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Risk of infections among persons treated with opioids for chronic pain: A systematic review and meta-analysis protocol.

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ABSTRACT

Millions of persons with chronic pain across North American and European countries use opioids. Immunosuppressive properties of opioids and associated risks of infections result in avoidable morbidity and mortality.

Methods and Analysis. Methodology is based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement, the MOOSE Guidelines for Meta-Analyses and Systematic Reviews of Observational Studies, and the Cochrane Handbook for Systematic Review of Interventions. We plan to systematically search Ovid MEDLINE, CINAHL, PsycINFO, EMB Review, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, and Google Scholar databases from the inception date to December 2023. Primary studies full text (in English, French, Spanish, Hebrew, and German) reporting measurable outcomes in adults with chronic pain, all routes of opioid use, all types of infections and all settings will be included. We will identify a scope of reported infections, and the evidence on the association of opioid use (including specific opioid, dosage, formulation, and duration of use) with the risk of negative infectious outcomes. Opioid use-associated outcomes, comparing opioid use to another opioid or a non-opioid medication will be reported. Meta-analysis will incorporate individual risk factors. If data are insufficient, results will be synthesized narratively. Publication bias and confounding evaluation will be performed. The GRADE framework will be used.

Ethics and Dissemination. Approval for the use of published data is not required. Results will be published, presented at conferences, and discussed in deliberative dialogue groups.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- First-of-its-kind extensive comprehensive systematic review planned on the topic
- Inclusion of all types of opioids, doses, duration, and routes of administrations (except illicit self-injection)
- Multi-database and multi-lingual systematic search
- Limited to quantitative studies reporting measurable outcomes only

• We will not search for all specific infectious agents separately, which will probably result in missing some pertinent studies

INTRODUCTION

The COVID-19 pandemic brought to light synergistic public health crises of poorly managed chronic pain (CP) (1) and rising opioid prescribing rates (2, 3) culminating in increased prevalence of opioid use associated complications like acute overdoses or chronic hormonal and immune disturbances (4-6). CP, defined as pain lasting more than three months (7), is common worldwide, affecting 18% of the population across developing nations (8) to more than 20% of population in the U.S. and Canada (7). About 11% of young adults (9) and up to 85% of elderly patients (10) live with CP, including pain-related disability (11, 12) frequently associated with opioid use. Reportedly, the direct and indirect costs to society from pain and opioid crises pre-pandemic in Canada ranged anywhere from $38.3 to $40.4 billion annually (13).

The prevalence of opioid use in Canada is estimated more than 12% of the population (14), making Canada one of the leading opioid consumers in the world (988 mg morphine equivalent per 1000 inhabitants/day), with similar trends observed across the United States and European countries like Germany (15) and Netherlands (16). With age, the proportion of patients with CP using licit and illicit opioids increases (17), and so does the prevalence of opioid-related fatal and non-fatal adverse effects. In 2022 alone, the Canadian government reported ~20 opioid-related deaths and hundreds of hospitalizations daily (18). These statistics, however, do not include a much higher prevalence of opioid use associated long-term sequela.

Multimorbidity (19) and low socio-economic status (SES) are linked with CP (20) and opioid use, confounding the development of immunosuppression and poor health (21, 22) (Figure 1). CP disproportionately affects persons from marginalized (racialized, poor etc.) communities and the elderly (10, 23). As the World Health Organization pointed, "… health and illness follow a social gradient: the lower the socioeconomic position, the worse the health" (24). Furthermore, an overall link between multimorbidity, polypharmacy, neuro-immune disturbances and infections appears well established (25). Several common chronic disease states like metabolic syndrome,

inflammatory arthritis, major depression, various pain syndromes, prolonged stress, and post-traumatic stress disorder (26-28) are associated with long-term disturbances of the hypothalamic-pituitary-adrenal (HPA) axis, pro-inflammatory (e.g., cytokine-driven) systemic changes (26, 27), and various degrees of immunosuppression. Unsurprisingly, the risk of negative infectious outcomes in these persons is reportedly higher than in general population (29-33). Thus, the use of immunosuppressive analgesics like opioids becomes a careful balancing act against their potential capacity to further suppress HPA-immune axes.

Our knowledge of opioid-associated infections is not new (34-37). Among others, illicit injecting practices have been linked to an array of blood born infections like HIV, osteomyelitis, skin and epidural abscesses, and infective endocarditis (37-40). In the States (2002-2012), hospitalizations related to opioids and opioid-associated infections cost American Medicaid $15 billion and $700 million respectively (37). In Canadian Ontario (41), a significant increase in the rates of infective endocarditis (167%), spinal infections (394%), skin and soft tissue infections (147%) is also reported (2013-2019). The ten highest burden pathogens of interest (S. pneumoniae, Escherichia coli, Human Papillomavirus, Hepatitis B virus, HIV, HCV, Staphylococcus aureus, influenza virus, Clostridium difficile, rhinovirus) have accounted for >65% of health-adjusted life years lost due to premature morbidity and mortality (42). It is estimated that only antimicrobial-resistant (43) and hospital-acquired (44) infections cost Canadians additional $3.5 billion a year.

The importance of the confluent effect of the opioid-induced immunosuppression and the risk of infections is difficult to overestimate. There is an already good understanding (45, 46) of the effectiveness of the HIV and hepatitis C infections prevention strategies in persons who inject illicit opioids. In pain however, the CDC (11, 47), Canadian (48), and European (49, 50) pain and opioid prescribing guidelines although acknowledge the possibility of endocrine and immune disturbances, yet do not offer any guidance on balancing opioid use and risk of infections in these populations. No consensus has been reached regarding the risk of specific opioids and no corresponding prevention strategies have been identified.

Opioid use for CP presents a spectrum ranging from a sub-group of patients taking occasional small doses of opioids, to patients treated with regular medium-to-high-dose opioid therapy, and

all the way to another sub-group of patients who live with concomitant CP and opioid use disorder. It is estimated that >20% of patients with musculoskeletal CP overconsume or misuse opioids, and 15% live with opioid use disorder (51). Similarly, in a SR of 15 studies (52) looking at cancer-related CP, opioid misuse was reported being as high as 27.8%, and opioid use disorder ranged up to 20%. The data thus converge to demonstrate that although most patients with CP do not engage in risky behaviours, therapeutic and recreational uses might not always be easily separable. Many patients diagnosed with opioid misuse or use disorders, had their first exposure to an opioid in the context of CP diagnoses (53-55). More so, persistent opioid use could also develop post-acute trauma and surgery (56), leading to chronic opioid toxicity and its sequela.

Opioids belong to a diverse class of molecules, including natural ones like opium, morphine and codeine, their derivatives (e.g., heroin, hydromorphone, oxycodone) and synthetic ones (buprenorphine, tramadol, fentanyl etc.) They exert therapeutic and non-therapeutic effects via opioid receptors of the endogenous opioid system (4, 57), one of the most omnipresent neuro-transmitter systems in the mammalian organism closely involved in analgesia, stress and immune responses (4-6, 26, 58). It was shown that the mu-opioid receptors are found on immune cells like macrophages (59), T and B lymphocytes (60, 61), natural killer (62), and even glial cells (63) that provide support and protection for the neurons. Notably, opioid-induced glial changes are thought to be implicated in the development of opioid-induced hyperalgesia (abnormally increased pain) (64), a phenomenon that can drive prolonged opioid use and dose escalation. Aside from the dose and duration, immunosuppressive effects and risk of infections likely vary by specific opioid (6, 65).

