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Interventions for Physician Prescribers of Opioids for Chronic Non-Cancer Pain: Protocol for an Overview of Systematic Reviews

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ABSTRACT

Introduction: Interventions targeting behaviors of physician prescribers of opioids for chronic non-cancer pain have been introduced to combat the opioid crisis. Systematic reviews have evaluated effects of specific interventions (e.g., prescriber education, prescription drug monitoring programs) on prescriber behavior and patient and population health outcomes. Integration of findings across intervention types is needed to better understand the effects of prescriber-targeted interventions.

Methods and analysis: We will conduct an overview of systematic reviews. Eligible systematic reviews will include primary studies that evaluated any intervention targeting the behaviors of physician prescribers of opioids for chronic non-cancer pain in an outpatient or mixed setting, compared to no intervention, usual practice, or another active or control intervention. Eligible outcomes will pertain to the intervention effect on opioid prescribing behavior or patient and population health. We will search MEDLINE, Embase, and PsycInfo via Ovid; the Cochrane Database of Systematic Reviews; and Epistemonikos from inception. We will also hand-search reference lists for additional publications. Screening and data extraction will be conducted independently by two reviewers, with disagreements resolved by consensus or consultation with a third reviewer. The risk of bias of included systematic reviews will be assessed in duplicate by two reviewers using the Risk of Bias in Systematic Reviews tool. Results will be synthesized narratively by intervention type and grouped by outcome. To assist with result interpretation, outcomes will be labelled as intended or unintended according to intervention objectives, and as positive, negative, evidence of no effect, or inconclusive evidence according to intervention objectives (for prescriber outcomes) or effect on the population (for patient and population health outcomes).

Ethics and dissemination: As the proposed study will use published data, ethics approval is not required. Dissemination of results will be achieved through publication of a manuscript in a peer-reviewed journal and conference presentations.

Registration: PROSPERO (CRD42020156815).

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ARTICLE SUMMARY

Strengths and limitations of this study

- This study will provide a comprehensive overview of the effects of interventions targeting physician prescribers of opioids for chronic non-cancer pain on both prescriber behavior and patient and population health outcomes.
- Our expected results will inform physicians and policy makers of the benefits and potential harms of interventions targeting physician prescribers of opioids for chronic non-cancer pain and, by extension, their potential role in combatting the opioid crisis.
- Limitations of this study relate to those of the overview of systematic reviews methodology; namely, restriction of the interventions and outcomes synthesized to those captured in available systematic reviews, and risk of systematic reviews' conclusions being affected by publication bias.

INTRODUCTION

To combat the ongoing opioid crisis in North America, countries and jurisdictions have introduced interventions targeting the behaviors of physician prescribers of opioids for chronic non-cancer pain (CNCP) (pain lasting over three months not associated with a cancer diagnosis (1)). A wide range of interventions fall under this category, including prescriber education, prescription drug monitoring programs (PDMPs), pain clinic legislation (e.g., laws requiring that physician pain clinic owners be board-certified in pain management), and clinical guidelines (2). As these interventions have the potential to alter the way in which opioids are prescribed, it is highly important to consider not only the effects of these interventions on prescriber behavior, but also on patient and population health. Numerous systematic reviews have evaluated the effects of interventions targeting physician opioid prescribers for CNCP on opioid prescriber behaviors and outcomes among patients with CNCP and the general population (3-6). These systematic reviews vary not only in their populations and outcomes of interest, but also in the specific interventions evaluated (e.g., PDMPs). While the variability in these reviews' areas of focus means a wealth of information is spread across them, it makes it difficult to consider their findings holistically. A systematic synthesis of this heterogeneous systematic review evidence has yet to be performed and would be of great value in better understanding the effect of prescriber-targeted interventions on both prescriber behavior and patient and population health. Therefore, we will perform an overview of systematic reviews of the effect of interventions targeting the behaviors of physician opioid prescribers for CNCP in adults on prescriber behavior and patient and population health.

OBJECTIVE

Our objective is to synthesize the systematic review evidence on the effect of interventions targeting the behaviors of physician opioid prescribers for CNCP in adults on prescriber behavior and patient and population health.

METHODS AND ANALYSIS

This overview of systematic reviews will be guided by Chapter V of the *Cochrane Handbook for Systematic Reviews of Interventions* (7), along with elements from additional guidance documents described in a recent review (8). The overview of systematic reviews methodology was chosen to examine evidence across systematic reviews of interventions targeting physician prescribers of opioids for chronic non-cancer pain, as these systematic reviews address different outcomes (7). Our overview will be reported according to the Preferred Reporting Items for Overviews of systematic reviews including harms (PRIO-harms) pilot checklist (9). It has been registered on PROSPERO (CRD42020156815). Important protocol amendments will be documented in PROSPERO.

Eligibility Criteria

Population

This overview will be restricted to systematic reviews of studies conducted in healthcare professionals who prescribe opioids, with a focus on physician opioid prescribers (Table 1). For the purposes of this overview, "physician opioid prescribers" will be defined as medical doctors who prescribe opioids. Eligible systematic reviews will include primary studies evaluating interventions targeted exclusively at physician opioid prescribers or targeted at multiple healthcare professional populations including physician opioid prescribers. Reviews of interventions targeted

at multiple healthcare professional populations must include studies in which these interventions are delivered specifically or in part to physician opioid prescribers. Reviews limited to studies of interventions delivered exclusively to non-physician healthcare professionals (e.g., dentists, nurse practitioners, physician assistants, pharmacists) will be ineligible, as will reviews limited to studies of interventions delivered exclusively or in part to patients (e.g., structured pain management programs). Reviews which include some studies in eligible populations and some studies in ineligible populations will be included provided they report at least one outcome specific to an eligible population.

Intervention

We will include systematic reviews of any type of intervention(s) aimed at impacting opioid prescribing behavior, with a focus on those aimed at impacting opioid prescribing behavior for adult CNCP in an outpatient setting. Examples of eligible interventions include PDMPs, prescriber education (e.g., online courses, workshops, and tele-mentoring programs such as Project ECHO (10)), pain clinic legislation, clinical guidelines (e.g., the 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain (11)) evaluated as interventions, and interventions relating to naloxone co-prescription with opioids (e.g., naloxone education for prescribers and naloxone co-prescription requirements). Eligible systematic reviews will include primary studies of interventions targeted exclusively at impacting opioid prescribing behavior for adult CNCP in an outpatient or mixed outpatient/inpatient setting or targeted at impacting prescribing behavior for multiple opioid prescription indications including adult CNCP in an outpatient/mixed setting (e.g., adult CNCP in addition to other pain indications or opioid use disorder). For interventions targeting multiple prescription indications, eligible reviews must include primary studies specific to opioid prescribing in the context of adult CNCP or studies in a

mixed prescription indication context that includes adult CNCP. For interventions targeting a mixed prescription setting, eligible reviews will include primary studies in an exclusively outpatient setting or in a mixed setting. Reviews limited to studies of interventions exclusively targeting pediatric and non-CNCP prescription indications (e.g., acute pain, post-surgical pain, opioid use disorder) or palliative pain management will be excluded, as will reviews limited to studies exclusively targeting prescribing in an inpatient setting. Interventions exclusively targeting opioid prescription for cancer pain will be excluded as opioid prescription guidelines and use patterns differ between chronic non-cancer and cancer pain. Reviews which include some studies of eligible interventions and some studies of ineligible interventions will be eligible provided they report at least one outcome specific to an eligible intervention or group of interventions. We will not restrict by intervention components or method of delivery.

Comparators

Eligible systematic reviews may include one or both of the following types of primary studies: a) comparative studies that compared the intervention of interest against no intervention, usual care procedures, or other active (e.g., prescriber education vs. clinical guideline implementation) or control (e.g., attention control) interventions; or b) non-comparative studies (e.g., pre/post without comparator or time series without comparator).

Outcomes

Eligible systematic reviews will report outcomes pertaining to intervention effect on opioid prescribing behavior or patient and population health. Systematic reviews of intervention feasibility, acceptability (including healthcare professional and public perceptions of and attitudes towards interventions), and cost-effectiveness will be excluded.

Eligible opioid prescribing behavior outcomes will include:

1. Changes in opioid prescribing practices (e.g., changes in incidence or prevalence of opioid prescriptions, overall, by specific drug, or by release type [e.g., short-acting vs. long-acting/extended release]; changes in average duration or dosage of individual opioid prescriptions; changes in co-prescription of naloxone with opioids [e.g., changes in incidence or number of naloxone prescriptions]; changes in number of overlapping opioid and benzodiazepine prescriptions [e.g., changes in number of patients with benzodiazepine and opioid prescriptions overlapping by at least 1 common day]).
2. Changes in rates of prescribing of and referrals to alternative pain management therapies (e.g., changes in number of non-opioid analgesic prescriptions, changes in number of referrals to physical therapy).
3. Changes in intervention adherence, where these constitute a measure of intervention effect and a change in prescribing behavior (e.g., changes in prescriber adherence to CNCP opioid prescribing guideline recommendations following an educational intervention designed to improve prescriber adherence to said recommendations).

Eligible patient and population health outcomes will include:

1. Changes in patient-reported health and pain outcomes (e.g., changes in patient-reported physical functioning, quality of life, and pain outcomes, including both measures of pain intensity/severity and pain interference with functioning). These outcomes have been identified as core outcome domains among patients with chronic pain (12).
2. Changes in pharmaceutical or non-pharmaceutical opioid (e.g., heroin) related morbidity and mortality (e.g., changes in prevalence or incidence of fatal and non-fatal opioid

overdose, opioid-related hospitalizations, and opioid-related emergency department visits, overall or by specific drug; changes in incidence of opioid abuse treatment initiation or inpatient admissions for opioid abuse treatment).

3. Changes in prevalence or incidence of self-reported non-medical prescription opioid use or non-pharmaceutical opioid use.

Design

Inclusion will be restricted to systematic reviews with or without meta-analysis. The following criteria will be used to define eligibility as a systematic review: 1) methods are described, including a systematic search with inclusion/exclusion criteria; and 2) formal risk of bias assessment of included studies was performed (e.g., using the Cochrane Risk of Bias tool), with individual results reported for each study and each item/domain of the tool. We will include systematic reviews with and without meta-analysis. Data may be derived from any primary study type (e.g., randomized controlled trials or non-randomized studies of interventions) conducted in humans.

Forms of Publication

Studies will be restricted to English-language publications. Systematic review abstracts and conference proceedings will be included provided they meet the aforementioned systematic review criteria and contain sufficient detail to enable extraction of risk of bias assessments by study and tool domain/item. English-language abstracts of non-English language publications will not be eligible for inclusion, as records will be assessed for eligibility on the basis of the most complete version of the publication.

Data Sources

We will search the following databases from inception: MEDLINE, Embase, and PsycInfo via Ovid; the Cochrane Database of Systematic Reviews; and Epistemonikos. Reference lists of included publications will be hand-searched for eligible publications not identified in the search. We will not conduct an additional search for primary studies. If eligible systematic reviews are available only in protocol form, we will contact the authors to inquire whether a pre-publication version of the manuscript is available.

Search Strategy

The search was designed and will be executed by an experienced health sciences librarian (G.G.). Prior to execution, it will be peer-reviewed using Peer Review of Electronic Search Strategies (13). The search is tailored to each database and includes a combination of subject headings and terms related to opioids and prescribers, as applicable. We will apply a librarian-modified version of the PubMed systematic review filter, which includes additional search terms from the Canadian Agency for Drugs and Technologies in Health (CADTH) systematic review filter. Preliminary search strategies for all five databases are presented in Tables 2-6.

Study Selection

Search results from each database will be downloaded into EndNote and subsequently imported into DistillerSR (Evidence Partners, Ottawa, Canada). Duplicates will be identified and removed in DistillerSR. Screening will proceed through a three-stage process in DistillerSR. Two reviewers will first independently screen the titles of identified citations for eligibility. Citations considered potentially eligible by either reviewer in the title stage will move on to abstract screening. Two reviewers will then independently screen the abstracts of potentially eligible citations. Citations considered potentially eligible by one or both reviewers in the abstract stage will be retrieved in

full text, and the full text will then be reviewed for eligibility independently by two reviewers. Disagreements after full-text review will be resolved by consensus or consultation with a third reviewer, as necessary. The publications remaining after full-text review will be included in the overview of reviews. Publications excluded during the full-text review will be presented in the final manuscript in a table that includes the rationale for exclusion.

Overlap in primary studies is expected among eligible reviews addressing the same research question. We will address overlap between eligible reviews in a series of steps, beginning with creation of citation matrices to identify systematic reviews with complete overlap (14). Separate citation matrices will be created for each intervention type (e.g., PDMPs) to avoid underestimation of the degree of overlap, as some systematic reviews may include more than one intervention type. Complete overlap will be defined as two reviews that include all the same citations, or one review that includes all the citations of another. Each member of a pair of reviews with complete overlap will be assessed for exclusion based on meeting one of the following conditions: a) reports on no unique outcome area(s), contains no unique citations, and is at higher risk of bias compared to the other review; or b) reports on no unique outcome area(s), contains no unique citations, is at similar or higher risk of bias, and is less recent compared to the other review (e.g., a systematic review which has been updated) (15, 16). These decisions will be made by two reviewers and will be tracked in a table that presents the characteristics of excluded reviews. In all other cases, reviews with complete overlap will be included.

Data Extraction

Data will be extracted independently by two reviewers using pilot-tested forms in DistillerSR. The pilot-testing process will be carried out by two reviewers with a small sample of studies to identify

necessary adjustments to the extraction forms and to assess the feasibility of conducting independent extraction. When large amounts of non-numerical data are independently extracted into DistillerSR, it can result in high numbers of conflicts from slight wording differences, resulting in reduced efficiency of the conflict resolution process. If the pilot testing process reveals that independent extraction will be inadvisable for this reason, extraction will instead proceed via initial extraction by a first reviewer and subsequent validation by a second reviewer using the DistillerSR Quality Control function. Otherwise, extraction will proceed independently and disagreements between the two reviewers will be detected in DistillerSR. In either case, disagreements will be resolved by consensus or a third reviewer as necessary.

