 last 2 years C: Without history of OUD in last 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 mo	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 1000 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, follow-up 12 mo	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) in 1000 CNCP patients with OUD history

C = comparator; CNCP = chronic non-cancer pain; I = intervention; NA = Non-applicable; O = outcome; OAT = opioid agonist therapy; OUD = opioid use disorder; P = population; mOUD = buprenorphine and methadone; 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 1000 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

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