Clinical immunosuppression in acute post-operative settings (e.g., abdominal surgeries) with the use of remifentanil anesthesia is associated with higher infection rates at the surgical sites when compared with fentanyl (66). Buprenorphine appears to be one of the safest options (67, 68), and long-acting opioid formulations are associated with a greater HPA axis suppression (69, 70) and a higher risk of infectious complications (71, 72) than short-acting opioids. Thus, some authors categorize opioids into “more immunosuppressive” (e.g., morphine, fentanyl, codeine, dihydrocodeine, methadone) and “less immunosuppressive” (oxycodone, tramadol,

buprenorphine, hydromorphone) (73-78), although this classification lacks systematic evidence support and is not widely accepted.

Preliminary data in CP. Despite variations in methodological approaches (79), the trends across primary studies have been pointing to the same direction. A non-systematic biophysiological review (22) laid much support to the hypothesis that opioids in general, and especially long-term opioid therapy (> 3 months), can alter parameters of the innate and adaptive immunity in patients with CP in a clinically meaningful way. A preliminary search (August 15, 2023) of the Medline Ovid and Google Scholar databases in English revealed a sample of primary and synthesis studies on the topic (1, 22, 80-86) (71, 72, 87-98), analyzing the association with serious infections (pneumonia, bacteremia, sepsis, meningitis/encephalitis, septic arthritis/osteomyelitis, endocarditis, pyelonephritis, and cellulitis), and corresponding rates of hospitalizations, ICU admissions, and mortality. Thus, given the scope and severity of the converging public health crises and sufficient literature published to date, there is a critical need for systematically synthesized knowledge on the risk of opioid therapy and associated infectious in persons with CP using opioids, outside of the illicit self-injecting practices. To our knowledge, this SR will be the first one on the topic. It will contribute to informing clinical practice guidelines, opioid prescribing policies, and clinical practices across Canada and internationally.

Registration.

The protocol was registered in PROSPERO on 18 March 2023 (CRD42023402812)

REVIEW QUESTIONS AND OBJECTIVES

Review questions

The overarching review question for this SR is: What is the evidence on the association of opioid use with increased risks for infections, re-infections, and negative infectious outcomes among persons with chronic pain using opioids (excluding illicit self-injecting practices)?

The secondary review question is: Does the association between the use of opioids and risks for infectious outcomes depend on the specific opioid, dosage, formulation, and duration of use?

Objectives

Primary objectives are to:

1. Identify the scope of *infections in opioid users (IPO)* as described in studies selected for this systematic review.
2. Synthesize the evidence on the difference in the infection acquisition risks between persons with CP who use opioids versus a comparator as available in the literature.
3. Synthesize the evidence on the difference in *IPO*-related outcomes (i.e., hospitalizations, duration of hospital stays, intensive care unit (ICU) admissions, mortality, etc.) between persons with CP who use opioids versus a comparator.

Secondary objectives (data permitting) are to:

1. Examine if the risk for negative *IPO*-related outcomes is associated with the opioid dose, opioid formulation (long- vs short-acting) and duration of use.
2. Identify opioids associated with a higher risk of infection acquisition and/or negative *IPO*-related outcomes.
3. Identify specific individual-level characteristics that may be associated with an increased risk of infection acquisition and/or negative *IPO*-related outcomes.

METHODS AND ANALYSIS

The SR methodology is based on the MOOSE Guidelines for Meta-Analyses and Systematic Reviews of Observational Studies (99), and the Cochrane Handbook for Systematic Review of Interventions (100). The results will be reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (101). This protocol was registered in PROSPERO, and important protocol amendments will be documented in PROSPERO.

Operational definitions

1) *CP* includes cancer pain, cancer treatment-induced pain, and non-cancer pain (7, 102).
2) *Opioids* are substances exerting their physiologic effects via opioid receptors. All opioids and their formulations will be included in this SR.
3) *IPO* include all (bacterial, viral, and fungal) infections described in studies selected for this SR.

4) All *routes of administration* (oral, transdermal, intravenous, intra-thecal, etc.) will be included. Due to the potential risk of shared needle/syringe contamination unrelated to immunosuppressive properties of studied medicines, we will *exclude* illicit self-injection of opioids.

5) *Opioid use* of various duration will be considered, including *acute/short term* (< 12 weeks) and *chronic* (≥ 12 weeks) opioid use.

6) *Type of opioid use* will be categorized as *episodic* (total days of opioid supply <90 in 3 months or documented non-daily use) or *continuous* (total days of opioid supply ≥ 90 in 3 months or documented daily use).

7) *Outcomes* include infection acquisition rates, infections-related hospitalizations, duration of hospital stays, ICU admissions, and mortality.

8) *Dose reporting*. Whenever possible, we will convert and report morphine equivalent daily doses (MEDD) (47, 48).

Eligibility criteria

Eligibility criteria will be defined based on the PECO approach. *Participants* are patients with CP who use opioids, and who do not self-inject illegal/recreational opioids. *Exposure* is all opioid use, except illegal self-injection of opioids. *Comparator* is a population from the same setting (ICU, for example) using another opioid or a non-opioid medication. *Outcome* is the scope of the *IPO* and measurable infection-related outcomes (see Outcome reporting) (103).

We will include all relevant primary studies reporting all routes of opioid use by adult humans, all infections (including COVID-19) during opioid use period, and all settings. We will include full texts (in English, French, Spanish, Hebrew and German) reporting measurable outcomes and various designs (randomized and non-randomized trials, observational studies, case series, and mixed methods studies (quantitative portion)). Studies focusing on pediatric populations, palliative/end-of-life care, self-injection of illegal/recreational opioids, qualitative designs, opinions, commentary, abstracts, conference proceedings will be excluded.

Search strategy

Databases. An experienced medical liaison McGill librarian will be involved. We plan to systematically search Ovid MEDLINE, CINAHL, PsycINFO, EMB Review, EMBASE, Cochrane

Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, and Google Scholar databases from the inception date to December 2023 using a combination of medical subject headings (MeSH) and keywords. *Grey literature:* (Pro Quest, Dissertation and Theses; published reports) will be searched. The *Keywords and MeSH terms* will be entered for the concepts: "opioids", "infections", and "pain" using Boolean operator AND for: (1) all commonly used opioids (generic, brand names, and synonyms); (2) infections (all viral, bacterial, and other infections); and (3) pain (cancer, non-cancer). The search strategy will be adopted to each database (see example in Table 1.) Backward and forward citation searches will be performed

Table 1 Example search strategy (Medline via Ovid)