We will extract the following data on systematic review characteristics: first author, publication year, search period, number of databases searched and names, objectives, inclusion criteria (population, intervention, comparators, outcomes, study design), exclusion criteria, number of included primary studies, total number of participants, risk of bias tool used, and source of funding. The number of included primary studies and total number of participants will be extracted by intervention and by outcome. For reviews which report on both eligible and non-eligible interventions or report both eligible and non-eligible outcomes, we will only extract the number of included primary studies and total number of participants relevant to the eligible intervention(s)/outcome(s). We will also extract the following data on the characteristics of systematic reviews' included primary studies: first author, publication year, and risk of bias (as assessed by the systematic review). Primary study characteristics will only be extracted for those studies relevant to our review. Finally, we will extract outcomes pertaining to intervention effect on prescriber behavior and patient and population health. Outcome data will be extracted as they are presented in the systematic review, including effect estimates, 95% confidence intervals,

descriptive statistics (e.g., count data, means), and measures of heterogeneity. Both study-level and meta-analytic results will be extracted. We will additionally extract the number of primary studies the results are drawn from, evidence grade assessments (as available), and outcome data stratified by sex, gender, and ethnicity (as available). Where data are missing or confirmation is needed, review authors will be contacted.

Risk of Bias Assessment of Included Systematic Reviews

Two reviewers will independently assess the risk of bias of included systematic reviews using the Risk of Bias in Systematic Reviews (ROBIS) tool (17). ROBIS assesses concerns about bias in the review process in four domains: study eligibility criteria, identification and selection of studies, data collection and study appraisal, and synthesis and findings. Each domain includes 5-6 signalling questions to aid in the assessment, leading to a final rating of high, low, or unclear concern in each domain. Questions are answered as yes, probably yes, probably no, no, or no information. Answers of yes or probably yes to all signalling questions will result in a judgment of low concern for that domain. Answers of yes, probably yes, and no information will result in a judgement of unclear concern. Any answer of no or probably no will result in a judgement of high concern. Final assessments in each domain will be used in the assessment of risk of bias in the review, which is determined based on three signalling questions: 1) Did the interpretation of findings address all of the concerns identified in domains 1 to 4; 2) Was the relevance of identified studies to the review's research question appropriately considered; and 3) Did the reviewers avoid emphasizing results on the basis of their statistical significance. These signalling questions will be answered and interpreted in the same manner as for the individual domains, leading to a judgment of low, high, or unclear risk of bias in the review. We will not exclude any systematic reviews on the basis of risk of bias results.

Risk of Bias of Primary Studies Contained in Included Systematic Reviews

We will extract risk of bias assessments performed by included systematic reviews and present them in tabular form. These tables will be grouped by primary study and will include the systematic review of origin, the tool used, and the assessment results. Domain-specific and overall ratings will be extracted. Some primary studies may have more than one risk of bias assessment available due to inclusion in more than one systematic review. For these studies, we will extract and present all available risk of bias assessments.

Data Synthesis

We will use a qualitative, analytical approach to synthesize the evidence. We will create five types of summary tables; one to present characteristics of included systematic reviews, one to present primary study risk of bias assessments performed by included systematic reviews (outlined in the above section), one to present characteristics of interventions investigated by included systematic reviews, one to present ROBIS risk of bias assessments for each systematic review, and one to present their results. The table presenting characteristics of included systematic reviews will include first author, publication year, search period, number of databases searched and names, objectives, focus (population, intervention, comparators, outcomes, study design), number of relevant included primary studies and total number of participants (separated by intervention or outcome as applicable), risk of bias tool used, and source of funding. The table presenting characteristics of investigated interventions will include interventions' target population(s), target prescription indication(s), target prescription setting(s), major components, objectives, and country or jurisdiction of origin. The table presenting ROBIS risk of bias assessments for each systematic review will include scores in each domain (low/high/unclear) and the risk of bias in the

review (low/high/unclear). The tables presenting results of included systematic reviews will be grouped by outcome and will include relevant outcome data from each systematic review, the number of included systematic reviews assessing the outcome, the number of primary studies and study participants represented, and evidence grade assessments from each systematic review (as available). Separate tables will be created for each intervention type (e.g., PDMPs, clinical guidelines) and country of origin as needed (e.g., Canadian vs. American clinical guidelines), as opioid prescription guidelines and legislation vary by country.

To assist in the interpretation of our results, we will label outcomes relating to intervention effect as a) intended or unintended and b) positive, negative, evidence of no effect, or inconclusive evidence. Labelling will be conducted in duplicate by two reviewers, with disagreements resolved via consensus or consultation with a third reviewer as necessary. Labelling outcomes as intended and unintended will enable separation of the intended effects of investigated interventions on a given population from their potential unintended effects (18). The categorization of an outcome as intended or unintended will be determined according to the objectives of the intervention in question, as defined by included publications and summarized in our table of intervention characteristics. Outcomes which align with the objectives of an intervention (i.e., planned effects) will be categorized as intended outcomes, and outcomes which do not align with the objectives of an intervention (i.e., unplanned effects) will be categorized as unintended outcomes. Labelling outcomes as positive, negative, evidence of no effect, and inconclusive evidence will enable identification of the effects of each investigated intervention, including potential benefits and harms in the case of patient and population health outcomes. For outcomes related to an intervention's objectives, categorization as positive or negative will be determined according to their alignment with intervention objectives. A decrease in overall opioid prescribing rates

following the implementation of an intervention designed to reduce opioid prescribing, for example, would be categorized as a positive effect, while an increase in these rates would be categorized as a negative effect. For outcomes unrelated to an intervention's objectives, categorization as positive or negative will be determined according to the effect they represent on the associated population. For example, an increase in rates of opioid overdose in the general population following the implementation of an intervention would be categorized as a negative effect, while a decrease in these rates would be categorized as a positive effect. Outcomes for which an effect is not demonstrated will be categorized as evidence of no effect if this conclusion is supported by precise estimates that rule out clinically-important differences, and inconclusive evidence if insufficient evidence is available to judge whether an effect is present.

Addressing Overlap between Included Systematic Reviews

To address overlap between included systematic reviews, citation matrices that were created for each intervention type in the screening stage will be updated to reflect final inclusion/exclusion decisions. They will then be used to calculate corrected covered area (CCA) scores by intervention type using the following formula (19):

$$CCA = \frac{N - r}{(r \times c) - r},$$

where N is the total number of primary studies across all reviews (including duplicates), r is the number of unique primary studies across all reviews, and c is the number of reviews. The CCA score ranges from 0-100%, with a higher CCA score reflecting a higher degree of overlap. Citation matrices will also be created, and CCA scores calculated, within intervention types by outcome category (e.g., patient-reported health and pain outcomes) (14). CCA scores for each intervention

type overall and by outcome category will be reported in our results tables and taken into account in our synthesis. When CCA scores are high (>15) (19) and findings between reviews are discrepant, reasons for discrepancy will be explored (e.g., differences in methodology, exclusions of studies from meta-analyses) and the findings of reviews that are of lower risk of bias and are more comprehensive will be focused on in our synthesis. When CCA scores are high between reviews and findings are concordant, the probable role of overlap will be noted in our synthesis to reduce the risk of biasing our results.

Patient and Public Involvement

This protocol was developed in collaboration with two employees of Health Canada (S.J. and A.T.). They will be involved throughout the systematic review and in dissemination of our findings.

CONCLUSION

This overview of systematic reviews will synthesize the systematic review evidence on the effect of interventions targeting the behaviors of physician opioid prescribers for CNCP in adults on opioid prescriber behavior and patient and population health. This overview will, to our knowledge, be the first to provide a comprehensive overview of the effect of these interventions on prescriber behavior and patient and population health. Our expected results will inform physicians and policy makers of the benefits and potential harms of these interventions and, by extension, their role in combatting the opioid crisis.

ETHICS AND DISSEMINATION

As the planned project is an overview of systematic reviews of published data, there are no ethical or safety concerns. Dissemination plans include publication of our results in a peer-reviewed journal and presentation at conferences. We will additionally curate our results for dissemination to non-scientific audiences.

AUTHORS' CONTRIBUTIONS

EW and SW composed the protocol manuscript. All authors contributed to protocol design and revisions.

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COMPETING INTERESTS

The authors declare no competing interests.

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Table 1: Eligibility criteria for overview of systematic reviews of the effect of interventions targeting behaviors of physician prescribers of opioids for adult chronic non-cancer pain on prescriber behavior and patient and population health

PICO element	Inclusion	Exclusion
Population	This overview will be restricted to systematic reviews of studies conducted in healthcare professionals who prescribe opioids, with a focus on physician opioid prescribers (medical doctors who prescribe opioids). Eligible systematic reviews will include primary studies evaluating interventions targeted exclusively at physician opioid prescribers or targeted at multiple healthcare professional populations including physician opioid prescribers. Reviews of interventions targeted at multiple healthcare professional populations must include studies in which these interventions are delivered specifically or in part to physician opioid prescribers. Reviews which include some studies in eligible populations and some studies in ineligible populations will be included provided they report at least one outcome specific to an eligible population.	Reviews limited to studies of interventions delivered exclusively to non-physician healthcare professionals (dentists, nurse practitioners, physician assistants, pharmacists, etc.) Reviews limited to studies of interventions delivered exclusively or in part to patients (e.g., structured pain management programs).
Intervention	We will include systematic reviews of any type of intervention(s) aimed at impacting opioid prescribing behavior, with a focus on those aimed at impacting opioid prescribing behavior for adult CNCP in an outpatient setting. Examples of eligible interventions include PDMPs, prescriber education (e.g., online courses, workshops, and tele-mentoring programs such as Project ECHO), pain clinic legislation, clinical guidelines (e.g., the 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain) evaluated as interventions, and interventions relating to naloxone co-prescription with opioids (e.g., naloxone education for prescribers and naloxone co-prescription requirements). Eligible systematic reviews will include primary studies of interventions targeted exclusively at impacting opioid prescribing behavior for adult CNCP in an outpatient/mixed setting or targeted at impacting prescribing behavior for multiple opioid prescription indications including adult CNCP in an outpatient/mixed setting (e.g., adult CNCP in addition to other pain indications or opioid use disorder). For interventions targeting multiple prescription indications, eligible reviews must include primary studies specific to opioid prescribing in the context of adult CNCP and/or studies in a mixed prescription indication context that includes adult CNCP. For interventions targeting a mixed prescription setting, eligible	Reviews limited to studies of interventions not aimed at impacting opioid prescribing behavior. Reviews limited to studies exclusively targeting non-adult CNCP prescription indications (e.g., acute pain, post-surgical pain, cancer pain, pediatric CNCP, opioid use disorder) or palliative pain management. Reviews limited to studies exclusively targeting prescribing in an inpatient setting. Reviews which do not report any outcomes specific to an eligible intervention or group of interventions.

	reviews will include primary studies in an exclusively outpatient setting or in a mixed outpatient/inpatient setting. Reviews which include some studies of eligible interventions and some studies of ineligible interventions will be included provided they report at least one outcome specific to an eligible intervention or group of interventions.	
Comparators	Eligible systematic reviews may include one or both of the following types of primary studies: a) comparative studies that evaluated intervention effect against no intervention, usual care procedures, or other active (e.g., prescriber education vs. clinical guideline implementation) or control (e.g., attention control) interventions b) non-comparative studies (e.g., pre/post without comparator or time series without comparator).	
Outcomes	Eligible systematic reviews will report at least one outcome pertaining to intervention effect on opioid prescribing behavior or patient and population health. Eligible opioid prescribing behavior outcomes will include: 1. Changes in opioid prescribing practices (e.g., changes in incidence and/or prevalence of opioid prescriptions, overall, by specific drug, or by release type [e.g., short-acting vs. long-acting/extended release]; changes in average duration or dosage of individual opioid prescriptions; changes in co-prescription of naloxone with opioids [e.g., changes in incidence or number of naloxone prescriptions]; changes in number of overlapping opioid and benzodiazepine prescriptions [e.g., changes in number of patients with benzodiazepine and opioid prescriptions overlapping by at least 1 common day]). 2. Changes in rates of prescribing of and referrals to alternative pain management therapies (e.g., changes in number of non-opioid analgesic prescriptions, changes in number of referrals to physical therapy). 3. Changes in intervention adherence, where these constitute a measure of intervention effect and a change in prescribing behavior (e.g., changes in prescriber adherence to CNCP opioid prescribing guideline recommendations following an educational intervention designed to improve prescriber adherence to said recommendations). Eligible patient and population health outcomes will include: 1. Changes in patient-reported health and pain outcomes (e.g., changes in patient-reported physical functioning, quality of life, and pain outcomes, including both measures of pain intensity/severity and pain interference with functioning).	Systematic reviews that exclusively report outcomes not related to intervention effect on prescribing behavior or patient and population health., e.g.: - Feasibility - Acceptability (including healthcare professional and public perceptions of and attitudes towards interventions) - Cost-effectiveness - Intervention adherence (where this does not constitute a measure of intervention effect)

	2. Changes in pharmaceutical or non-pharmaceutical opioid (e.g., heroin) related morbidity and mortality (e.g., changes in prevalence or incidence of fatal and non-fatal opioid overdose, opioid-related hospitalizations, and opioid-related emergency department visits, overall or by specific drug; changes in incidence of opioid abuse treatment initiation or inpatient admissions for opioid abuse treatment). 3. Changes in prevalence or incidence of self-reported non-medical prescription opioid use or non-pharmaceutical opioid use.	
Study Design	Systematic reviews with or without meta-analysis. Reviews must meet the following criteria to be considered systematic: a) Methods are described, including a systematic search with inclusion/exclusion criteria. b) Formal risk of bias assessment of included studies was performed (e.g., using the Cochrane Risk of Bias tool), with individual results reported for each study and item/domain of the tool. We will include systematic reviews with or without meta-analysis. Data may be derived from any primary study type (e.g., experimental or observational) conducted in humans.	Any review or study that does not meet the criteria of a systematic review, including: - Overviews of systematic reviews - Non-systematic reviews - Primary studies - Commentaries
Forms of publication	Language: English* Systematic review abstracts and conference proceedings will be eligible provided they meet the aforementioned systematic review criteria and include sufficient detail to enable extraction of risk of bias assessments per study and tool domain/item. *English-language abstracts of non-English language publications will not be eligible for inclusion, as records will be assessed for eligibility on the basis of the most complete version of the publication.	Non-English language publications