	Description
1	(exp analgesics, opioid/ or exp opioid-related disorders/or (narcotic* or opiate* or opioid* or bezitramide or or anpec or ardinex or asimadolin* or astramorph or avinza or or acetylmethadol or alfentanil or anileridine or Belladonna or Benzomorphan* biodalgic or bpethidine or buprenorphine or carfentanil or codeine or codinovo or contramal or demerol or dicodid or dihydrocodeinone or dihydrohydroxycodeinone or dihydromorphinone or dihydrone or dilaudid or dinarkon or dolantin or dolargan or dolcontral or dolosal or dolsin or dur?gesic or dur?morph or epimorph or eucodal or exalgo or fentanest or fentanyl or fentora or fortral or heroin or hycodan or hycon or hydrocodeinonebitartrate or hydrocodone or hydrocodone* or hydromorphon or hydromorphone or hydroxyacetanilide or hydroxycodeinon or hysingla or isocodeine or isonipecain or jutadol or kadian or l dromoran or laudacon or levodroman or levodromoran or levo-dromoran or levorphan or levorphanol or lexir or lidol or lorcet or lortab or lydol or meperidine hydrochloride or methadone or morfin or morfine or morphia or morphin or morphine or morphinium or morphium or ms contin or n methylmorphine or narcotic or n-methylmorphine or nobligan or norco or numorphan or operidine or opiate or opioid* or opium or opso or oramorph sr or oripavine or oxecta or oxiconum or oxycodeinon or oxycodone or oxycone or oxycontin or oxymorphone or palladone or pancodine or pentazocine or percocet or pethidine or phentanyl or prontofort or propoxyphene or robidone or roxicet or roxicodone or skenan or sublimaze or suboxone or takadol or tapentadol or talwin or thebaine or theocodin or theradol or tiral or topalgic or tradol or tradolpuren or tradonal or tralgiol or trama or tramadin or tramadoc or tramadol or tramadolhameln or tramadolor or tramadorsch or tramadura or tramagetic or tramagit or tramake or tramal or tramex or tramundin or trasedal or ultram or vicodin or zamudol or zohydro or zumalgic or zydol or zytram).tw,sh,kw,kf,oa,nm
2	(Infections[Mesh] OR Infect*[tw] OR communicable disease*[tw] OR virus disease*[tw] OR viral disease* OR viral illness*[tw] OR viral infection*[tw] OR bacterial infection*[tw])
3	Pain[Mesh] OR Acute Pain[tw] OR Chronic Pain[tw] OR Cancer Pain[tw] OR Pain Management[tw])
4	#1 AND #2 AND #3
	Filters: in the last 10 years, Humans, English, French, German, Hebrew, Spanish Adult: 19+ years

Study selection

The Covidence systematic review software (104) will be used to perform screening, quality assessment and data extraction, and to document decisions on inclusion/exclusion. First, two independent reviewers will screen manuscripts by titles and abstracts. We will calculate kappa-statistic (inter-rater agreement) to ensure consistency of the selection process (105, 106). Before

screening, a stepwise calibration test will be performed on a sample of 30 studies, with the aim of achieving 80% agreement between reviewers. We will report changes to the inclusion and exclusion criteria that result from the calibration as deviations from the published protocol. All potentially relevant studies will be carried forward at each step. The remaining full texts will be reviewed for eligibility independently by two researchers. Disagreements will be resolved by consensus with a third reviewer.

Data extraction

To extract the data, we will adopt a modified Effective Practice and Organisation of Care (EPOC) Cochrane Data Collection forms (100, 107). The extracted data will be categorized into: 1) the patients' characteristics (sex at birth, gender, age, sociodemographic, psychosocial, and available medical characteristics (immunosuppression, number of co-morbidities); 2) opioid use status (continuous, episodic or no use, opioid formulation, opioid type and dose); 3) infection-related factors, such as infection diagnosis (e.g., pneumonia), infection type (bacterial, viral, fungal) and, if available, specific infectious agent (e.g., *Clostridium*); 4) clinical settings (e.g., community, hospital, intensive care unit); and 5) clinical disciplines (e.g., orthopedic surgery) and 6) measurable outcomes (e.g., duration of hospital stays; intensive care unit admissions) and severity (requiring intubation, mechanical ventilation, sepsis, septic shock, mortality). One researcher will extract the data and another researcher will check the extracted data for errors and plausibility.

Outcome reporting

For *primary objective 1*, all infections reported in quantitative studies will be documented, and relevant details on the population, settings, and opioid use will be described. For *primary objective 2*, we will synthesize the evidence on the differences of infection acquisition risks between persons who use opioids versus a comparator. For *primary objective 3*, we will synthesize the evidence on the differences in *IPO*-related measurable outcomes (e.g., duration of hospital stays) and severity (e.g., septic shock) between persons who use opioids versus comparator. For primary objectives 2 and 3, meta-analysis of the extracted effect measures will be performed; pooled effect measures will be reported (if feasible).

For *secondary objective* 1, if data allow, we will synthesize the evidence on the relationships between the opioid dose, duration of use, opioid formulation (long- vs short-acting) and reported

IPO outcomes. For *secondary objective 2*, if data allow, we will identify specific opioids that are associated with a higher risk of infection acquisition and poor outcomes. If data allow, for *secondary objective 3*, we will identify individual risk factors (e.g., age, gender, ethnicity, comorbidities) that are associated with a higher risk of infection acquisition and poor outcomes. Tabulated data and qualitative descriptions will be provided for secondary objectives 1, 2 and 3.

Risk of bias in individual studies

We will review included articles and assess the risk of bias for each outcome of interest. Disagreements will be discussed until a consensus is reached. In case of unresolved disagreement, a third reviewer will be invited to appraise the study. We will employ a validated EPHPP (Canadian *Effective Public Healthcare Panacea Project*) Quality Assessment Tool (108) based on eight categories universally applicable to quantitative studies that has a good inter- and intra-rater reliability (109, 110). The EPHPP tool is widely cited and was chosen for its excellent properties in evaluating studies in the pain field (110). We will record the study's funding sources and authors' conflicts of interest statements.

Data synthesis

The PRISMA flowchart (111, 112) will be used to describe the study selection process. We will tabulate the data on included studies and their populations, the identified risk factors, and the outcome characteristics, using frequency counts. All measurable outcomes extracted from the included studies will be used in data synthesis. If two or more studies for a specific measurable outcome are available, we will perform meta-analysis using the Review Manager (RevMan) software (113). Standardized mean difference with 95% CI for continuous outcomes, and odds ratios, relative risk ratios or hazard ratios with 95% CI for dichotomous outcomes will be used in meta-analysis. Whenever possible, we will transform other effect estimates into these effect measures. Higgins' I^2 statistics (100, 114) (i.e., the percentage of variability in the effect size estimates due to heterogeneity) will be calculated. Based on our pilot search, we anticipate some data heterogeneity, which will require the use of a random-effect model to calculate the pooled effect sizes. If sufficient data on the adjusted effect measures are available, we will calculate both pooled adjusted and crude effect sizes (see sensitivity analysis). If the information on the specific opioids-related (opioid dose, opioid formulation, treatment duration) and individual-level

characteristics are available, we will conduct subgroup analysis and will report group-specific effect estimates. The results of meta-analysis will be presented as forest plots. If data are insufficient to conduct meta-analysis for one of the objectives, we will use a narrative approach to data synthesis.

SGBA+ analysis

Integrating sex and gender is of crucial importance to our study as both variables exhibit multi-directional effects and can be confounders or effect modifiers (see Figure 1). We will apply a broad theoretical and empirical framework to understand the development of *IPO*s and underlying mechanisms, integrating up-to-date sex and gender, pain, and addiction literature. Thus, rather than focusing on the artificially binary categories such as man/woman (for gender) or male/female (for sex), we will take the real-life complexity of these characteristics into consideration. The following categories will be reflected in our data extraction sheet: sex assigned at birth (Female, Male, Intersex) and gender identity (Woman, Man, Transgender, Gender fluid or Gender nonbinary, Two-Spirit (Indigenous), and Other). The authors of primary studies will be contacted to obtain missing data on non-binary sex and gender categories, and their responses will be thoroughly documented. We will stratify our analysis by sex /gender categories and will report sex or gender-specific effect measures separately. We will ensure inclusion of sex and gender-specific effect measure estimates in the discussion, as well as the issue of missing non-binary data.

Publication bias, confounding, sensitivity analysis and quality of cumulative evidence

Publication bias will be assessed examining funnel plots for each outcome, for which more than 10 studies were included in the meta-analysis (100).

Confounding. Sex/gender, history of opioid use, the use of other immunosuppressive medications etc. may have confounding of effect modifying effects in the association between opioid use and risk for infectious outcomes (see Fig. 1). As our pilot search showed, most studies are of observational design, and thus may be prone to the confounding by indication bias. For example, it may seem that patients prescribed opioids are likely to have a more severe disease than persons not prescribed opioids, and the more severe disease may be an independent risk for infections. Indeed, this scenario is possible, but not unique. a disease severity is not always reflective of the

analgesia requirements. For example, when compared to controls, patients who sustained small burns and those with the largest burn surfaces, were respectively 1.73 (95% CI, 1.20 –2.49) and 1.02 (95% CI, 0.71–1.46) times more likely (98) receive opioids. From our clinical experience and the literature, the decision to prescribe opioids is multi-fold. Thus, most public insurances in Canada cover opioid therapy and frequently do not cover non-pharmacological treatments for CP. This makes opioids an ultimate choice for the poor, not working (e.g., students, elderly) and marginalised populations in Canada. Furthermore, the initial doses in opioid-naïve patients will be lower than among patients taking opioids chronically. Moreover, there is an increasing emphasis in anesthesia protocols to reduce reliance on opioid analgesics (115, 116). In addition, CP literature identifies depression (117, 118), anxiety, and catastrophizing (119) as drivers of opioid dose escalation and chronicity of use. A history of sexual abuse in men, patients' family and personal history of other substance misuse/use disorders are the known risk factors (120) for the problematic opioid use in the future. The attempts to account for the complexity and known confounders, effect modifiers, and important covariates will be made in the analysis. In case these data will be missing from the primary studies, the authors will be contacted. If sufficient data on the important covariates are identified, a subgroup analysis will be conducted, and the subgroup-specific effect estimates will be reported. Epidemiologic biases that can lead to over-/under-estimations of effect sizes or spurious associations will be discussed as study limitations.

Sensitivity analysis. To assess the robustness of our results on each outcome of interest, we will perform sensitivity analyses. First, the pooled effect size estimation will be repeated by including only studies with a low risk of bias, and the results will be compared with the main analysis. Second, we will compare the pooled effect estimates from RCTs and the observational studies. Then, we will evaluate the possible effect of covariates included in the calculation of adjusted effect sizes in original studies on the pooled effect size. For this, we will estimate the pooled crude effect size for each outcome of interest using crude (non-adjusted) effect sizes for separate studies, if available. The effect estimates will be compared with the adjusted effect estimates obtained in the main analysis.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) (121) framework will be used for the assessment of the quality of cumulative evidence for each outcome of interest. A certainty rating (very low, low, moderate, or high) will be assigned.

PATIENT AND PUBLIC INVOLVEMENT

This manuscript is a protocol for SR. As SR results are available, we will organize downstream deliberative dialogue groups with patients, care providers and decision makers to develop the most optimal ways for knowledge uptake and implementation across clinical settings in Canada, the United States, Israel, Germany and other European countries.

ETHICS and DISSEMINATION

This review is based on already published literature thus, no ethics review was requested. Results will be published, presented at conferences, and discussed in deliberative dialogue groups.

Timeline for review

At the time of submission, we had already started database searches.

AUTHORS CONTRIBUTIONS

Irina Kudrina: Conceptualization, writing original draft, methodology, review and editing.
Gaberielle Pagé: methodology, review and editing.
Manon Choinière: methodology, review and editing.
Yoram Shir: review and editing.
Maayan BenSasoon: review and editing.
Bertrand Lebouché: review and editing.
Mark J. Eisenberg: review and editing.
Svetlana Puzhko: Conceptualization, methodology, review and editing.

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COMPETING INTERESTS STATEMENT

Authors of this manuscript declare no conflict of interest and no competing interests.

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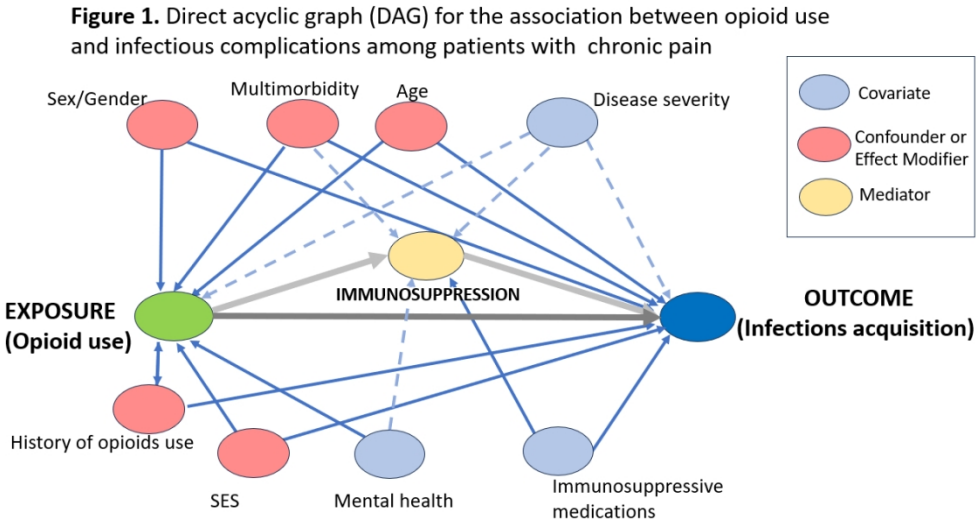

Figure 1. Direct acyclic graph (DAG) for the association between opioid use and infectious complications among patients with chronic pain

702x390mm (47 x 47 DPI)

Reporting checklist for protocol of a systematic review and meta analysis.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	N/A

Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	5
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	13
Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	6
Support			
Sources	#5a	Indicate sources of financial or other support for the review	13
Sponsor	#5b	Provide name for the review funder and / or sponsor	N/A
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	N/A
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is	2

		already known	
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	7
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	7
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	8
Study records - data collection	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any	9

process		processes for obtaining and confirming data from investigators	
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	9
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	10
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	10
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	11
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	12
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within	12

		studies)	
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	12

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Risk of infections among persons treated with opioids for chronic pain: A systematic review and meta-analysis protocol

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ABSTRACT

Introduction. Millions of persons with chronic pain across North America and Europe use opioids. While immunosuppressive properties of opioids are associated with risks of infections, these outcomes could be mitigated through careful patient selection and monitoring practices, when appropriate. It is important to recognize that some patients do benefit from a carefully tailored opioid therapy. Enough primary studies have been published to date regarding the opioids' role in potential immunosuppression presenting as an increased rate of infection acquisition, infectious complications and mortality. There is thus a critical need for a consensus in this area.

Methods and Analysis. Methodology is based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement, the MOOSE Guidelines for Meta-Analyses and Systematic Reviews of Observational Studies, and the Cochrane Handbook for Systematic Review of Interventions. We plan to systematically search Ovid MEDLINE, CINAHL, PsycINFO, EMB Review, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, and Google Scholar databases from the inception date to December 2023. Primary studies full text reporting measurable outcomes in adults with chronic pain, all routes of opioid use, all types of infections and all settings will be included. We will identify a scope of reported infections, and the evidence on the association of opioid use (including specific opioid, dosage, formulation, and duration of use) with the risk of negative infectious outcomes. Opioid use-associated outcomes, comparing opioid use to another opioid or a non-opioid medication will be reported. Meta-analysis will incorporate individual risk factors. If data are insufficient, results will be synthesized narratively. Publication bias and confounding evaluation will be performed. The GRADE framework will be used.

Ethics and Dissemination. Approval for the use of published data is not required**.** Results will be published, presented at conferences, and discussed in deliberative dialogue groups.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- First-of-its-kind extensive comprehensive systematic review planned on the topic
- Inclusion of all types of opioids, doses, routes of administrations (except illicit self-injection)
- Multi-database and multi-lingual systematic search
- Limited to quantitative studies reporting measurable outcomes only
- Not searching for specific infectious agents might result in some pertinent studies being missed

INTRODUCTION

The COVID-19 pandemic brought to light synergistic public health crises of poorly managed chronic pain (CP) (1) and rising opioid prescribing rates (2, 3) culminating in increased prevalence of opioid use associated complications like acute overdoses or chronic hormonal and immune disturbances (4-6). CP, defined as pain lasting more than three months (7), is common worldwide, affecting 18% of the population across developing nations (8) to more than 20% of population in the United States (U.S.) and Canada (9). About 11% of young adults (10) and up to 85% of elderly patients (11) live with CP, including pain-related disability (12, 13) frequently associated with opioid use. Reportedly, the direct and indirect costs to society from pain and opioid crises pre-pandemic in Canada ranged anywhere from $38.3 to $40.4 billion annually (14).

The prevalence of opioid use in Canada is estimated more than 12% of the population (15), making Canada one of the leading opioid consumers in the world (988 mg morphine equivalent per 1000 inhabitants/day), with similar trends observed across the U.S. and European countries like Germany (16) and Netherlands (17). With age, the proportion of patients with CP using licit and illicit opioids increases (18), and so does the prevalence of opioid-related fatal and non-fatal adverse effects. In 2022 alone, the Canadian government reported ~20 opioid-related deaths and hundreds of hospitalizations daily (19). These statistics, however, do not include a much higher prevalence of opioid use associated long-term sequela.

Multimorbidity (20) and low socio-economic status (SES) are linked with CP (21) and opioid use, confounding the development of immunosuppression and poor health (22, 23) (Figure 1). CP disproportionately affects persons from marginalized (racialized, poor etc.) communities and the elderly (11, 24). As the World Health Organization pointed, "… health and illness follow a social gradient: the lower the socioeconomic position, the worse the health" (25). Furthermore, an overall link between multimorbidity, polypharmacy, neuro-immune disturbances and infections appears well established (26). Several common chronic disease states like metabolic syndrome, inflammatory arthritis, major depression, various pain syndromes, prolonged stress, and post-traumatic stress disorder (27-29) are associated with long-term disturbances of the hypothalamic-pituitary-adrenal (HPA) axis, pro-inflammatory (e.g., cytokine-driven) systemic changes (27, 28), and various degrees of immunosuppression. Unsurprisingly, the risk of negative infectious

outcomes in these persons is reportedly higher than in general population (30-34). Thus, the use of immunosuppressive analgesics like opioids becomes a careful balancing act against their potential capacity to further suppress HPA-immune axes.

Our knowledge of *opioid-associated infections* is not new (35-38). It is important to distinguish between infections resulting from unsterile injection practices, such as those leading to bloodborne infections like HIV, osteomyelitis, skin and epidural abscesses, and infective endocarditis (38-41), and infections resulting from the immunosuppressive effects of opioids, which impact immune-related receptors in the human body and affect innate and adaptive immune system responses. The recent reviews (42, 43) of the pre-clinical and clinical evidence postulate that the most plausible mechanism of immunosuppression by opioids would involve mu-opioid receptors expressed by mammalian tissues. In addition, opioids affect intestinal microbiome, permeability and bacterial dissemination as well as the modulation of the central nervous system-HPA axis. Together, these lead to a plethora of closely intertwined effects involving suppression of immune cells proliferation, reduction in anti-bacterial activity, migration and antigen presentation by the innate immune system (macrophages, neutrophiles, dendritic, NK and mast cell activation) and several changes in adaptive immunity (T and B cells).

In the U.S. (2002-2012), hospitalizations related to opioids and opioid-associated infections cost American Medicaid $15 billion and $700 million respectively (38). In the province of Ontario (Canada), a significant increase in the rates of infective endocarditis (167%), spinal infections (394%), skin and soft tissue infections (147%) is also reported (2013-2019). The ten highest burden pathogens of interest (S. pneumoniae, Escherichia coli, Human Papillomavirus, Hepatitis B virus, HIV, HCV, Staphylococcus aureus, influenza virus, Clostridium difficile, rhinovirus) have accounted for >65% of health-adjusted life years lost due to premature morbidity and mortality (44). It is estimated that only antimicrobial-resistant (45) and hospital-acquired (46) infections cost Canadians additional $3.5 billion a year.

The importance of the confluent effect of the opioid-induced immunosuppression and the risk of infections is difficult to overestimate. There is an already good understanding (47, 48) of the effectiveness of the HIV and hepatitis C infections prevention strategies in persons who inject

illicit opioids. In the field of pain however, the CDC (12, 49), Canadian (50), and European (51, 52) opioid prescribing guidelines although acknowledge the possibility of endocrine and immune disturbances, yet do not offer any guidance on balancing opioid use and risk of infections in these populations. No consensus has been reached regarding the risk of specific opioids and no corresponding prevention strategies have been identified.

Opioid use for CP presents a spectrum ranging from a sub-group of patients taking occasional small doses of opioids to patients treated with regular medium-to-high-dose opioid therapy, and all the way to another sub-group of patients who live with concomitant CP and opioid use disorder. It is estimated that >20% of patients with musculoskeletal CP overconsume or misuse opioids, and about 15% live with opioid use disorder (53). Similarly, in a SR of 15 studies (54) looking at cancer-related CP, opioid misuse was reported being as high as 27.8%, and opioid use disorder ranged up to 20%. The data thus converge to demonstrate that although most patients with CP do not engage in risky behaviours, therapeutic and recreational uses might not always be easily separable. Many patients diagnosed with opioid misuse or use disorders, had their first exposure to an opioid in the context of CP diagnoses (55-57). More so, persistent opioid use could also develop post-acute trauma and surgery (58), leading to chronic opioid toxicity and its sequela.

Opioids belong to a diverse class of molecules, including natural ones like opium, morphine and codeine, their derivatives (e.g., heroin, hydromorphone, oxycodone) and synthetic ones (buprenorphine, tramadol, fentanyl etc.) They exert therapeutic and non-therapeutic effects via opioid receptors of the endogenous opioid system (4, 59), one of the most omnipresent neuro-transmitter systems in the mammalian organism closely involved in analgesia, stress and immune responses (4-6, 27, 60). It was shown that the mu-opioid receptors are found on immune cells like macrophages (61), T and B lymphocytes (62, 63), natural killer (64), and even glial cells (65) that provide support and protection for the neurons. Notably, opioid-induced glial changes are thought to be implicated in the development of opioid-induced hyperalgesia (abnormally increased pain) (66), a phenomenon that can drive prolonged opioid use and dose escalation. Aside from the dose and duration, immunosuppressive effects and risk of infections likely vary by specific opioid (6, 67).

Clinical immunosuppression in acute post-operative settings (e.g., abdominal surgeries) with the use of remifentanil anesthesia is associated with higher infection rates at the surgical sites when compared with fentanyl (68). Buprenorphine appears to be one of the safer options (69, 70), and long-acting opioid formulations are associated with a greater HPA axis suppression (71, 72) and a higher risk of infectious complications (73, 74) than short-acting opioids. Thus, some authors categorize opioids into "more immunosuppressive" (e.g., morphine, fentanyl, codeine, dihydrocodeine, methadone) and "less immunosuppressive" (oxycodone, tramadol, buprenorphine, hydromorphone) (75-80), although this classification lacks systematic evidence support and is not widely accepted.

Preliminary data in CP. Despite variations in methodological approaches (81), the trends across primary studies have been pointing to the same direction. A non-systematic biophysiological review (23) laid much support to the hypothesis that opioids in general, and especially long-term opioid therapy (> 3 months), can alter parameters of the innate and adaptive immunity in patients with CP in a clinically meaningful way. A preliminary search (August 15, 2023) of the Medline Ovid and Google Scholar databases in English revealed a sample of primary and synthesis studies on the topic (1, 23, 82-88) (73, 74, 89-100), analyzing the association with serious infections (pneumonia, bacteremia, sepsis, meningitis/encephalitis, septic arthritis/osteomyelitis, endocarditis, pyelonephritis, and cellulitis), and corresponding rates of hospitalizations, ICU admissions, and mortality. The current public health crisis is primarily related to illicit fentanyl and associated analogues, rather than prescription opioids. Moreover, as the prevalence of licit (prescribed and over-the-counter pharmaceutical) and illicit (not prescribed, pharmaceutical and non-pharmaceutical) opioid use remains a serious concern, and given that sufficient literature has been published to date on the topic, there is a critical need for systematically synthesized knowledge on the risk of opioid-use associated infections in persons with CP, outside of the illicit self-injecting practices. To our knowledge, this SR will be the first one on the topic. It will contribute to informing clinical practice guidelines, opioid prescribing policies, and clinical practices across Canada and internationally.

Registration. The protocol was registered in PROSPERO on 18 March 2023 (CRD42023402812)

REVIEW QUESTIONS AND OBJECTIVES

Review questions

The overarching review question for this SR is: What is the evidence on the association of opioid use with increased risks for infections, re-infections, and negative infectious outcomes among persons with chronic pain using opioids (excluding illicit self-injecting practices)?

The secondary review question is: Does the association between the use of opioids and risks for infectious outcomes depend on the specific opioid, dosage, formulation, and duration of use?

Objectives

Primary objectives are to:

1. Identify the scope of *infections in opioid users (IPO)* as described in studies selected for this systematic review.
2. Synthesize the evidence on the difference in the infection acquisition risks between persons with CP who use opioids versus a comparator as available in the literature.
3. Synthesize the evidence on the difference in *IPO*-related outcomes (i.e., hospitalizations, duration of hospital stays, intensive care unit (ICU) admissions, mortality, etc.) between persons with CP who use opioids versus a comparator.

Secondary objectives (data permitting) are to:

1. Examine if the risk for negative *IPO*-related outcomes is associated with the opioid dose, opioid formulation (long- vs short-acting) and duration of use.
2. Identify opioids associated with a higher risk of infection acquisition and/or negative *IPO*-related outcomes.
3. Identify specific individual-level characteristics that may be associated with an increased risk of infection acquisition and/or negative *IPO*-related outcomes.

METHODS AND ANALYSIS

The SR methodology is based on the MOOSE Guidelines for Meta-Analyses and Systematic Reviews of Observational Studies (101), and the Cochrane Handbook for Systematic Review of

Interventions (102). The results will be reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (103). This protocol was registered in PROSPERO and important protocol amendments will also be documented in PROSPERO.

Operational definitions

1) *Chronic pain* includes cancer pain, cancer treatment-induced pain, and non-cancer pain (7, 104).
2) *Opioids* are natural compounds, semi-synthetic or synthetic molecules exerting their main physiologic effects via opioid receptors (mu, delta, kappa). All opioids and their formulations mentioned in the identified primary studies will be included in this SR. For specific opioid names in the search strategy, please refer to Table 1.
3) *IPO* include all (bacterial, viral, and fungal) infections described in studies selected for this SR.
4) All *routes of administration* (oral, transdermal, intravenous, intra-thecal, etc.) will be included. Due to the potential risk of shared needle/syringe contamination unrelated to immunosuppressive properties of studied medicines, we will *exclude* illicit self-injections of opioids.
5) Various o*pioid use durations* will be considered: *acute* (1-7 days), *short-term* (8-30 days), *medium-term* (>30 -120 days) and *chronic* (> 120 days).
6) *Type of opioid use* will be categorized as *episodic* (non-daily, or one to six days a week) or *continuous* (daily or seven days a week).
7) *Outcomes* include infection acquisition rates, infections-related hospitalizations, duration of hospital stays, ICU admissions, and mortality.
8) *Dose reporting*. All reported doses will be recalculated in morphine equivalent daily dose (MEDD) based on the Utah university conversion table (12, 105), whenever data permit. For any studies reporting on opioids for which conversion values are not available, a narrative summary will be generated.

Eligibility criteria

Eligibility criteria will be defined based on the PECO approach. *Participants* are patients with CP who use opioids (with or without opioid dependence and/or opioid use disorder), and who do not self-inject illegal/recreational opioids. *Exposure* is all opioid use, except illegal self-injection of opioids and kratom plant. *Comparator* is a population from the same setting (ICU, for example)

using another opioid or a non-opioid medication. *Outcome* is the scope of the *IPO* and measurable infection-related outcomes (see Outcome reporting) (106).

We will include all relevant primary studies reporting all routes of opioid use by adult humans, all infections (including COVID-19) during opioid use period, and all settings. We will include full texts in any language (translated with Deepl https://www.deepl.com/en/app (107) or Google Translate) reporting measurable outcomes and various designs (randomized and non-randomized trials, observational studies, case series, and mixed methods studies (quantitative portion)). Studies focusing on pediatric populations, palliative/end-of-life care, self-injection of illegal/recreational opioids, qualitative designs, opinions, commentary, abstracts, conference proceedings will be excluded.

Search strategy

Databases. An experienced medical liaison McGill librarian will be involved. We plan to systematically search Ovid MEDLINE, CINAHL, PsycINFO, EMB Review, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, and Google Scholar databases from the inception date to December 2023 using a combination of medical subject headings (MeSH) and keywords. *Grey literature:* (Pro Quest, Dissertation and Theses; published reports) will be searched. The *Keywords and MeSH terms* will be entered for the concepts: "opioids", "infections", and "pain" using Boolean operator AND for: (1) all commonly used opioids (generic, brand names, and synonyms); (2) infections (all viral, bacterial, and other infections); and (3) pain (cancer, non-cancer). The search strategy will be adapted to each database (see example in Table 1.) Backward and forward citation searches will be performed