CNCP = chronic non-cancer pain

Table 2: Search Strategy (MEDLINE via Ovid)

Search Number	Description
1	exp analgesics, opioid/ or exp opioid-related disorders/ or (narcotic* or opiate* or opioid* or acetylmethadol or alfentanil or anileridine or Belladonna or Benzomorphan* or bezitramide or buprenorphine or butorphanol or Codeine or Dextromethorphan or Dextromoramide or Dextropropoxyphene or dezocine or Diamorphine or dihydrocodeine or Diphenylpropylamine or Ethylmorphine or Fentanyl* or Heroin or Hydrocodon* or Hydromorphon* or ketobemidone or levacetylmethadol or Meperidine or Meptazinol or methadone or Morphan* or Morphine* or nalbuphine or nicomorphine or normethadone or Opium or Oripavine or Oxycodone or Oxymorphone or Papaveretum or Pentazocine or pethidin* or Phenazocine or Phenoperidine or phentanyl or Phenylpiperidine or Piritramide or remifentanil or Sufentanil or sulfentanil or sulfentanyl or tapentadol or Tilidine or Tramadol*).mp. or (analgesic*).ti.
2	practice patterns, physicians'/ or exp prescriptions/ or exp prescription drug monitoring programs/ or (doctor* or physician* or surgeon* or dispens* or prescribe* or prescribing or deprescrib* or overprescri* or prescription* or script? or stewardship* or refill* or taper*).mp.
3	1 and 2
4	systematic review/ or meta analysis/ or "systematic review as topic"/ or exp "meta-analysis as topic"/ or technology assessment, biomedical/
5	(meta analy* or metaanaly* or technology assessment* or hta or htas or ((evidence or mixed method* or rapid or systematic) adj3 (overview or review or metareview or metasynthesis))).ti. or (cochrane database of systematic reviews or technology assessment*).jw.
6	4 or 5
7	3 and 6

Table 3: Search Strategy (Embase via Ovid)

Search Number	Description
1	exp narcotic analgesic agent/
2	controlled substance/
3	(narcotic* or opiate* or opioid* or acetylmethadol or alfentanil or anileridine or Belladonna or Benzomorphan* or bezitramide or buprenorphine or butorphanol or Codeine or Dextromethorphan or Dextromoramide or Dextropropoxyphene or dezocine or Diamorphine or dihydrocodeine or Diphenylpropylamine or Ethylmorphine or Fentanyl* or Heroin or Hydrocodon* or Hydromorphon* or ketobemidone or levacetylmethadol or Meperidine or Meptazinol or methadone or Morphan* or Morphine* or nalbuphine or nicomorphine or normethadone or Opium or Oripavine or Oxycodone or Oxymorphone or Papaveretum or Pentazocine or pethidin* or Phenazocine or Phenoperidine or phentanyl or Phenylpiperidine or Piritramide or remifentanil or Sufentanil or sulfentanil or sulfentanyl or tapentadol or Tilidine or Tramadol*).mp. or analgesic*.ti.
4	1 or 2 or 3
5	prescription/ or prescription drug monitoring program/ or (doctor* or physician* or surgeon* or dispens* or prescribe* or prescribing or deprescrib* or overprescri* or prescription* or script? or stewardship* or refill* or taper*).mp.
6	4 and 5
7	systematic review/ or exp meta analysis/ or "systematic review (topic)"/ or "meta analysis (topic)"/ or biomedical technology assessment/
8	(meta analy* or metaanaly* or technology assessment* or hta or htas or ((evidence or mixed method* or rapid or systematic) adj3 (review or metareview or metasynthesis))).ti.
9	(cochrane database of systematic review or technology assessment*).jw.
10	7 or 8 or 9
11	6 and 10

Table 4: Search Strategy (PsycINFO via Ovid)

Search Number	Description
1	exp narcotic drugs/ or (narcotic* or opiate* or opioid* or acetylmethadol or alfentanil or anileridine or Belladonna or Benzomorphan* or bezitramide or buprenorphine or butorphanol or Codeine or Dextromethorphan or Dextromoramide or Dextropropoxyphene or dezocine or Diamorphine or dihydrocodeine or Diphenylpropylamine or Ethylmorphine or Fentanyl* or Heroin or Hydrocodon* or Hydromorphon* or ketobemidone or levacetylmethadol or Meperidine or Meptazinol or methadone or Morphan* or Morphine* or nalbuphine or nicomorphine or normethadone or Opium or Oripavine or Oxycodone or Oxymorphone or Papaveretum or Pentazocine or pethidin* or Phenazocine or Phenoperidine or phentanyl or Phenylpiperidine or Piritramide or remifentanil or Sufentanil or sulfentanil or sulfentanyl or tapentadol or Tilidine or Tramadol*).mp.
2	exp "prescribing (drugs)"/ or prescription drugs/ or (doctor* or physician* or surgeon* or dispens* or overprescri* or prescribe* or prescribing or deprescrib* or prescription* or script? or stewardship* or refill* or taper*).mp.
3	1 and 2
4	meta analysis/
5	(systematic review or meta analysis or metasynthesis).md.
6	(meta analy* or metaanaly* or technology assessment* or hta or htas or ((evidence or mixed method* or rapid or systematic) adj3 (review or metareview or metasynthesis)).ti.
7	or/4-6
8	3 and 7

Table 5: Search Strategy (Cochrane Database of Systematic Reviews)

Search Number	Description
1 Title Abstract Keyword	narcotic* or opiate* or opioid* or acetylmethadol or alfentanil or anileridine or Belladonna or Benzomorphan* or bezitramide or buprenorphine or butorphanol or Codeine or Dextromethorphan or Dextromoramide or Dextropropoxyphene or dezocine or Diamorphine or dihydrocodeine or Diphenylpropylamine or Ethylmorphine or Fentanyl* or Heroin or Hydrocodon* or Hydromorphon* or ketobemidone or levacetylmethadol or Meperidine or Meptazinol or methadone or Morphan* or Morphine* or nalbuphine or nicomorphine or normethadone or Opium or Oripavine or Oxycodone or Oxymorphone or Papaveretum or Pentazocine or pethidin* or Phenazocine or Phenoperidine or phentanyl or Phenylpiperidine or Piritramide or remifentanil or Sufentanil or sulfentanil or sulfentanyl or tapentadol or Tilidine or Tramadol*
2 Title Abstract Keyword	doctor* or physician* or surgeon* or dispens* or prescribe* or prescribing or deprescrib* or overprescri* or prescription* or script* or stewardship* or refill* or taper*
3	1 and 2
Search limits	Cochrane Reviews Cochrane Protocols

Table 6: Search Strategy (Epistemonikos)

Search Number	Description
1 (Title/ Abstract)	narcotic* OR opiate* OR opioid* OR acetylmethadol OR alfentanil OR anileridine OR Belladonna OR Benzomorphan* OR bezitramide OR buprenorphine OR butorphanol OR Codeine OR Dextromethorphan OR Dextromoramide OR Dextropropoxyphene OR dezocine OR Diamorphine OR dihydrocodeine OR Diphenylpropylamine OR Ethylmorphine OR Fentanyl* OR Heroin OR Hydrocodon* OR Hydromorphon* OR ketobemidone OR levacetylmethadol OR Meperidine OR Meptazinol OR methadone OR Morphan* OR Morphine* OR nalbuphine OR nicomorphine OR normethadone OR Opium OR Oripavine OR Oxycodone OR Oxymorphone OR Papaveretum OR Pentazocine OR pethidin* OR Phenazocine OR Phenoperidine OR phentanyl OR Phenylpiperidine OR Piritramide OR remifentanil OR Sufentanil OR sulfentanil OR sulfentanyl OR tapentadol OR Tilidine OR Tramadol*
2 (Title/ Abstract)	doctor* OR physician* OR surgeon* OR dispens* OR prescribe* OR prescribing OR deprescrib* OR overprescri* OR prescription* OR script* OR stewardship* OR refill* OR taper*
3	1 and 2
Filters	Publication type: Systematic Review Systematic Review Question: Interventions

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

Based on the PRISMA-P guidelines.

		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 - not an update
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	6
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1, emails of all co-authors provided on PROSPERO registration
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	19

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	19
Sponsor	#5b	Provide name for the review funder and / or sponsor	19
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	19
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	5
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
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	6-10
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	11
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	11, 25-29
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	11-12
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)	11-12

Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	12-14
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	13-14
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8-10; 13-14
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	14-15
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	n/a - quantitative synthesis not appropriate
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,	n/a - quantitative synthesis not appropriate

		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)	n/a - meta-analytic results will be extracted from included systematic reviews as available (p. 14)
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	15-18
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	n/a
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	n/a - GRADE assessments will be extracted as reported in included systematic reviews, if performed (p. 14)

Notes:

- 1b: n/a - not an update
- 3a: 1, emails of all co-authors provided on PROSPERO registration
- 13: 8-10; 13-14
- 15a: n/a - quantitative synthesis not appropriate

- 15b: n/a - quantitative synthesis not appropriate
- 15c: n/a - meta-analytic results will be extracted from included systematic reviews as available (p. 14)
- 17: n/a - GRADE assessments will be extracted as reported in included systematic reviews, if performed (p. 14) The PRISMA-P elaboration and explanation paper is distributed under the terms of the Creative Commons Attribution License CC-BY. This checklist was completed on 09. January 2022 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

Interventions for Physician Prescribers of Opioids for Chronic Non-Cancer Pain: Protocol for an Overview of Systematic Reviews

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Interventions for Physician Prescribers of Opioids for Chronic Non-Cancer Pain: Protocol for an Overview of Systematic Reviews

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ABSTRACT

Introduction: Interventions targeting behaviours of physician prescribers of opioids for chronic non-cancer pain have been introduced to combat the opioid crisis. Systematic reviews have evaluated effects of specific interventions (e.g., prescriber education, prescription drug monitoring programs) on patient and population health outcomes and prescriber behaviour. Integration of findings across intervention types is needed to better understand the effects of prescriber-targeted interventions.

Methods and analysis: We will conduct an overview of systematic reviews. Eligible systematic reviews will include primary studies that evaluated any intervention targeting the behaviours of physician prescribers of opioids for chronic non-cancer pain in an outpatient or mixed setting, compared to no intervention, usual practice, or another active or control intervention. Eligible outcomes will pertain to the intervention effect on patient and population health or opioid prescribing behaviour. We will search MEDLINE, Embase, and PsycInfo via Ovid; the Cochrane Database of Systematic Reviews; and Epistemonikos from inception. We will also hand-search reference lists for additional publications. Screening and data extraction will be conducted independently by two reviewers, with disagreements resolved by consensus or consultation with a third reviewer. The risk of bias of included systematic reviews will be assessed in duplicate by two reviewers using the Risk of Bias in Systematic Reviews tool. Results will be synthesized narratively by intervention type and grouped by outcome. To assist with result interpretation, outcomes will be labelled as intended or unintended according to intervention objectives, and as positive, negative, evidence of no effect, or inconclusive evidence according to effect on the population (for patient and population health outcomes) or intervention objectives (for prescriber outcomes).

Ethics and dissemination: As the proposed study will use published data, ethics approval is not required. Dissemination of results will be achieved through publication of a manuscript in a peer-reviewed journal and conference presentations.

Registration: PROSPERO (CRD42020156815).

Word count: 300/300

ARTICLE SUMMARY

Strengths and limitations of this study

- The overview of systematic reviews methodology will enable examination of the diverse body of evidence contained across systematic reviews of interventions targeting physician prescribers of opioids for chronic non-cancer pain.
- Design of the protocol was guided by Chapter V of the *Cochrane Handbook for Systematic Reviews of Interventions*, along with elements from additional guidance documents for overviews of systematic reviews.
- Limitations of this study relate to those of the overview of systematic reviews methodology; namely, restriction of the interventions and outcomes synthesized to those captured in available systematic reviews, and risk of systematic reviews' conclusions being affected by publication bias.

INTRODUCTION

To combat the ongoing opioid crisis in North America, countries and jurisdictions have introduced interventions targeting the behaviours of physician prescribers of opioids for chronic non-cancer pain (CNCP) (pain lasting over three months not associated with a cancer diagnosis (1)). A wide range of interventions fall under this category, including prescriber education, prescription drug monitoring programs (PDMPs), pain clinic legislation (e.g., laws requiring that physician pain clinic owners be board-certified in pain management), and clinical guidelines (2). As these interventions have the potential to alter the way in which opioids are prescribed, it is highly important to consider not only the effects of these interventions on prescriber behaviour, but also on patient and population health. Numerous systematic reviews have evaluated the effects of interventions targeting physician opioid prescribers for CNCP on opioid prescriber behaviours and outcomes among patients with CNCP and the general population (3-6). These systematic reviews vary not only in their populations and outcomes of interest, but also in the specific interventions evaluated (e.g., PDMPs). While the variability in these reviews' areas of focus means a wealth of information is spread across them, it makes it difficult to consider their findings holistically. A systematic synthesis of this heterogeneous systematic review evidence has yet to be performed and would be of great value in better understanding the effect of prescriber-targeted interventions on both patient and population health and prescriber behaviour. Therefore, we will perform an overview of systematic reviews of the effect of interventions targeting the behaviours of physician opioid prescribers for CNCP in adults on patient and population health and prescriber behaviour.

OBJECTIVE

Our objective is to synthesize the systematic review evidence on the effect of interventions targeting the behaviours of physician opioid prescribers for CNCP in adults on patient and population health and prescriber behaviour.

METHODS AND ANALYSIS

This overview of systematic reviews will be guided by Chapter V of the *Cochrane Handbook for Systematic Reviews of Interventions* (7), along with elements from additional guidance documents described in a recent review (8). The overview of systematic reviews methodology was chosen to examine evidence across systematic reviews of interventions targeting physician prescribers of opioids for chronic non-cancer pain, as these systematic reviews address different outcomes (7). Our overview will be reported according to the Preferred Reporting Items for Overviews of systematic reviews including harms (PRIO-harms) pilot checklist (9). It has been registered on PROSPERO (CRD42020156815). Important protocol amendments will be documented in PROSPERO.

Eligibility Criteria

Population

This overview will be restricted to systematic reviews of studies conducted in healthcare professionals who prescribe opioids, with a focus on physician opioid prescribers (Table 1). For the purposes of this overview, "physician opioid prescribers" will be defined as medical doctors who prescribe opioids. Eligible systematic reviews will include primary studies evaluating interventions targeted exclusively at physician opioid prescribers or targeted at multiple healthcare professional populations including physician opioid prescribers. Reviews of interventions targeted

at multiple healthcare professional populations must include studies in which these interventions are delivered specifically or in part to physician opioid prescribers. Reviews limited to studies of interventions delivered exclusively to non-physician healthcare professionals (e.g., dentists, nurse practitioners, physician assistants, pharmacists) will be ineligible, as will reviews limited to studies of interventions delivered exclusively or in part to patients (e.g., structured pain management programs). Reviews which include some studies in eligible populations and some studies in ineligible populations will be included provided they report at least one outcome specific to an eligible population.

Intervention

We will include systematic reviews of any type of intervention(s) aimed at impacting opioid prescribing behaviour, with a focus on those aimed at impacting opioid prescribing behaviour for adult CNCP in an outpatient setting. Examples of eligible interventions include PDMPs, prescriber education (e.g., online courses, workshops, and tele-mentoring programs such as Project ECHO (10)), pain clinic legislation, clinical guidelines (e.g., the 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain (11)) evaluated as interventions, and interventions relating to naloxone co-prescription with opioids (e.g., naloxone education for prescribers and naloxone co-prescription requirements). Eligible systematic reviews will include primary studies of interventions targeted exclusively at impacting opioid prescribing behaviour for adult CNCP in an outpatient or mixed outpatient/inpatient setting or targeted at impacting prescribing behaviour for multiple opioid prescription indications including adult CNCP in an outpatient/mixed setting (e.g., adult CNCP in addition to other pain indications or opioid use disorder). For interventions targeting multiple prescription indications, eligible reviews must include primary studies specific to opioid prescribing in the context of adult CNCP or studies in a

mixed prescription indication context that includes adult CNCP. For interventions targeting a mixed prescription setting, eligible reviews will include primary studies in an exclusively outpatient setting or in a mixed setting. Reviews limited to studies of interventions exclusively targeting paediatric and non-CNCP prescription indications (e.g., acute pain, post-surgical pain, opioid use disorder) or palliative pain management will be excluded, as will reviews limited to studies exclusively targeting prescribing in an inpatient setting. Interventions exclusively targeting opioid prescription for cancer pain will be excluded as opioid prescription guidelines and use patterns differ between chronic non-cancer and cancer pain. Reviews which include some studies of eligible interventions and some studies of ineligible interventions will be eligible provided they report at least one outcome specific to an eligible intervention or group of interventions. We will not restrict by intervention components or method of delivery.

Comparators

Eligible systematic reviews may include one or both of the following types of primary studies: a) comparative studies that compared the intervention of interest against no intervention, usual care procedures, or other active (e.g., prescriber education vs. clinical guideline implementation) or control (e.g., attention control) interventions; or b) non-comparative studies (e.g., time series without comparator).

Outcomes

Eligible systematic reviews will report outcomes pertaining to intervention effect on patient and population health or opioid prescribing behaviour. Systematic reviews of intervention feasibility, acceptability (including healthcare professional and public perceptions of and attitudes towards interventions), and cost-effectiveness will be excluded.

Eligible patient and population health outcomes will include:

1. Changes in patient-reported health and pain outcomes (e.g., changes in patient-reported physical functioning, quality of life, and pain outcomes, including both measures of pain intensity/severity and pain interference with functioning). These outcomes have been identified as core outcome domains among patients with chronic pain (12).
2. Changes in pharmaceutical or non-pharmaceutical opioid (e.g., heroin) related morbidity and mortality (e.g., changes in prevalence or incidence of fatal and non-fatal opioid overdose, opioid-related hospitalizations, and opioid-related emergency department visits, overall or by specific drug; changes in incidence of opioid abuse treatment initiation or inpatient admissions for opioid abuse treatment).
3. Changes in prevalence or incidence of self-reported non-medical prescription opioid use or non-pharmaceutical opioid use.

Eligible opioid prescribing behaviour outcomes will include:

1. Changes in opioid prescribing practices (e.g., changes in incidence or prevalence of opioid prescriptions, overall, by specific drug, or by release type [e.g., short-acting vs. long-acting/extended release]; changes in average duration or dosage of individual opioid prescriptions; changes in co-prescription of naloxone with opioids [e.g., changes in incidence or number of naloxone prescriptions]; changes in number of overlapping opioid and benzodiazepine prescriptions [e.g., changes in number of patients with benzodiazepine and opioid prescriptions overlapping by at least 1 common day]).

2. Changes in rates of prescribing of and referrals to alternative pain management therapies (e.g., changes in number of non-opioid analgesic prescriptions, changes in number of referrals to physical therapy).
3. Changes in intervention adherence, where these constitute a measure of intervention effect and a change in prescribing behaviour (e.g., changes in prescriber adherence to CNCP opioid prescribing guideline recommendations following an educational intervention designed to improve prescriber adherence to said recommendations).

Design

Inclusion will be restricted to systematic reviews with or without meta-analysis. The following criteria will be used to define eligibility as a systematic review: 1) methods are described, including a systematic search with inclusion/exclusion criteria; and 2) formal risk of bias assessment of included studies was performed (e.g., using the Cochrane Risk of Bias tool), with individual results reported for each study and each item/domain of the tool. We will include systematic reviews with and without meta-analysis. Data may be derived from any primary study type (e.g., randomized controlled trials or non-randomized studies of interventions) conducted in humans.

Forms of Publication

Studies will be restricted to English-language publications. Systematic review abstracts and conference proceedings will be included provided they meet the aforementioned systematic review criteria and contain sufficient detail to enable extraction of risk of bias assessments by study and tool domain/item. English-language abstracts of non-English language publications will not be eligible for inclusion, as records will be assessed for eligibility on the basis of the most complete version of the publication.

Data Sources

We will search the following databases from inception: MEDLINE, Embase, and PsycInfo via Ovid; the Cochrane Database of Systematic Reviews; and Epistemonikos. Reference lists of included publications will be hand-searched for eligible publications not identified in the search. We will not conduct an additional search for primary studies. If eligible systematic reviews are available only in protocol form, we will contact the authors to inquire whether a pre-publication version of the manuscript is available.

Search Strategy

The search was designed and will be executed by an experienced health sciences librarian (G.G.). Prior to execution, it will be peer-reviewed using Peer Review of Electronic Search Strategies (13). The search is tailored to each database and includes a combination of subject headings and terms related to opioids and prescribers, as applicable. We will apply a librarian-modified version of the PubMed systematic review filter, which includes additional search terms from the Canadian Agency for Drugs and Technologies in Health (CADTH) systematic review filter. Preliminary search strategies for all five databases are presented in Tables 2-6.

Study Selection

Search results from each database will be downloaded into EndNote and subsequently imported into DistillerSR (Evidence Partners, Ottawa, Canada). Duplicates will be identified and removed in DistillerSR. Screening will proceed through a three-stage process in DistillerSR. Two reviewers will first independently screen the titles of identified citations for eligibility. Citations considered potentially eligible by either reviewer in the title stage will move on to abstract screening. Two

reviewers will then independently screen the abstracts of potentially eligible citations. Citations considered potentially eligible by one or both reviewers in the abstract stage will be retrieved in full text, and the full text will then be reviewed for eligibility independently by two reviewers. Disagreements after full-text review will be resolved by consensus or consultation with a third reviewer, as necessary. The publications remaining after full-text review will be included in the overview of reviews. Publications excluded during the full-text review will be presented in the final manuscript in a table that includes the rationale for exclusion.

Overlap in primary studies is expected among eligible reviews addressing the same research question. We will address overlap between eligible reviews in a series of steps, beginning with creation of citation matrices to identify systematic reviews with complete overlap (14). Separate citation matrices will be created for each intervention type (e.g., PDMPs) to avoid underestimation of the degree of overlap, as some systematic reviews may include more than one intervention type. Complete overlap will be defined as two reviews that include all the same citations, or one review that includes all the citations of another. Each member of a pair of reviews with complete overlap will be assessed for exclusion based on meeting one of the following conditions: a) reports on no unique outcome area(s), contains no unique citations, and is at higher risk of bias compared to the other review; or b) reports on no unique outcome area(s), contains no unique citations, is at similar or higher risk of bias, and is less recent compared to the other review (e.g., a systematic review which has been updated) (15, 16). These decisions will be made by two reviewers and will be tracked in a table that presents the characteristics of excluded reviews. In all other cases, reviews with complete overlap will be included.

Data Extraction

Data will be extracted independently by two reviewers using pilot-tested forms in DistillerSR. The pilot-testing process will be carried out by two reviewers with a small sample of studies to identify necessary adjustments to the extraction forms and to assess the feasibility of conducting independent extraction. When large amounts of non-numerical data are independently extracted into DistillerSR, it can result in high numbers of conflicts from slight wording differences, resulting in reduced efficiency of the conflict resolution process. If the pilot testing process reveals that independent extraction will be inadvisable for this reason, extraction will instead proceed via initial extraction by a first reviewer and subsequent validation by a second reviewer using the DistillerSR Quality Control function. Otherwise, extraction will proceed independently and disagreements between the two reviewers will be detected in DistillerSR. In either case, disagreements will be resolved by consensus or a third reviewer as necessary.

We will extract the following data on systematic review characteristics: first author, publication year, search period, number of databases searched and names, objectives, inclusion criteria (population, intervention, comparators, outcomes, study design), exclusion criteria, number of included primary studies, total number of participants, risk of bias tool used, and source of funding. The number of included primary studies and total number of participants will be extracted by intervention and by outcome. For reviews which report on both eligible and non-eligible interventions or report both eligible and non-eligible outcomes, we will only extract the number of included primary studies and total number of participants relevant to the eligible intervention(s)/outcome(s). We will also extract the following data on the characteristics of systematic reviews' included primary studies: first author, publication year, and risk of bias (as assessed by the systematic review). Primary study characteristics will only be extracted for those studies relevant to our review. Finally, we will extract outcomes pertaining to intervention effect

on prescriber behaviour and patient and population health. Outcome data will be extracted as they are presented in the systematic review, including effect estimates, 95% confidence intervals, descriptive statistics (e.g., count data, means), and measures of heterogeneity. Both study-level and meta-analytic results will be extracted. We will additionally extract the number of primary studies the results are drawn from, evidence grade assessments (as available). We will also extract outcome data stratified by sex; gender; ethnicity; Indigenous identity; and efficacy, effectiveness, and efficiency study design (as available). Where data are missing or confirmation is needed, review authors will be contacted.

Risk of Bias Assessment of Included Systematic Reviews

Two reviewers will independently assess the risk of bias of included systematic reviews using the Risk of Bias in Systematic Reviews (ROBIS) tool (17). ROBIS assesses concerns about bias in the review process in four domains: study eligibility criteria, identification and selection of studies, data collection and study appraisal, and synthesis and findings. Each domain includes 5-6 signalling questions to aid in the assessment, leading to a final rating of high, low, or unclear concern in each domain. Questions are answered as yes, probably yes, probably no, no, or no information. Answers of yes or probably yes to all signalling questions will result in a judgment of low concern for that domain. Answers of yes, probably yes, and no information will result in a judgement of unclear concern. Any answer of no or probably no will result in a judgement of high concern. Final assessments in each domain will be used in the assessment of risk of bias in the review, which is determined based on three signalling questions: 1) Did the interpretation of findings address all of the concerns identified in domains 1 to 4; 2) Was the relevance of identified studies to the review's research question appropriately considered; and 3) Did the reviewers avoid emphasizing results on the basis of their statistical significance. These signalling questions will be

answered and interpreted in the same manner as for the individual domains, leading to a judgment of low, high, or unclear risk of bias in the review. We will not exclude any systematic reviews on the basis of risk of bias results.

Risk of Bias of Primary Studies Contained in Included Systematic Reviews

We will extract risk of bias assessments performed by included systematic reviews and present them in tabular form. These tables will be grouped by primary study and will include the systematic review of origin, the tool used, and the assessment results. Domain-specific and overall ratings will be extracted. Some primary studies may have more than one risk of bias assessment available due to inclusion in more than one systematic review. For these studies, we will extract and present all available risk of bias assessments.

Data Synthesis

We will use a qualitative, analytical approach to synthesize the evidence. We will create five types of summary tables; one to present characteristics of included systematic reviews, one to present primary study risk of bias assessments performed by included systematic reviews (outlined in the above section), one to present characteristics of interventions investigated by included systematic reviews, one to present ROBIS risk of bias assessments for each systematic review, and one to present their results. The table presenting characteristics of included systematic reviews will include first author, publication year, search period, number of databases searched and names, objectives, focus (population, intervention, comparators, outcomes, study design), number of relevant included primary studies and total number of participants (separated by intervention or outcome as applicable), risk of bias tool used, and source of funding. The table presenting characteristics of investigated interventions will include interventions' target population(s), target

prescription indication(s), target prescription setting(s), major components, objectives, and country or jurisdiction of origin. The table presenting ROBIS risk of bias assessments for each systematic review will include scores in each domain (low/high/unclear) and the risk of bias in the review (low/high/unclear). The tables presenting results of included systematic reviews will be grouped by outcome and will include relevant outcome data from each systematic review, the number of included systematic reviews assessing the outcome, the number of primary studies and study participants represented, and evidence grade assessments from each systematic review (as available). Separate tables will be created for each intervention type (e.g., PDMPs, clinical guidelines) and country of origin as needed (e.g., Canadian vs. American clinical guidelines), as opioid prescription guidelines and legislation vary by country. When patient and population health outcomes are available for an intervention, these will be made the priority of our synthesis and conclusions to reflect their higher importance compared to prescriber behaviour outcomes in determining best practices.