Table 1. PubMed search strategy example

1	(Opioid [Mesh] OR narcotic*[tw] OR analgetic*[tw] OR (actiq or adolonta or amadol or analgesic* or anpec or ardinex or asimadolin* or astramorph or avinza or biodalgic or pethidine or buprenorphine or carfentanil or codeine or codinovo or contramal or demerol or dicodid or dihydrocodeinone or dihydrohydroxycodeinone or dihydromorphinone or dihydrone or dilaudid or dinarkon or dolantin or dolargan or dolcontral or dolosal or dolsin or duragesic or duramorph or epimorph or eucodal or exalgo or fentanest or fentanyl or fentora or fortral or heroin or hycodan or hycon or hydrocodeinonebitartrate or

	hydrocodone or hydrocodone* or hydromorphon or hydromorphone or hydroxyacetanilide or hydroxycodeinon or hysingla or isocodeine or isonipecain or jutadol or kadian or dromoran or laudacon or levodroman or levodromoran or levo-dromoran or levorphan or levorphanol or lexir or lidol or lorcet or lortab or lydol or meperidine hydrochloride or methadone or morfin or morfine or morphia or morphin or morphine or morphinium or morphium or ms contin or n methylmorphine or narcotic or n-methylmorphine or nobligan or norco or numorphan or operidine or opiate or opioid* or opso or oramorph sr or oripavine or oxecta or oxiconum or oxycodeinon or oxycodone or oxycone or oxycontin or oxymorphone or palladone or pancodine or pentazocine or percocet or pethidine or phentanyl or prontofort or propoxyphene or robidone or roxicet or roxicodone or skenan or sublimaze or suboxone or takadol or tapentadol or talwin or thebaine or theocodin or theradol or tiral or topalgic or tradol or tradolpuren or tradonal or tralgiol or trama or tramadin or tramadoc or tramadol or tramadolhameln or tramadolor or tramadorsch or tramadura or tramagetic or tramagit or tramake or tramal or tramex or tramundin or trasedal or ultram or vicodin or zamudol or zohydro or zumalgic or zydol or zytram).tw,sh,kw,kf,oa,nm
2	(Infections[Mesh] OR Infect*[tw] OR communicable disease*[tw] OR virus disease*[tw] OR viral disease* OR viral illness*[tw] OR viral infection*[tw] OR bacterial infection*[tw])
3	Pain[Mesh] OR Acute Pain[tw] OR Chronic Pain[tw] OR Cancer Pain[tw] OR Pain Management[tw])
4	#1 AND #2 AND #3
	Filters: Adults > 18 year of age

Study selection

The Covidence systematic review software (108) will be used to perform screening, quality assessment and data extraction, and to document decisions on inclusion/exclusion. First, two independent reviewers will screen manuscripts by titles and abstracts. We will calculate kappa-statistic (inter-rater agreement) to ensure consistency of the selection process (109, 110). Before screening, a stepwise calibration test will be performed on a sample of 30 studies, with the aim of achieving 80% agreement between reviewers. We will report changes to the inclusion and exclusion criteria that result from the calibration as deviations from the published protocol. All potentially relevant studies will be carried forward at each step. The remaining full texts will be

reviewed for eligibility independently by two researchers. Disagreements will be resolved by consensus with a third reviewer.

Data extraction

To extract the data, we will adopt a modified Effective Practice and Organisation of Care (EPOC) Cochrane Data Collection forms (102, 111). The extracted data will be categorized into: 1) patients' characteristics (sex at birth, gender, age, sociodemographic, psychosocial, and available medical characteristics (immunosuppression, number of co-morbidities)); 2) opioid use status (continuous, episodic or no use, opioid formulation, opioid type, and dose); 3) infection-related factors, such as infection diagnosis (e.g., pneumonia), infection type (bacterial, viral, fungal) and, if available, specific infectious agent (e.g., *Clostridium*); 4) clinical settings (e.g., community, hospital, intensive care unit); and 5) clinical disciplines (e.g., orthopedic surgery), and 6) measurable outcomes (e.g., duration of hospital stays; intensive care unit admissions) and severity (requiring intubation, mechanical ventilation, sepsis, septic shock, mortality). One researcher will extract the data and another researcher will check the extracted data for errors and plausibility.

Outcome reporting

For *primary objective 1*, all infections reported in quantitative studies will be documented, and relevant details on the population, settings, and opioid use will be described. For *primary objective 2*, we will synthesize the evidence on the differences of infection acquisition risks between persons who use opioids versus a comparator. For *primary objective 3*, we will synthesize the evidence on the differences in *IPO*-related measurable outcomes (e.g., duration of hospital stays) and severity (e.g., septic shock) between persons who use opioids versus comparator. For *primary objectives 2 and 3*, meta-analysis of the extracted effect measures will be performed; pooled effect measures will be reported (if feasible).

For *secondary objective* 1, if data allow, we will synthesize the evidence on the relationships between the opioid dose, duration of use, opioid formulation (long- vs short-acting) and reported *IPO* outcomes. "Opioid-naïve" period prior to exposure, when reported by the primary studies, will be recorded. For *secondary objective 2*, if data allow, we will identify specific opioids that are associated with a higher risk of infection acquisition and poor outcomes. If data allow, for *secondary objective 3*, we will identify individual risk factors (e.g., age, gender, ethnicity,

comorbidities) that are associated with a higher risk of infection acquisition and poor outcomes. Tabulated data and qualitative descriptions will be provided for *secondary objectives 1, 2 and 3*. Studies on chronic malignant pain as well as non-malignant pain will be reported separately as well as pooled.

Risk of bias in individual studies

We will review included articles and assess the risk of bias for each outcome of interest. Disagreements will be discussed until a consensus is reached. In case of unresolved disagreement, a third reviewer will be invited to appraise the study. We will employ a validated EPHPP (Canadian *Effective Public Healthcare Panacea Project*) Quality Assessment Tool (112) based on eight categories universally applicable to quantitative studies that has a good inter- and intra-rater reliability (113, 114). The EPHPP tool is widely cited and was chosen for its excellent properties in evaluating studies in the pain field (114). We will record the study's funding sources and authors' conflicts of interest statements.

Data synthesis

The PRISMA flowchart (115, 116) will be used to describe the study selection process. We will tabulate the data on included studies and their populations, the identified risk factors, and the outcome characteristics, using frequency counts. All measurable outcomes extracted from the included studies will be used in data synthesis. If two or more studies for a specific measurable outcome are available, we will perform meta-analysis using the Review Manager (RevMan) software (117). Standardized mean difference with 95% CI for continuous outcomes, and odds ratios, relative risk ratios or hazard ratios with 95% CI for dichotomous outcomes will be used in meta-analysis. Whenever possible, we will transform other effect estimates into these effect measures. Higgins' I^2 statistics (102, 118) (i.e., the percentage of variability in the effect size estimates due to heterogeneity) will be calculated. The I2 statistic is a relative measure of heterogeneity and will be assessed in conjunction with prediction intervals. According to Cochrane recommendations, an I^2 statistic of 30-60% and 50-90% may respectively represent moderate and substantial heterogeneity. Heterogeneity above 75% would be defined as considerable (119). Prediction intervals, which are easier to interpret and relate to clinical implications, estimate a prespecified (95% CI) range of treatment effects expected in future settings (120, 121). If the range

of treatment effects shown by prediction intervals includes both positive and negative clinically relevant effects, the meta-analysis results will be considered inconclusive. Based on our pilot search, we anticipate some data heterogeneity, which will require the use of a random-effect model to calculate the pooled effect sizes. If sufficient data on the adjusted effect measures are available, we will calculate both pooled adjusted and crude effect sizes (see sensitivity analysis). If the information on the specific opioids-related (opioid dose, opioid formulation, treatment duration) and individual-level characteristics are available, we will conduct subgroup analysis and will report group-specific effect estimates. The results of meta-analysis will be presented as forest plots. If data are insufficient to conduct meta-analysis for one of the objectives, we will use a narrative approach to data synthesis.

Sex and gender-based analysis

Integrating sex and gender is of crucial importance to our study as both variables exhibit multi-directional effects and can be confounders or effect modifiers (see Figure 1). We will apply a broad theoretical and empirical framework to understand the development of *IPO*s and underlying mechanisms, integrating up-to-date sex and gender, pain, and addiction literature. Thus, rather than focusing on the artificially binary categories such as male/female (for sex) or man/woman (for gender), we will take the real-life complexity of these characteristics into consideration. Variables from the studies that mention "sex", "biological sex", "sex assigned at birth", "male and female" and similar binary terminology, will be treated in the category of *sex*. The rest of the studies that mention gender-related terminology such as "man and woman", "transgender", "gender fluid", "gender nonbinary", two-spirit (Indigenous) etc. will be assigned to the *gender* variable. The authors of primary studies will be contacted to obtain clarifications, missing data on non-binary sex and gender categories, and their responses will be thoroughly documented. We will stratify our analysis by sex /gender categories and will report sex or gender-specific effect measures separately. We will ensure inclusion of sex and gender-specific effect measure estimates in the discussion, as well as the issue of missing non-binary data.

Publication bias, confounding, sensitivity analysis and quality of cumulative evidence

Publication bias will be assessed examining funnel plots for each outcome, for which more than 10 studies will be included in the meta-analysis (102).

Confounding. Sex/gender, history of opioid use, the use of other immunosuppressive medications etc. may have confounding or effect modifying effects in the association between opioid use and risk for infectious outcomes (see Figure 1). As our pilot search showed, most studies use an observational design, and thus may be prone to the confounding by indication bias. For example, it may seem that patients prescribed opioids are likely to have a more severe disease than persons not prescribed opioids, and the more severe disease may be an independent risk for infections. Indeed, this scenario is possible, but not unique. Disease severity is not always reflective of the analgesia requirements. For example, when compared to controls, patients who sustained small burns and those with the largest burn surfaces, were respectively 1.73 (95% CI, 1.20 –2.49) and 1.02 (95% CI, 0.71–1.46) times more likely (100) receive opioids. From our clinical experience and the literature, the decision to prescribe opioids is multi-fold. Thus, most public insurances in Canada cover opioid therapy and frequently do not cover non-pharmacological treatments for CP. This makes opioids an ultimate choice for the poor, not working (e.g., students, elderly) and marginalised populations in Canada. Furthermore, the initial doses in opioid-naïve patients will be lower than among patients taking opioids chronically. Moreover, there is an increasing emphasis in anesthesia protocols to reduce reliance on opioid analgesics (122, 123). In addition, CP literature identifies depression (124, 125), anxiety, and pain catastrophizing (126) as drivers of opioid dose escalation and chronicity of use. A history of sexual abuse in men and a family and personal history of other substance misuse/use disorders are known risk factors (127) for the problematic opioid use in the future. The attempts to account for the complexity and known confounders, effect modifiers, and important covariates will be made in the analysis. In case these data will be missing from the primary studies, the authors will be contacted. If sufficient data on the important covariates are identified, a subgroup analysis will be conducted, and the subgroup-specific effect estimates will be reported. Epidemiologic biases that can lead to over-/under-estimations of effect sizes or spurious associations will be discussed as study limitations.

Sensitivity analysis. To assess the robustness of our results on each outcome of interest, we will perform sensitivity analyses. First, the pooled effect size estimation will be repeated by including only studies with a low risk of bias, and the results will be compared with the main analysis. Second, we will compare the pooled effect estimates from randomized controlled trials and

observational studies. Then, we will evaluate the possible effect of covariates included in the calculation of adjusted effect sizes in original studies on the pooled effect size. For this, we will estimate the pooled crude effect size for each outcome of interest using crude (non-adjusted) effect sizes for separate studies, if available. The effect estimates will be compared with the adjusted effect estimates obtained in the main analysis.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) (128) framework will be used for the assessment of the quality of cumulative evidence for each outcome of interest. A certainty rating (very low, low, moderate, or high) will be assigned.

PATIENT AND PUBLIC INVOLVEMENT

Two patient representatives will be a part of the SR study team. We will report their contribution in the resulting SR manuscript. As SR results are available, we will organize downstream deliberative dialogue groups with patients, care providers and decision makers to develop the most optimal ways for knowledge uptake and implementation across clinical settings in Canada, U.S., Israel, Germany, and other European countries.

ETHICS AND DISSEMINATION

This review is based on already published literature thus, no ethics review is requested. Results will be published, presented at conferences, and discussed in deliberative dialogue groups.

Timeline for review

At the time of re-submission of our manuscript, we had already started database searches.

AUTHORS CONTRIBUTIONS

Irina Kudrina: Conceptualization, writing original draft, methodology, review and editing. This author is the guarantor of the study and accepts full responsibility for the finished work and/or the conduct of the study, has access to the data, and controls the decision to publish.

Gaberielle Pagé: methodology, review and editing.

Manon Choinière: methodology, review and editing.

Yoram Shir: review and editing.

Maayan BenSasoon: review and editing.

Bertrand Lebouché: review and editing.

Mark J. Eisenberg: review and editing.

Svetlana Puzhko: Conceptualization, methodology, review and editing.

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COMPETING INTERESTS STATEMENT

Authors of this manuscript declare no conflict of interest and no competing interests.

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Figure 1. Direct acyclic graph (DAG) for the association between opioid use and infectious complications among patients with chronic pain.

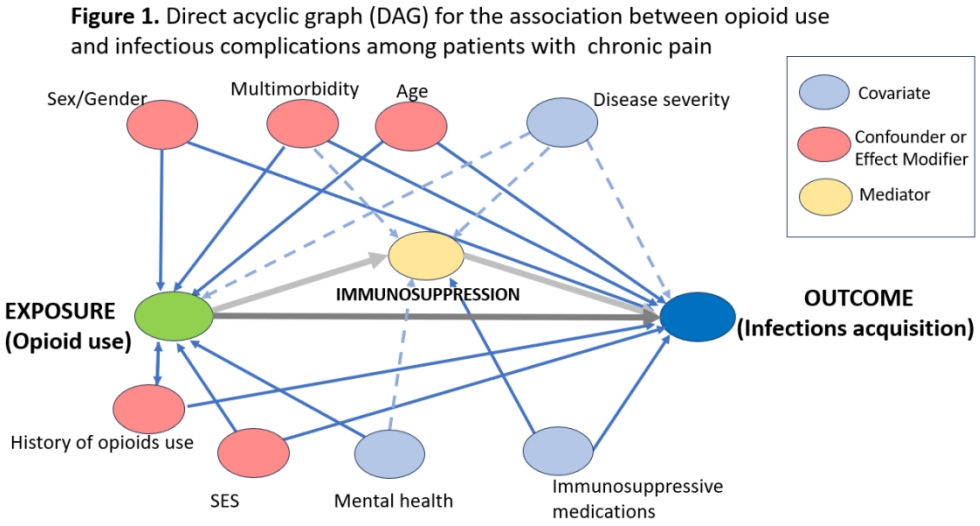

Figure 1. Direct acyclic graph (DAG) for the association between opioid use and infectious complications among patients with chronic pain

702x390mm (47 x 47 DPI)

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		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	N/A

Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	5
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	13
Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	6
Support			
Sources	#5a	Indicate sources of financial or other support for the review	13
Sponsor	#5b	Provide name for the review funder and / or sponsor	N/A
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	N/A
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is	2

		already known	
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	7
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	7
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	8
Study records - data collection	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any	9

process		processes for obtaining and confirming data from investigators	
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	9
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	10
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	10
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	11
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	12
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within	12

		studies)	
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	12