To assist in the interpretation of our results, we will label outcomes relating to intervention effect as a) intended or unintended and b) positive, negative, evidence of no effect, or inconclusive evidence. Labelling will be conducted in duplicate by two reviewers, with disagreements resolved via consensus or consultation with a third reviewer as necessary. Labelling outcomes as intended and unintended will enable separation of the intended effects of investigated interventions on a given population from their potential unintended effects (18). The categorization of an outcome as intended or unintended will be determined according to the objectives of the intervention in question, as defined by included publications and summarized in our table of intervention characteristics. Outcomes which align with the objectives of an intervention (i.e., planned effects) will be categorized as intended outcomes, and outcomes which do not align with the objectives of

an intervention (i.e., unplanned effects) will be categorized as unintended outcomes. Labelling outcomes as positive, negative, evidence of no effect, and inconclusive evidence will enable identification of the effects of each investigated intervention, including potential benefits and harms in the case of patient and population health outcomes. For outcomes related to an intervention's objectives, categorization as positive or negative will be determined according to their alignment with intervention objectives. A decrease in overall opioid prescribing rates following the implementation of an intervention designed to reduce opioid prescribing, for example, would be categorized as a positive effect, while an increase in these rates would be categorized as a negative effect. For outcomes unrelated to an intervention's objectives, categorization as positive or negative will be determined according to the effect they represent on the associated population. For example, an increase in rates of opioid overdose in the general population following the implementation of an intervention would be categorized as a negative effect, while a decrease in these rates would be categorized as a positive effect. Outcomes for which an effect is not demonstrated will be categorized as evidence of no effect if this conclusion is supported by precise estimates that rule out clinically-important differences, and inconclusive evidence if insufficient evidence is available to judge whether an effect is present.

Addressing Overlap between Included Systematic Reviews

To address overlap between included systematic reviews, citation matrices that were created for each intervention type in the screening stage will be updated to reflect final inclusion/exclusion decisions. They will then be used to calculate corrected covered area (CCA) scores by intervention type using the following formula (19):

$$CCA = \frac{N - r}{(r \times c) - r},$$

where N is the total number of primary studies across all reviews (including duplicates), r is the number of unique primary studies across all reviews, and c is the number of reviews. The CCA score ranges from 0-100%, with a higher CCA score reflecting a higher degree of overlap. Citation matrices will also be created, and CCA scores calculated, within intervention types by outcome category (e.g., patient-reported health and pain outcomes) (14). CCA scores for each intervention type overall and by outcome category will be reported in our results tables and taken into account in our synthesis. When CCA scores are high (>15) (19) and findings between reviews are discrepant, reasons for discrepancy will be explored (e.g., differences in methodology, exclusions of studies from meta-analyses) and the findings of reviews that are of lower risk of bias and are more comprehensive will be focused on in our synthesis. When CCA scores are high between reviews and findings are concordant, the probable role of overlap will be noted in our synthesis to reduce the risk of biasing our results.

Patient and Public Involvement

This protocol was developed in collaboration with two employees of Health Canada (S.J. and A.T.). They will be involved throughout the systematic review and in dissemination of our findings.

ETHICS AND DISSEMINATION

As the planned project is an overview of systematic reviews of published data, there are no ethical or safety concerns. Dissemination plans include publication of our results in a peer-reviewed journal and presentation at conferences. We will additionally curate our results for dissemination to non-scientific audiences.

AUTHORS' CONTRIBUTIONS

EW and SW contributed to protocol design and drafted the protocol manuscript. ME, KF, GG, BT, IK, EP, MM, JK, SJ, and AT contributed to protocol design and revisions, drawing upon their respective areas of expertise. All authors approved the final version of the manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

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Table 1: Eligibility criteria for overview of systematic reviews of the effect of interventions targeting behaviours of physician prescribers of opioids for adult chronic non-cancer pain on prescriber behaviour and patient and population health

PICO element	Inclusion	Exclusion
Population	This overview will be restricted to systematic reviews of studies conducted in healthcare professionals who prescribe opioids, with a focus on physician opioid prescribers (medical doctors who prescribe opioids). Eligible systematic reviews will include primary studies evaluating interventions targeted exclusively at physician opioid prescribers or targeted at multiple healthcare professional populations including physician opioid prescribers. Reviews of interventions targeted at multiple healthcare professional populations must include studies in which these interventions are delivered specifically or in part to physician opioid prescribers. Reviews which include some studies in eligible populations and some studies in ineligible populations will be included provided they report at least one outcome specific to an eligible population.	Reviews limited to studies of interventions delivered exclusively to non-physician healthcare professionals (dentists, nurse practitioners, physician assistants, pharmacists, etc.) Reviews limited to studies of interventions delivered exclusively or in part to patients (e.g., structured pain management programs).
Intervention	We will include systematic reviews of any type of intervention(s) aimed at impacting opioid prescribing behaviour, with a focus on those aimed at impacting opioid prescribing behaviour for adult CNCP in an outpatient setting. Examples of eligible interventions include PDMPs, prescriber education (e.g., online courses, workshops, and tele-mentoring programs such as Project ECHO), pain clinic legislation, clinical guidelines (e.g., the 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain) evaluated as interventions, and interventions relating to naloxone co-prescription with opioids (e.g., naloxone education for prescribers and naloxone co-prescription requirements). Eligible systematic reviews will include primary studies of interventions targeted exclusively at impacting opioid prescribing behaviour for adult CNCP in an outpatient/mixed setting or targeted at impacting prescribing behaviour for multiple opioid prescription indications including adult CNCP in an outpatient/mixed setting (e.g., adult CNCP in addition to other pain indications or opioid use disorder). For interventions targeting multiple prescription indications, eligible reviews must include primary studies specific to opioid prescribing in the context of adult CNCP and/or studies in a mixed prescription indication context that includes adult CNCP. For interventions targeting a mixed prescription setting, eligible	Reviews limited to studies of interventions not aimed at impacting opioid prescribing behaviour. Reviews limited to studies exclusively targeting non-adult CNCP prescription indications (e.g., acute pain, post-surgical pain, cancer pain, paediatric CNCP, opioid use disorder) or palliative pain management. Reviews limited to studies exclusively targeting prescribing in an inpatient setting. Reviews which do not report any outcomes specific to an eligible intervention or group of interventions.

	reviews will include primary studies in an exclusively outpatient setting or in a mixed outpatient/inpatient setting. Reviews which include some studies of eligible interventions and some studies of ineligible interventions will be included provided they report at least one outcome specific to an eligible intervention or group of interventions.	
Comparators	Eligible systematic reviews may include one or both of the following types of primary studies: a) comparative studies that evaluated intervention effect against no intervention, usual care procedures, or other active (e.g., prescriber education vs. clinical guideline implementation) or control (e.g., attention control) interventions b) non-comparative studies (e.g., time series without comparator).	
Outcomes	Eligible systematic reviews will report at least one outcome pertaining to intervention effect on patient and population health or opioid prescribing behaviour. Eligible patient and population health outcomes will include: 1. Changes in patient-reported health and pain outcomes (e.g., changes in patient-reported physical functioning, quality of life, and pain outcomes, including both measures of pain intensity/severity and pain interference with functioning). 2. Changes in pharmaceutical or non-pharmaceutical opioid (e.g., heroin) related morbidity and mortality (e.g., changes in prevalence or incidence of fatal and non-fatal opioid overdose, opioid-related hospitalizations, and opioid-related emergency department visits, overall or by specific drug; changes in incidence of opioid abuse treatment initiation or inpatient admissions for opioid abuse treatment). 3. Changes in prevalence or incidence of self-reported non-medical prescription opioid use or non-pharmaceutical opioid use. Eligible opioid prescribing behaviour outcomes will include: 1. Changes in opioid prescribing practices (e.g., changes in incidence and/or prevalence of opioid prescriptions, overall, by specific drug, or by release type [e.g., short-acting vs. long-acting/extended release]; changes in average duration or dosage of individual opioid prescriptions; changes in co-prescription of naloxone with opioids [e.g., changes in incidence or number of naloxone prescriptions]; changes in number of overlapping opioid and benzodiazepine prescriptions [e.g., changes in number of patients with benzodiazepine and opioid prescriptions overlapping by at least 1 common day]).	Systematic reviews that exclusively report outcomes not related to intervention effect on patient and population health or opioid prescribing behaviour, e.g.: - Feasibility - Acceptability (including healthcare professional and public perceptions of and attitudes towards interventions) - Cost-effectiveness - Intervention adherence (where this does not constitute a measure of intervention effect)

	2. Changes in rates of prescribing of and referrals to alternative pain management therapies (e.g., changes in number of non-opioid analgesic prescriptions, changes in number of referrals to physical therapy). 3. Changes in intervention adherence, where these constitute a measure of intervention effect and a change in prescribing behaviour (e.g., changes in prescriber adherence to CNCP opioid prescribing guideline recommendations following an educational intervention designed to improve prescriber adherence to said recommendations).	
Study Design	Systematic reviews with or without meta-analysis. Reviews must meet the following criteria to be considered systematic: a) Methods are described, including a systematic search with inclusion/exclusion criteria. b) Formal risk of bias assessment of included studies was performed (e.g., using the Cochrane Risk of Bias tool), with individual results reported for each study and item/domain of the tool. We will include systematic reviews with or without meta-analysis. Data may be derived from any primary study type (e.g., experimental or observational) conducted in humans.	Any review or study that does not meet the criteria of a systematic review, including: - Overviews of systematic reviews - Non-systematic reviews - Primary studies - Commentaries
Forms of publication	Language: English* Systematic review abstracts and conference proceedings will be eligible provided they meet the aforementioned systematic review criteria and include sufficient detail to enable extraction of risk of bias assessments per study and tool domain/item. *English-language abstracts of non-English language publications will not be eligible for inclusion, as records will be assessed for eligibility on the basis of the most complete version of the publication.	Non-English language publications

CNCP = chronic non-cancer pain

Table 2: Search Strategy (MEDLINE via Ovid)

Search Number	Description
1	exp analgesics, opioid/ or exp opioid-related disorders/ or (narcotic* or opiate* or opioid* or acetylmethadol or alfentanil or anileridine or Belladonna or Benzomorphan* or bezitramide or buprenorphine or butorphanol or Codeine or Dextromethorphan or Dextromoramide or Dextropropoxyphene or dezocine or Diamorphine or dihydrocodeine or Diphenylpropylamine or Ethylmorphine or Fentanyl* or Heroin or Hydrocodon* or Hydromorphon* or ketobemidone or levacetylmethadol or Meperidine or Meptazinol or methadone or Morphan* or Morphine* or nalbuphine or nicomorphine or normethadone or Opium or Oripavine or Oxycodone or Oxymorphone or Papaveretum or Pentazocine or pethidin* or Phenazocine or Phenoperidine or phentanyl or Phenylpiperidine or Piritramide or remifentanil or Sufentanil or sulfentanil or sulfentanyl or tapentadol or Tilidine or Tramadol*).mp. or (analgesic*).ti.
2	practice patterns, physicians'/ or exp prescriptions/ or exp prescription drug monitoring programs/ or (doctor* or physician* or surgeon* or dispens* or prescribe* or prescribing or deprescrib* or overprescri* or prescription* or script? or stewardship* or refill* or taper*).mp.
3	1 and 2
4	systematic review/ or meta analysis/ or "systematic review as topic"/ or exp "meta-analysis as topic"/ or technology assessment, biomedical/
5	(meta analy* or metaanaly* or technology assessment* or hta or htas or ((evidence or mixed method* or rapid or systematic) adj3 (overview or review or metareview or metasynthesis))).ti. or (cochrane database of systematic reviews or technology assessment*).jw.
6	4 or 5
7	3 and 6

Table 3: Search Strategy (Embase via Ovid)

Search Number	Description
1	exp narcotic analgesic agent/
2	controlled substance/
3	(narcotic* or opiate* or opioid* or acetylmethadol or alfentanil or anileridine or Belladonna or Benzomorphan* or bezitramide or buprenorphine or butorphanol or Codeine or Dextromethorphan or Dextromoramide or Dextropropoxyphene or dezocine or Diamorphine or dihydrocodeine or Diphenylpropylamine or Ethylmorphine or Fentanyl* or Heroin or Hydrocodon* or Hydromorphon* or ketobemidone or levacetylmethadol or Meperidine or Meptazinol or methadone or Morphan* or Morphine* or nalbuphine or nicomorphine or normethadone or Opium or Oripavine or Oxycodone or Oxymorphone or Papaveretum or Pentazocine or pethidin* or Phenazocine or Phenoperidine or phentanyl or Phenylpiperidine or Piritramide or remifentanil or Sufentanil or sulfentanil or sulfentanyl or tapentadol or Tilidine or Tramadol*).mp. or analgesic*.ti.
4	1 or 2 or 3
5	prescription/ or prescription drug monitoring program/ or (doctor* or physician* or surgeon* or dispens* or prescribe* or prescribing or deprescrib* or overprescri* or prescription* or script? or stewardship* or refill* or taper*).mp.
6	4 and 5
7	systematic review/ or exp meta analysis/ or "systematic review (topic)"/ or "meta analysis (topic)"/ or biomedical technology assessment/
8	(meta analy* or metaanaly* or technology assessment* or hta or htas or ((evidence or mixed method* or rapid or systematic) adj3 (review or metareview or metasynthesis))).ti.
9	(cochrane database of systematic review or technology assessment*).jw.
10	7 or 8 or 9
11	6 and 10

Table 4: Search Strategy (PsycINFO via Ovid)

Search Number	Description
1	exp narcotic drugs/ or (narcotic* or opiate* or opioid* or acetylmethadol or alfentanil or anileridine or Belladonna or Benzomorphan* or bezitramide or buprenorphine or butorphanol or Codeine or Dextromethorphan or Dextromoramide or Dextropropoxyphene or dezocine or Diamorphine or dihydrocodeine or Diphenylpropylamine or Ethylmorphine or Fentanyl* or Heroin or Hydrocodon* or Hydromorphon* or ketobemidone or levacetylmethadol or Meperidine or Meptazinol or methadone or Morphan* or Morphine* or nalbuphine or nicomorphine or normethadone or Opium or Oripavine or Oxycodone or Oxymorphone or Papaveretum or Pentazocine or pethidin* or Phenazocine or Phenoperidine or phentanyl or Phenylpiperidine or Piritramide or remifentanil or Sufentanil or sulfentanil or sulfentanyl or tapentadol or Tilidine or Tramadol*).mp.
2	exp "prescribing (drugs)"/ or prescription drugs/ or (doctor* or physician* or surgeon* or dispens* or overprescri* or prescribe* or prescribing or deprescrib* or prescription* or script? or stewardship* or refill* or taper*).mp.
3	1 and 2
4	meta analysis/
5	(systematic review or meta analysis or metasynthesis).md.
6	(meta analy* or metaanaly* or technology assessment* or hta or htas or ((evidence or mixed method* or rapid or systematic) adj3 (review or metareview or metasynthesis)).ti.
7	or/4-6
8	3 and 7

Table 5: Search Strategy (Cochrane Database of Systematic Reviews)

Search Number	Description
1 Title Abstract Keyword	narcotic* or opiate* or opioid* or acetylmethadol or alfentanil or anileridine or Belladonna or Benzomorphan* or bezitramide or buprenorphine or butorphanol or Codeine or Dextromethorphan or Dextromoramide or Dextropropoxyphene or dezocine or Diamorphine or dihydrocodeine or Diphenylpropylamine or Ethylmorphine or Fentanyl* or Heroin or Hydrocodon* or Hydromorphon* or ketobemidone or levacetylmethadol or Meperidine or Meptazinol or methadone or Morphan* or Morphine* or nalbuphine or nicomorphine or normethadone or Opium or Oripavine or Oxycodone or Oxymorphone or Papaveretum or Pentazocine or pethidin* or Phenazocine or Phenoperidine or phentanyl or Phenylpiperidine or Piritramide or remifentanil or Sufentanil or sulfentanil or sulfentanyl or tapentadol or Tilidine or Tramadol*
2 Title Abstract Keyword	doctor* or physician* or surgeon* or dispens* or prescribe* or prescribing or deprescrib* or overprescri* or prescription* or script* or stewardship* or refill* or taper*
3	1 and 2
Search limits	Cochrane Reviews Cochrane Protocols

Table 6: Search Strategy (Epistemonikos)

Search Number	Description
1 (Title/ Abstract)	narcotic* OR opiate* OR opioid* OR acetylmethadol OR alfentanil OR anileridine OR Belladonna OR Benzomorphan* OR bezitramide OR buprenorphine OR butorphanol OR Codeine OR Dextromethorphan OR Dextromoramide OR Dextropropoxyphene OR dezocine OR Diamorphine OR dihydrocodeine OR Diphenylpropylamine OR Ethylmorphine OR Fentanyl* OR Heroin OR Hydrocodon* OR Hydromorphon* OR ketobemidone OR levacetylmethadol OR Meperidine OR Meptazinol OR methadone OR Morphan* OR Morphine* OR nalbuphine OR nicomorphine OR normethadone OR Opium OR Oripavine OR Oxycodone OR Oxymorphone OR Papaveretum OR Pentazocine OR pethidin* OR Phenazocine OR Phenoperidine OR phentanyl OR Phenylpiperidine OR Piritramide OR remifentanil OR Sufentanil OR sulfentanil OR sulfentanyl OR tapentadol OR Tilidine OR Tramadol*
2 (Title/ Abstract)	doctor* OR physician* OR surgeon* OR dispens* OR prescribe* OR prescribing OR deprescrib* OR overprescri* OR prescription* OR script* OR stewardship* OR refill* OR taper*
3	1 and 2
Filters	Publication type: Systematic Review Systematic Review Question: Interventions

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

Based on the PRISMA-P guidelines.

		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 - not an update
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	6
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1, emails of all co-authors provided on PROSPERO registration
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	19

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	19
Sponsor	#5b	Provide name for the review funder and / or sponsor	19
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	19
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	5
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
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	6-10
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	11
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	11, 25-29
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	11-12
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)	11-12

Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	12-14
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	13-14
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8-10; 13-14
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	14-15
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	n/a - quantitative synthesis not appropriate
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,	n/a - quantitative synthesis not appropriate

		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)	n/a - meta-analytic results will be extracted from included systematic reviews as available (p. 14)
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	15-18
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	n/a
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	n/a - GRADE assessments will be extracted as reported in included systematic reviews, if performed (p. 14)

Notes:

- 1b: n/a - not an update
- 3a: 1, emails of all co-authors provided on PROSPERO registration
- 13: 8-10; 13-14
- 15a: n/a - quantitative synthesis not appropriate

- 15b: n/a - quantitative synthesis not appropriate
- 15c: n/a - meta-analytic results will be extracted from included systematic reviews as available (p. 14)
- 17: n/a - GRADE assessments will be extracted as reported in included systematic reviews, if performed (p. 14) The PRISMA-P elaboration and explanation paper is distributed under the terms of the Creative Commons Attribution License CC-BY. This checklist was completed on 09. January 2022 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

Interventions for Physician Prescribers of Opioids for Chronic Non-Cancer Pain: Protocol for an Overview of Systematic Reviews

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Keywords:	PAIN MANAGEMENT, Substance misuse < PSYCHIATRY, PUBLIC HEALTH, EPIDEMIOLOGY

Interventions for Physician Prescribers of Opioids for Chronic Non-Cancer Pain: Protocol for an Overview of Systematic Reviews

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Keywords: opioid, overview, systematic review, umbrella review, prescribing

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ABSTRACT

Introduction: Interventions targeting behaviours of physician prescribers of opioids for chronic non-cancer pain have been introduced to combat the opioid crisis. Systematic reviews have evaluated effects of specific interventions (e.g., prescriber education, prescription drug monitoring programs) on patient and population health outcomes and prescriber behaviour. Integration of findings across intervention types is needed to better understand the effects of prescriber-targeted interventions.

Methods and analysis: We will conduct an overview of systematic reviews. Eligible systematic reviews will include primary studies that evaluated any intervention targeting the behaviours of physician prescribers of opioids for chronic non-cancer pain in an outpatient or mixed setting, compared to no intervention, usual practice, or another active or control intervention. Eligible outcomes will pertain to the intervention effect on patient and population health or opioid prescribing behaviour. We will search MEDLINE, Embase, and PsycInfo via Ovid; the Cochrane Database of Systematic Reviews; and Epistemonikos from inception. We will also hand-search reference lists for additional publications. Screening and data extraction will be conducted independently by two reviewers, with disagreements resolved by consensus or consultation with a third reviewer. The risk of bias of included systematic reviews will be assessed in duplicate by two reviewers using the Risk of Bias in Systematic Reviews tool. Results will be synthesized narratively by intervention type and grouped by outcome. To assist with result interpretation, outcomes will be labelled as intended or unintended according to intervention objectives, and as positive, negative, evidence of no effect, or inconclusive evidence according to effect on the population (for patient and population health outcomes) or intervention objectives (for prescriber outcomes).

Ethics and dissemination: As the proposed study will use published data, ethics approval is not required. Dissemination of results will be achieved through publication of a manuscript in a peer-reviewed journal and conference presentations.

Registration: PROSPERO (CRD42020156815).

Word count: 300/300

ARTICLE SUMMARY

Strengths and limitations of this study

- The overview of systematic reviews methodology will enable examination of the diverse body of evidence contained across systematic reviews of interventions targeting physician prescribers of opioids for chronic non-cancer pain.
- Design of the protocol was guided by Chapter V of the *Cochrane Handbook for Systematic Reviews of Interventions*, along with elements from additional guidance documents for overviews of systematic reviews.
- Limitations of this study relate to those of the overview of systematic reviews methodology; namely, restriction of the interventions and outcomes synthesized to those captured in available systematic reviews, and risk of systematic reviews' conclusions being affected by publication bias.

INTRODUCTION

To combat the ongoing opioid crisis in North America, countries and jurisdictions have introduced interventions targeting the behaviours of physician prescribers of opioids for chronic non-cancer pain (CNCP) (pain lasting over three months not associated with a cancer diagnosis (1)). A wide range of interventions fall under this category, including prescriber education, prescription drug monitoring programs (PDMPs), pain clinic legislation (e.g., laws requiring that physician pain clinic owners be board-certified in pain management), and clinical guidelines (2). As these interventions have the potential to alter the way in which opioids are prescribed, it is highly important to consider not only the effects of these interventions on prescriber behaviour, but also on patient and population health. Numerous systematic reviews have evaluated the effects of interventions targeting physician opioid prescribers for CNCP on opioid prescriber behaviours and outcomes among patients with CNCP and the general population (3-6). These systematic reviews vary not only in their populations and outcomes of interest, but also in the specific interventions evaluated (e.g., PDMPs). While the variability in these reviews' areas of focus means a wealth of information is spread across them, it makes it difficult to consider their findings holistically. A systematic synthesis of this heterogeneous systematic review evidence has yet to be performed and would be of great value in better understanding the effect of prescriber-targeted interventions on both patient and population health and prescriber behaviour. Therefore, we will perform an overview of systematic reviews of the effect of interventions targeting the behaviours of physician opioid prescribers for CNCP in adults on patient and population health and prescriber behaviour.

OBJECTIVE

Our objective is to synthesize the systematic review evidence on the effect of interventions targeting the behaviours of physician opioid prescribers for CNCP in adults on patient and population health and prescriber behaviour.

METHODS AND ANALYSIS

This overview of systematic reviews will be guided by Chapter V of the *Cochrane Handbook for Systematic Reviews of Interventions* (7), along with elements from additional guidance documents described in a recent review (8). The overview of systematic reviews methodology was chosen to examine evidence across systematic reviews of interventions targeting physician prescribers of opioids for chronic non-cancer pain, as these systematic reviews address different outcomes (7). Our overview will be reported according to the Preferred Reporting Items for Overviews of systematic reviews including harms (PRIO-harms) pilot checklist (9). It has been registered on PROSPERO (CRD42020156815). Important protocol amendments will be documented in PROSPERO.

Eligibility Criteria

Population

This overview will be restricted to systematic reviews of studies conducted in healthcare professionals who prescribe opioids, with a focus on physician opioid prescribers (Table 1). For the purposes of this overview, "physician opioid prescribers" will be defined as medical doctors who prescribe opioids. Eligible systematic reviews will include primary studies evaluating interventions targeted exclusively at physician opioid prescribers or targeted at multiple healthcare professional populations including physician opioid prescribers. Reviews of interventions targeted

at multiple healthcare professional populations must include studies in which these interventions are delivered specifically or in part to physician opioid prescribers. Reviews limited to studies of interventions delivered exclusively to non-physician healthcare professionals (e.g., dentists, nurse practitioners, physician assistants, pharmacists) will be ineligible, as will reviews limited to studies of interventions delivered exclusively or in part to patients (e.g., structured pain management programs). Reviews which include some studies in eligible populations and some studies in ineligible populations will be included provided they report at least one outcome specific to an eligible population.

Intervention

We will include systematic reviews of any type of intervention(s) aimed at impacting opioid prescribing behaviour, with a focus on those aimed at impacting opioid prescribing behaviour for adult CNCP in an outpatient setting. Examples of eligible interventions include PDMPs, prescriber education (e.g., online courses, workshops, and tele-mentoring programs such as Project ECHO (10)), pain clinic legislation, clinical guidelines (e.g., the 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain (11)) evaluated as interventions, and interventions relating to naloxone co-prescription with opioids (e.g., naloxone education for prescribers and naloxone co-prescription requirements). Eligible systematic reviews will include primary studies of interventions targeted exclusively at impacting opioid prescribing behaviour for adult CNCP in an outpatient or mixed outpatient/inpatient setting or targeted at impacting prescribing behaviour for multiple opioid prescription indications including adult CNCP in an outpatient/mixed setting (e.g., adult CNCP in addition to other pain indications or opioid use disorder). For interventions targeting multiple prescription indications, eligible reviews must include primary studies specific to opioid prescribing in the context of adult CNCP or studies in a

mixed prescription indication context that includes adult CNCP. For interventions targeting a mixed prescription setting, eligible reviews will include primary studies in an exclusively outpatient setting or in a mixed setting. Reviews limited to studies of interventions exclusively targeting paediatric and non-CNCP prescription indications (e.g., acute pain, post-surgical pain, opioid use disorder) or palliative pain management will be excluded, as will reviews limited to studies exclusively targeting prescribing in an inpatient setting. Interventions exclusively targeting opioid prescription for cancer pain will be excluded as opioid prescription guidelines and use patterns differ between chronic non-cancer and cancer pain. Interventions targeting opioid prescription within opioid treatment programs will not be eligible. Reviews which include some studies of eligible interventions and some studies of ineligible interventions will be eligible provided they report at least one outcome specific to an eligible intervention or group of interventions. We will not restrict by intervention components or method of delivery.

Comparators

Eligible systematic reviews may include one or both of the following types of primary studies: a) comparative studies that compared the intervention of interest against no intervention, usual care procedures, or other active (e.g., prescriber education vs. clinical guideline implementation) or control (e.g., attention control) interventions; or b) non-comparative studies (e.g., time series without comparator).

Outcomes

Eligible systematic reviews will report outcomes pertaining to intervention effect on patient and population health or opioid prescribing behaviour. Systematic reviews of intervention feasibility,

acceptability (including healthcare professional and public perceptions of and attitudes towards interventions), and cost-effectiveness will be excluded.

Eligible patient and population health outcomes will include:

1. Changes in patient-reported health and pain outcomes (e.g., changes in patient-reported physical functioning, quality of life, and pain outcomes, including both measures of pain intensity/severity and pain interference with functioning). These outcomes have been identified as core outcome domains among patients with chronic pain (12).
2. Changes in pharmaceutical or non-pharmaceutical opioid (e.g., heroin) related morbidity and mortality (e.g., changes in prevalence or incidence of fatal and non-fatal opioid overdose, opioid-related hospitalizations, and opioid-related emergency department visits, overall or by specific drug; changes in incidence of opioid abuse treatment initiation or inpatient admissions for opioid abuse treatment).
3. Changes in prevalence or incidence of self-reported non-medical prescription opioid use or non-pharmaceutical opioid use.

Eligible opioid prescribing behaviour outcomes will include:

1. Changes in opioid prescribing practices (e.g., changes in incidence or prevalence of opioid prescriptions, overall, by specific drug, or by release type [e.g., short-acting vs. long-acting/extended release]; changes in average duration or dosage of individual opioid prescriptions; changes in co-prescription of naloxone with opioids [e.g., changes in incidence or number of naloxone prescriptions]; changes in number of overlapping opioid and benzodiazepine prescriptions [e.g., changes in number of patients with benzodiazepine and opioid prescriptions overlapping by at least 1 common day]).

2. Changes in rates of prescribing of and referrals to alternative pain management therapies (e.g., changes in number of non-opioid analgesic prescriptions, changes in number of referrals to physical therapy).
3. Changes in intervention adherence, where these constitute a measure of intervention effect and a change in prescribing behaviour (e.g., changes in prescriber adherence to CNCP opioid prescribing guideline recommendations following an educational intervention designed to improve prescriber adherence to said recommendations).

Design

Inclusion will be restricted to systematic reviews with or without meta-analysis. The following criteria will be used to define eligibility as a systematic review: 1) methods are described, including a systematic search with inclusion/exclusion criteria; and 2) formal risk of bias assessment of included studies was performed (e.g., using the Cochrane Risk of Bias tool), with individual results reported for each study and each item/domain of the tool. We will include systematic reviews with and without meta-analysis. Data may be derived from any primary study type (e.g., randomized controlled trials or non-randomized studies of interventions) conducted in humans.

Forms of Publication

Studies will be restricted to English-language publications. Systematic review abstracts and conference proceedings will be included provided they meet the aforementioned systematic review criteria and contain sufficient detail to enable extraction of risk of bias assessments by study and tool domain/item. English-language abstracts of non-English language publications will not be eligible for inclusion, as records will be assessed for eligibility on the basis of the most complete version of the publication.

Data Sources

We will search the following databases from inception: MEDLINE, Embase, and PsycInfo via Ovid; the Cochrane Database of Systematic Reviews; and Epistemonikos. Reference lists of included publications will be hand-searched for eligible publications not identified in the search. We will not conduct an additional search for primary studies. If eligible systematic reviews are available only in protocol form, we will contact the authors to inquire whether a pre-publication version of the manuscript is available.

Search Strategy

The search was designed and will be executed by an experienced health sciences librarian (G.G.). Prior to execution, it will be peer-reviewed using Peer Review of Electronic Search Strategies (13). The search is tailored to each database and includes a combination of subject headings and terms related to opioids and prescribers, as applicable. We will apply a librarian-modified version of the PubMed systematic review filter, which includes additional search terms from the Canadian Agency for Drugs and Technologies in Health (CADTH) systematic review filter. Preliminary search strategies for all five databases are presented in Tables 2-6.

Study Selection

Search results from each database will be downloaded into EndNote and subsequently imported into DistillerSR (Evidence Partners, Ottawa, Canada). Duplicates will be identified and removed in DistillerSR. Screening will proceed through a three-stage process in DistillerSR. Two reviewers will first independently screen the titles of identified citations for eligibility. Citations considered potentially eligible by either reviewer in the title stage will move on to abstract screening. Two

reviewers will then independently screen the abstracts of potentially eligible citations. Citations considered potentially eligible by one or both reviewers in the abstract stage will be retrieved in full text, and the full text will then be reviewed for eligibility independently by two reviewers. Disagreements after full-text review will be resolved by consensus or consultation with a third reviewer, as necessary. The publications remaining after full-text review will be included in the overview of reviews. Publications excluded during the full-text review will be presented in the final manuscript in a table that includes the rationale for exclusion.

Overlap in primary studies is expected among eligible reviews addressing the same research question. We will address overlap between eligible reviews in a series of steps, beginning with creation of citation matrices to identify systematic reviews with complete overlap (14). Separate citation matrices will be created for each intervention type (e.g., PDMPs) to avoid underestimation of the degree of overlap, as some systematic reviews may include more than one intervention type. Complete overlap will be defined as two reviews that include all the same citations, or one review that includes all the citations of another. Each member of a pair of reviews with complete overlap will be assessed for exclusion based on meeting one of the following conditions: a) reports on no unique outcome area(s), contains no unique citations, and is at higher risk of bias compared to the other review; or b) reports on no unique outcome area(s), contains no unique citations, is at similar or higher risk of bias, and is less recent compared to the other review (e.g., a systematic review which has been updated) (15, 16). These decisions will be made by two reviewers and will be tracked in a table that presents the characteristics of excluded reviews. In all other cases, reviews with complete overlap will be included.

Data Extraction

Data will be extracted independently by two reviewers using pilot-tested forms in DistillerSR. The pilot-testing process will be carried out by two reviewers with a small sample of studies to identify necessary adjustments to the extraction forms and to assess the feasibility of conducting independent extraction. When large amounts of non-numerical data are independently extracted into DistillerSR, it can result in high numbers of conflicts from slight wording differences, resulting in reduced efficiency of the conflict resolution process. If the pilot testing process reveals that independent extraction will be inadvisable for this reason, extraction will instead proceed via initial extraction by a first reviewer and subsequent validation by a second reviewer using the DistillerSR Quality Control function. Otherwise, extraction will proceed independently and disagreements between the two reviewers will be detected in DistillerSR. In either case, disagreements will be resolved by consensus or a third reviewer as necessary.

We will extract the following data on systematic review characteristics: first author, publication year, search period, number of databases searched and names, objectives, inclusion criteria (population, intervention, comparators, outcomes, study design), exclusion criteria, number of included primary studies, total number of participants, risk of bias tool used, and source of funding. The number of included primary studies and total number of participants will be extracted by intervention and by outcome. For reviews which report on both eligible and non-eligible interventions or report both eligible and non-eligible outcomes, we will only extract the number of included primary studies and total number of participants relevant to the eligible intervention(s)/outcome(s). We will also extract the following data on the characteristics of systematic reviews' included primary studies: first author, publication year, and risk of bias (as assessed by the systematic review). Primary study characteristics will only be extracted for those studies relevant to our review. Finally, we will extract outcomes pertaining to intervention effect

on prescriber behaviour and patient and population health. Outcome data will be extracted as they are presented in the systematic review, including effect estimates, 95% confidence intervals, descriptive statistics (e.g., count data, means), and measures of heterogeneity. Both study-level and meta-analytic results will be extracted. We will additionally extract the number of primary studies the results are drawn from, evidence grade assessments (as available). We will also extract outcome data stratified by sex; gender; ethnicity; Indigenous identity; and efficacy, effectiveness, and efficiency study design (as available). Where data are missing or confirmation is needed, review authors will be contacted.

Risk of Bias Assessment of Included Systematic Reviews

Two reviewers will independently assess the risk of bias of included systematic reviews using the Risk of Bias in Systematic Reviews (ROBIS) tool (17). ROBIS assesses concerns about bias in the review process in four domains: study eligibility criteria, identification and selection of studies, data collection and study appraisal, and synthesis and findings. Each domain includes 5-6 signalling questions to aid in the assessment, leading to a final rating of high, low, or unclear concern in each domain. Questions are answered as yes, probably yes, probably no, no, or no information. Answers of yes or probably yes to all signalling questions will result in a judgment of low concern for that domain. Answers of yes, probably yes, and no information will result in a judgement of unclear concern. Any answer of no or probably no will result in a judgement of high concern. Final assessments in each domain will be used in the assessment of risk of bias in the review, which is determined based on three signalling questions: 1) Did the interpretation of findings address all of the concerns identified in domains 1 to 4; 2) Was the relevance of identified studies to the review's research question appropriately considered; and 3) Did the reviewers avoid emphasizing results on the basis of their statistical significance. These signalling questions will be

answered and interpreted in the same manner as for the individual domains, leading to a judgment of low, high, or unclear risk of bias in the review. We will not exclude any systematic reviews on the basis of risk of bias results.

Risk of Bias of Primary Studies Contained in Included Systematic Reviews

We will extract risk of bias assessments performed by included systematic reviews and present them in tabular form. These tables will be grouped by primary study and will include the systematic review of origin, the tool used, and the assessment results. Domain-specific and overall ratings will be extracted. Some primary studies may have more than one risk of bias assessment available due to inclusion in more than one systematic review. For these studies, we will extract and present all available risk of bias assessments.

Data Synthesis

We will use a qualitative, analytical approach to synthesize the evidence. We will create five types of summary tables; one to present characteristics of included systematic reviews, one to present primary study risk of bias assessments performed by included systematic reviews (outlined in the above section), one to present characteristics of interventions investigated by included systematic reviews, one to present ROBIS risk of bias assessments for each systematic review, and one to present their results. The table presenting characteristics of included systematic reviews will include first author, publication year, search period, number of databases searched and names, objectives, focus (population, intervention, comparators, outcomes, study design), number of relevant included primary studies and total number of participants (separated by intervention or outcome as applicable), risk of bias tool used, and source of funding. The table presenting characteristics of investigated interventions will include interventions' target population(s), target

prescription indication(s), target prescription setting(s), major components, objectives, and country or jurisdiction of origin. The table presenting ROBIS risk of bias assessments for each systematic review will include scores in each domain (low/high/unclear) and the risk of bias in the review (low/high/unclear). The tables presenting results of included systematic reviews will be grouped by outcome and will include relevant outcome data from each systematic review, the number of included systematic reviews assessing the outcome, the number of primary studies and study participants represented, and evidence grade assessments from each systematic review (as available). Separate tables will be created for each intervention type (e.g., PDMPs, clinical guidelines) and country of origin as needed (e.g., Canadian vs. American clinical guidelines), as opioid prescription guidelines and legislation vary by country. When patient and population health outcomes are available for an intervention, these will be made the priority of our synthesis and conclusions to reflect their higher importance compared to prescriber behaviour outcomes in determining best practices.

To assist in the interpretation of our results, we will label outcomes relating to intervention effect as a) intended or unintended and b) positive, negative, evidence of no effect, or inconclusive evidence. Labelling will be conducted in duplicate by two reviewers, with disagreements resolved via consensus or consultation with a third reviewer as necessary. Labelling outcomes as intended and unintended will enable separation of the intended effects of investigated interventions on a given population from their potential unintended effects (18). The categorization of an outcome as intended or unintended will be determined according to the objectives of the intervention in question, as defined by included publications and summarized in our table of intervention characteristics. Outcomes which align with the objectives of an intervention (i.e., planned effects) will be categorized as intended outcomes, and outcomes which do not align with the objectives of

an intervention (i.e., unplanned effects) will be categorized as unintended outcomes. Labelling outcomes as positive, negative, evidence of no effect, and inconclusive evidence will enable identification of the effects of each investigated intervention, including potential benefits and harms in the case of patient and population health outcomes. For outcomes related to an intervention's objectives, categorization as positive or negative will be determined according to their alignment with intervention objectives. A decrease in overall opioid prescribing rates following the implementation of an intervention designed to reduce opioid prescribing, for example, would be categorized as a positive effect, while an increase in these rates would be categorized as a negative effect. For outcomes unrelated to an intervention's objectives, categorization as positive or negative will be determined according to the effect they represent on the associated population. For example, an increase in rates of opioid overdose in the general population following the implementation of an intervention would be categorized as a negative effect, while a decrease in these rates would be categorized as a positive effect. Outcomes for which an effect is not demonstrated will be categorized as evidence of no effect if this conclusion is supported by precise estimates that rule out clinically-important differences, and inconclusive evidence if insufficient evidence is available to judge whether an effect is present.

Addressing Overlap between Included Systematic Reviews

To address overlap between included systematic reviews, citation matrices that were created for each intervention type in the screening stage will be updated to reflect final inclusion/exclusion decisions. They will then be used to calculate corrected covered area (CCA) scores by intervention type using the following formula (19):

$$CCA = \frac{N - r}{(r \times c) - r},$$

where N is the total number of primary studies across all reviews (including duplicates), r is the number of unique primary studies across all reviews, and c is the number of reviews. The CCA score ranges from 0-100%, with a higher CCA score reflecting a higher degree of overlap. Citation matrices will also be created, and CCA scores calculated, within intervention types by outcome category (e.g., patient-reported health and pain outcomes) (14). CCA scores for each intervention type overall and by outcome category will be reported in our results tables and taken into account in our synthesis. When CCA scores are high (>15) (19) and findings between reviews are discrepant, reasons for discrepancy will be explored (e.g., differences in methodology, exclusions of studies from meta-analyses) and the findings of reviews that are of lower risk of bias and are more comprehensive will be focused on in our synthesis. When CCA scores are high between reviews and findings are concordant, the probable role of overlap will be noted in our synthesis to reduce the risk of biasing our results.

Patient and Public Involvement

This protocol was developed in collaboration with two employees of Health Canada (S.J. and A.T.). They will be involved throughout the systematic review and in dissemination of our findings.

ETHICS AND DISSEMINATION

As the planned project is an overview of systematic reviews of published data, there are no ethical or safety concerns. Dissemination plans include publication of our results in a peer-reviewed journal and presentation at conferences. We will additionally curate our results for dissemination to non-scientific audiences.

AUTHORS' CONTRIBUTIONS

EW and SW contributed to protocol design and drafted the protocol manuscript. ME, KF, GG, BT, IK, EP, MM, JK, SJ, and AT contributed to protocol design and revisions, drawing upon their respective areas of expertise. All authors approved the final version of the manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

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Table 1: Eligibility criteria for overview of systematic reviews of the effect of interventions targeting behaviours of physician prescribers of opioids for adult chronic non-cancer pain on prescriber behaviour and patient and population health

PICO element	Inclusion	Exclusion
Population	This overview will be restricted to systematic reviews of studies conducted in healthcare professionals who prescribe opioids, with a focus on physician opioid prescribers (medical doctors who prescribe opioids). Eligible systematic reviews will include primary studies evaluating interventions targeted exclusively at physician opioid prescribers or targeted at multiple healthcare professional populations including physician opioid prescribers. Reviews of interventions targeted at multiple healthcare professional populations must include studies in which these interventions are delivered specifically or in part to physician opioid prescribers. Reviews which include some studies in eligible populations and some studies in ineligible populations will be included provided they report at least one outcome specific to an eligible population.	Reviews limited to studies of interventions delivered exclusively to non-physician healthcare professionals (dentists, nurse practitioners, physician assistants, pharmacists, etc.) Reviews limited to studies of interventions delivered exclusively or in part to patients (e.g., structured pain management programs).
Intervention	We will include systematic reviews of any type of intervention(s) aimed at impacting opioid prescribing behaviour, with a focus on those aimed at impacting opioid prescribing behaviour for adult CNCP in an outpatient setting. Examples of eligible interventions include PDMPs, prescriber education (e.g., online courses, workshops, and tele-mentoring programs such as Project ECHO), pain clinic legislation, clinical guidelines (e.g., the 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain) evaluated as interventions, and interventions relating to naloxone co-prescription with opioids (e.g., naloxone education for prescribers and naloxone co-prescription requirements). Eligible systematic reviews will include primary studies of interventions targeted exclusively at impacting opioid prescribing behaviour for adult CNCP in an outpatient/mixed setting or targeted at impacting prescribing behaviour for multiple opioid prescription indications including adult CNCP in an outpatient/mixed setting (e.g., adult CNCP in addition to other pain indications or opioid use disorder). For interventions targeting multiple prescription indications, eligible reviews must include primary studies specific to opioid prescribing in the context of adult CNCP and/or studies in a mixed prescription indication context that includes adult CNCP. For interventions targeting a mixed prescription setting, eligible	Reviews limited to studies of interventions not aimed at impacting opioid prescribing behaviour. Reviews limited to studies exclusively targeting non-adult CNCP prescription indications (e.g., acute pain, post-surgical pain, cancer pain, paediatric CNCP, opioid use disorder) or palliative pain management. Reviews limited to studies exclusively targeting prescribing in an inpatient setting. Reviews which do not report any outcomes specific to an eligible intervention or group of interventions.

	reviews will include primary studies in an exclusively outpatient setting or in a mixed outpatient/inpatient setting. Reviews which include some studies of eligible interventions and some studies of ineligible interventions will be included provided they report at least one outcome specific to an eligible intervention or group of interventions.	
Comparators	Eligible systematic reviews may include one or both of the following types of primary studies: a) comparative studies that evaluated intervention effect against no intervention, usual care procedures, or other active (e.g., prescriber education vs. clinical guideline implementation) or control (e.g., attention control) interventions b) non-comparative studies (e.g., time series without comparator).	
Outcomes	Eligible systematic reviews will report at least one outcome pertaining to intervention effect on patient and population health or opioid prescribing behaviour. Eligible patient and population health outcomes will include: 1. Changes in patient-reported health and pain outcomes (e.g., changes in patient-reported physical functioning, quality of life, and pain outcomes, including both measures of pain intensity/severity and pain interference with functioning). 2. Changes in pharmaceutical or non-pharmaceutical opioid (e.g., heroin) related morbidity and mortality (e.g., changes in prevalence or incidence of fatal and non-fatal opioid overdose, opioid-related hospitalizations, and opioid-related emergency department visits, overall or by specific drug; changes in incidence of opioid abuse treatment initiation or inpatient admissions for opioid abuse treatment). 3. Changes in prevalence or incidence of self-reported non-medical prescription opioid use or non-pharmaceutical opioid use. Eligible opioid prescribing behaviour outcomes will include: 1. Changes in opioid prescribing practices (e.g., changes in incidence and/or prevalence of opioid prescriptions, overall, by specific drug, or by release type [e.g., short-acting vs. long-acting/extended release]; changes in average duration or dosage of individual opioid prescriptions; changes in co-prescription of naloxone with opioids [e.g., changes in incidence or number of naloxone prescriptions]; changes in number of overlapping opioid and benzodiazepine prescriptions [e.g., changes in number of patients with benzodiazepine and opioid prescriptions overlapping by at least 1 common day]).	Systematic reviews that exclusively report outcomes not related to intervention effect on patient and population health or opioid prescribing behaviour, e.g.: - Feasibility - Acceptability (including healthcare professional and public perceptions of and attitudes towards interventions) - Cost-effectiveness - Intervention adherence (where this does not constitute a measure of intervention effect)

	2. Changes in rates of prescribing of and referrals to alternative pain management therapies (e.g., changes in number of non-opioid analgesic prescriptions, changes in number of referrals to physical therapy). 3. Changes in intervention adherence, where these constitute a measure of intervention effect and a change in prescribing behaviour (e.g., changes in prescriber adherence to CNCP opioid prescribing guideline recommendations following an educational intervention designed to improve prescriber adherence to said recommendations).	
Study Design	Systematic reviews with or without meta-analysis. Reviews must meet the following criteria to be considered systematic: a) Methods are described, including a systematic search with inclusion/exclusion criteria. b) Formal risk of bias assessment of included studies was performed (e.g., using the Cochrane Risk of Bias tool), with individual results reported for each study and item/domain of the tool. We will include systematic reviews with or without meta-analysis. Data may be derived from any primary study type (e.g., experimental or observational) conducted in humans.	Any review or study that does not meet the criteria of a systematic review, including: - Overviews of systematic reviews - Non-systematic reviews - Primary studies - Commentaries
Forms of publication	Language: English* Systematic review abstracts and conference proceedings will be eligible provided they meet the aforementioned systematic review criteria and include sufficient detail to enable extraction of risk of bias assessments per study and tool domain/item. *English-language abstracts of non-English language publications will not be eligible for inclusion, as records will be assessed for eligibility on the basis of the most complete version of the publication.	Non-English language publications

CNCP = chronic non-cancer pain

Table 2: Search Strategy (MEDLINE via Ovid)

Search Number	Description
1	exp analgesics, opioid/ or exp opioid-related disorders/ or (narcotic* or opiate* or opioid* or acetylmethadol or alfentanil or anileridine or Belladonna or Benzomorphan* or bezitramide or buprenorphine or butorphanol or Codeine or Dextromethorphan or Dextromoramide or Dextropropoxyphene or dezocine or Diamorphine or dihydrocodeine or Diphenylpropylamine or Ethylmorphine or Fentanyl* or Heroin or Hydrocodon* or Hydromorphon* or ketobemidone or levacetylmethadol or Meperidine or Meptazinol or methadone or Morphan* or Morphine* or nalbuphine or nicomorphine or normethadone or Opium or Oripavine or Oxycodone or Oxymorphone or Papaveretum or Pentazocine or pethidin* or Phenazocine or Phenoperidine or phentanyl or Phenylpiperidine or Piritramide or remifentanil or Sufentanil or sulfentanil or sulfentanyl or tapentadol or Tilidine or Tramadol*).mp. or (analgesic*).ti.
2	practice patterns, physicians'/ or exp prescriptions/ or exp prescription drug monitoring programs/ or (doctor* or physician* or surgeon* or dispens* or prescribe* or prescribing or deprescrib* or overprescri* or prescription* or script? or stewardship* or refill* or taper*).mp.
3	1 and 2
4	systematic review/ or meta analysis/ or "systematic review as topic"/ or exp "meta-analysis as topic"/ or technology assessment, biomedical/
5	(meta analy* or metaanaly* or technology assessment* or hta or htas or ((evidence or mixed method* or rapid or systematic) adj3 (overview or review or metareview or metasynthesis))).ti. or (cochrane database of systematic reviews or technology assessment*).jw.
6	4 or 5
7	3 and 6

Table 3: Search Strategy (Embase via Ovid)

Search Number	Description
1	exp narcotic analgesic agent/
2	controlled substance/
3	(narcotic* or opiate* or opioid* or acetylmethadol or alfentanil or anileridine or Belladonna or Benzomorphan* or bezitramide or buprenorphine or butorphanol or Codeine or Dextromethorphan or Dextromoramide or Dextropropoxyphene or dezocine or Diamorphine or dihydrocodeine or Diphenylpropylamine or Ethylmorphine or Fentanyl* or Heroin or Hydrocodon* or Hydromorphon* or ketobemidone or levacetylmethadol or Meperidine or Meptazinol or methadone or Morphan* or Morphine* or nalbuphine or nicomorphine or normethadone or Opium or Oripavine or Oxycodone or Oxymorphone or Papaveretum or Pentazocine or pethidin* or Phenazocine or Phenoperidine or phentanyl or Phenylpiperidine or Piritramide or remifentanil or Sufentanil or sulfentanil or sulfentanyl or tapentadol or Tilidine or Tramadol*).mp. or analgesic*.ti.
4	1 or 2 or 3
5	prescription/ or prescription drug monitoring program/ or (doctor* or physician* or surgeon* or dispens* or prescribe* or prescribing or deprescrib* or overprescri* or prescription* or script? or stewardship* or refill* or taper*).mp.
6	4 and 5
7	systematic review/ or exp meta analysis/ or "systematic review (topic)"/ or "meta analysis (topic)"/ or biomedical technology assessment/
8	(meta analy* or metaanaly* or technology assessment* or hta or htas or ((evidence or mixed method* or rapid or systematic) adj3 (review or metareview or metasynthesis))).ti.
9	(cochrane database of systematic review or technology assessment*).jw.
10	7 or 8 or 9
11	6 and 10

Table 4: Search Strategy (PsycINFO via Ovid)

Search Number	Description
1	exp narcotic drugs/ or (narcotic* or opiate* or opioid* or acetylmethadol or alfentanil or anileridine or Belladonna or Benzomorphan* or bezitramide or buprenorphine or butorphanol or Codeine or Dextromethorphan or Dextromoramide or Dextropropoxyphene or dezocine or Diamorphine or dihydrocodeine or Diphenylpropylamine or Ethylmorphine or Fentanyl* or Heroin or Hydrocodon* or Hydromorphon* or ketobemidone or levacetylmethadol or Meperidine or Meptazinol or methadone or Morphan* or Morphine* or nalbuphine or nicomorphine or normethadone or Opium or Oripavine or Oxycodone or Oxymorphone or Papaveretum or Pentazocine or pethidin* or Phenazocine or Phenoperidine or phentanyl or Phenylpiperidine or Piritramide or remifentanil or Sufentanil or sulfentanil or sulfentanyl or tapentadol or Tilidine or Tramadol*).mp.
2	exp "prescribing (drugs)"/ or prescription drugs/ or (doctor* or physician* or surgeon* or dispens* or overprescri* or prescribe* or prescribing or deprescrib* or prescription* or script? or stewardship* or refill* or taper*).mp.
3	1 and 2
4	meta analysis/
5	(systematic review or meta analysis or metasynthesis).md.
6	(meta analy* or metaanaly* or technology assessment* or hta or htas or ((evidence or mixed method* or rapid or systematic) adj3 (review or metareview or metasynthesis)).ti.
7	or/4-6
8	3 and 7

Table 5: Search Strategy (Cochrane Database of Systematic Reviews)

Search Number	Description
1 Title Abstract Keyword	narcotic* or opiate* or opioid* or acetylmethadol or alfentanil or anileridine or Belladonna or Benzomorphan* or bezitramide or buprenorphine or butorphanol or Codeine or Dextromethorphan or Dextromoramide or Dextropropoxyphene or dezocine or Diamorphine or dihydrocodeine or Diphenylpropylamine or Ethylmorphine or Fentanyl* or Heroin or Hydrocodon* or Hydromorphon* or ketobemidone or levacetylmethadol or Meperidine or Meptazinol or methadone or Morphan* or Morphine* or nalbuphine or nicomorphine or normethadone or Opium or Oripavine or Oxycodone or Oxymorphone or Papaveretum or Pentazocine or pethidin* or Phenazocine or Phenoperidine or phentanyl or Phenylpiperidine or Piritramide or remifentanil or Sufentanil or sulfentanil or sulfentanyl or tapentadol or Tilidine or Tramadol*
2 Title Abstract Keyword	doctor* or physician* or surgeon* or dispens* or prescribe* or prescribing or deprescrib* or overprescri* or prescription* or script* or stewardship* or refill* or taper*
3	1 and 2
Search limits	Cochrane Reviews Cochrane Protocols

Table 6: Search Strategy (Epistemonikos)

Search Number	Description
1 (Title/ Abstract)	narcotic* OR opiate* OR opioid* OR acetylmethadol OR alfentanil OR anileridine OR Belladonna OR Benzomorphan* OR bezitramide OR buprenorphine OR butorphanol OR Codeine OR Dextromethorphan OR Dextromoramide OR Dextropropoxyphene OR dezocine OR Diamorphine OR dihydrocodeine OR Diphenylpropylamine OR Ethylmorphine OR Fentanyl* OR Heroin OR Hydrocodon* OR Hydromorphon* OR ketobemidone OR levacetylmethadol OR Meperidine OR Meptazinol OR methadone OR Morphan* OR Morphine* OR nalbuphine OR nicomorphine OR normethadone OR Opium OR Oripavine OR Oxycodone OR Oxymorphone OR Papaveretum OR Pentazocine OR pethidin* OR Phenazocine OR Phenoperidine OR phentanyl OR Phenylpiperidine OR Piritramide OR remifentanil OR Sufentanil OR sulfentanil OR sulfentanyl OR tapentadol OR Tilidine OR Tramadol*
2 (Title/ Abstract)	doctor* OR physician* OR surgeon* OR dispens* OR prescribe* OR prescribing OR deprescrib* OR overprescri* OR prescription* OR script* OR stewardship* OR refill* OR taper*
3	1 and 2
Filters	Publication type: Systematic Review Systematic Review Question: Interventions

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

Based on the PRISMA-P guidelines.

		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 - not an update
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	6
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1, emails of all co-authors provided on PROSPERO registration
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	19

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	19
Sponsor	#5b	Provide name for the review funder and / or sponsor	19
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	19
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	5
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
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	6-10
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	11
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	11, 25-29
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	11-12
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)	11-12

Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	12-14
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	13-14
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8-10; 13-14
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	14-15
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	n/a - quantitative synthesis not appropriate
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,	n/a - quantitative synthesis not appropriate

		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)	n/a - meta-analytic results will be extracted from included systematic reviews as available (p. 14)
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	15-18
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	n/a
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	n/a - GRADE assessments will be extracted as reported in included systematic reviews, if performed (p. 14)

Notes:

- 1b: n/a - not an update
- 3a: 1, emails of all co-authors provided on PROSPERO registration
- 13: 8-10; 13-14
- 15a: n/a - quantitative synthesis not appropriate

- 15b: n/a - quantitative synthesis not appropriate
- 15c: n/a - meta-analytic results will be extracted from included systematic reviews as available (p. 14)
- 17: n/a - GRADE assessments will be extracted as reported in included systematic reviews, if performed (p. 14) The PRISMA-P elaboration and explanation paper is distributed under the terms of the Creative Commons Attribution License CC-BY. This checklist was completed on 09. January 2022 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai