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Abstract

Introduction: In the context of the opioid crisis in North America, the benefits of evidence-based opioid agonist treatments (OAT) such as buprenorphine/naloxone have not been optimized due to low uptake. Numerous factors contribute to the underuse of buprenorphine, and theory-informed approaches to identify and address implementation barriers and facilitators are needed. This scoping review aims to characterise the barriers and facilitators at the patient, healthcare professional, organization, and system level according to the Theoretical Domains Framework (TDF), and identify gaps to inform practice and policy.

Methods and analysis: We will conduct a scoping review using established methods and follow the Preferred Reporting Items for Systematic Reviews and Meta-analysis extension for scoping reviews (PRISMA-ScR). We will identify English and French-language peer-reviewed literature by searching five electronic bibliographic databases, from inception, and use Google, websites of key organizations, and two or more custom search engines to identify relevant grey literature. Eligible records will be quantitative or qualitative studies that examine barriers and facilitators to buprenorphine use at the patient, healthcare professional, organization, and system level, and involve participants with diagnosis of opioid use disorder or professionals involved in their care. Two reviewers will be involved in independently screening, reviewing, and charting the data and calibration exercises will be conducted at each stage. We will conduct descriptive analysis for the charted data, and deductively code barriers and facilitators using the TDF.

Ethics and dissemination: As a scoping review of the literature, this study does not require ethics approval. Our dissemination strategy will focus on developing tailored activities to meet the needs of diverse knowledge user audiences. Barriers and facilitators mapped to the TDF can

be linked to evidence-based strategies for change to improve buprenorphine use and access, and enable practice to reduce opioid-related harms.

Registration: Open Science Framework (osf.io/mwctz; June 4, 2019)

Keywords: opioid agonist treatment; barriers and facilitators, scoping review, buprenorphine

Article summary

Strengths and limitations of the study

- This scoping review will contribute to the literature the first comprehensive understanding of the multiple levels of barriers and facilitators to buprenorphine use to advance the design and implementation of buprenorphine delivery in various settings
- Our methodology will follow the framework developed by Arksey and O'Malley and enhanced by Levac et al. and the Joanna Briggs Institute, limited to English and French published and grey literature.
- The Theoretical Domains Framework has been used extensively in health care implementation research, and enables our analysis to comprehensively account for individual, social, and environmental level influences on behavior.
- To manage the number and scope of included studies, we will select and use systematic review level evidence, and exclude the primary literature included in the systematic review if there is alignment with our research question and search strategy.

Introduction

Fatal and non-fatal opioid poisonings continue to escalate in North America, with an estimated 47,600 opioid-related deaths in the United States (U.S.)[1] and more than 10,000 in Canada between January 2016 and September 2018.[2] In response, strategies aimed at preventing and reducing opioid-related deaths have been established, including access to evidence-based treatment options for opioid use disorder (OUD). In the United States, approximately 7% of individuals with OUD receive specialty care with approved medications for OUD,[3] while the extent of the gap in treatment in Canada has not been characterised. Opioid agonist treatments (OAT) such as buprenorphine/naloxone have demonstrated effectiveness in reducing opioid-related morbidity and mortality. Further, the superior safety and side effect profile of buprenorphine and equivalent efficacy compared to methadone has led it to be the preferred first-line treatment for OUD in Canada.[4] Importantly, the superior safety profile of buprenorphine reduces the treatment burden for the patient, with more flexible dosing schedules and earlier provision of take-home prescriptions than methadone.[4] Given the evidence, and continuing opioid overdose crisis, widespread implementation and utilisation of evidence-based buprenorphine for OUD would maximize its benefit in the population. While approved for use in Canada since 2007 without any required exemptions for physicians,[5,6] implementation of buprenorphine has not been optimized. In British Columbia and Ontario, more than twice as many patients on OAT receive methadone compared with buprenorphine,[7,8] while many more may need treatment and not be engaged using either medication.

The body of literature relevant to the underuse of buprenorphine for OUD suggests a range of barriers, related to patients, healthcare professionals, organizations, and system level policies. Numerous factors such as patient preferences,[9,10] insufficient prescriber knowledge,[11-13]

inadequate time or resources,[11,12,14,15] institutional support,[16] stigma,[11,12] concern of diversion,[17-19] insurance coverage,[20] geographic barriers,[21] and limited numbers of prescribers[22,23] have been described as causes of limited access and use of buprenorphine. Though several barriers have been identified, there have been few studies that have explored and characterised these factors using theory. Three current systematic reviews of barriers to OAT are registered in PROSPERO,[24-26] of which one focuses on adolescents[25] and two focus on specific professional groups including pharmacists and physicians.[24,26] Furthermore, two of the reviews focus on OAT generally, including methadone.[24,25] To our knowledge, no existing research addresses the barriers and facilitators at multiple levels, and specific to buprenorphine use. Consequently, the literature on barriers and facilitators to buprenorphine use remains narrow in scope and under-theorized. Behaviour change theories and implementation frameworks can be effective tools to identify key behavioural influences related to adoption of evidence-based practices and potential strategies to address them.[27] A theory-informed approach to understanding implementation problems related to buprenorphine use can guide analysis of factors at multiple levels. This information can help to identify effective strategies that address barriers and leverage facilitators, which may ultimately reduce mortality during an opioid crisis.

This study addresses the question: What are the barriers and facilitators to buprenorphine use at the patient, healthcare professional, organization, and system level, experienced by people with a diagnosis of opioid use disorder or professionals involved in their care? The specific aims of this scoping review are to: (1) characterise the barriers and facilitators to buprenorphine use experienced by patients, healthcare professionals, organizations, and healthcare systems reported in the peer-reviewed and grey literature, and (2) identify gaps in the literature to inform future implementation practice. We will use the Theoretical Domains Framework (TDF)[27] as a

behaviour change theory to guide our review and we will apply an integrated knowledge translation (iKT) approach,[28] engaging knowledge users including harm reduction workers and people with lived experience of drug use (including opioid use), health system leaders and educators, primary care and addiction medicine prescribers, health service researchers, implementation science methodologists, and knowledge mobilization specialists throughout the study as members of the project team.

Methods and analysis

Due to the breadth of the literature on barriers and facilitators of buprenorphine use at multiple levels, a scoping review is an appropriate approach to address the broad aims of this study. Our scoping review methodology will follow the framework developed by Arksey and O'Malley[29] and enhanced by Levac et al.[30] and the Joanna Briggs Institute,[31] and includes five of the six outlined stages.[29] The optional sixth stage of consultations will be carried out in another phase of our research; however, we will have knowledge user involvement on the project team throughout. Our reporting will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping reviews (PRISMA-ScR) to ensure quality and transparency of the methods and results described in our review;[32] and for the protocol, see the accompanying Research Checklist - Preferred reporting items for systematic review and meta-analysis protocols, PRISMA-P. Our study does not require ethics approval since the proposed methodology consists of a review of publicly available peer-reviewed and grey literature. We have also registered this protocol in Open Science Framework (osf.io/mwctz; June 4, 2019). We will conduct the scoping review between June 2019 and March 2020, with preparation in May 2019 involving an initial assessment of search results and the application of selection criteria between reviewers.

Our objectives are to: 1) systematically scope the literature; 2) map barriers and facilitators at multiple levels according to the 14 theoretical domains of the TDF; and 3) identify gaps in the literature. We selected the TDF to inform our analysis because it has been used extensively in implementation research to identify barriers and facilitators to change (e.g., uptake of new treatments) among healthcare professionals and patients.[33] The TDF is a synthesis of thirty-three theories relevant to behaviour change into twelve domains, and then revised to fourteen domains, that influence behaviour change: knowledge; skills; social/professional role and identity; beliefs about capabilities; optimism; beliefs about consequences; reinforcement; intentions; goals; memory, attention, and decision processes; environmental context and resources; social influences; emotion; behavioural regulation.[27] The domains of the TDF comprehensively account for individual, social, and environmental level influences on behavior.

Additionally, the fourteen domains of the TDF link to the core dimension of the Behaviour Change Wheel (BCW), in which capability, opportunity, and motivation (COM-B) are conceptualised as the three interacting conditions that generate behaviour. Linkage to the BCW can guide the selection of intervention functions, policy categories, and behaviour change techniques (i.e., the active component on a behaviour change intervention)[34,35] to overcome barriers and enhance facilitators.

Search strategy

First, we will search MEDLINE, Embase, PsycINFO, CINAHL, and SociINDEX electronic databases for peer-reviewed literature using a comprehensive search strategy from inception to 2019. Two research librarians at Public Health Ontario (PHO) developed the search strategy in MEDLINE, which was then peer-reviewed by other members of PHO Library

Services (See Supplement 1). Key search concepts included buprenorphine, opioid agonist treatment, and barriers and facilitators. Due to its comprehensive search functions, the search strategy was first developed for MEDLINE, and will be modified for use in the other databases. We will review the first 10 search results per year between 2019 and 2009 to ensure that the search strategy is identifying relevant titles, and captures all sample articles identified prior to the search. The search strategy will include both English and French language publications, due to long-term experience with buprenorphine prescribing practices in France.[36]

Second, we will conduct a grey literature search following PHO grey literature standards where fidelity to the academic literature search is maintained within the constraints of our chosen records. The results and strategies for each source will be reported on PHO Grey Literature reporting form. We will search Google, websites of key organizations (e.g., Health Quality Ontario), and two or more custom search engines that capture national and international government and non-government organizations in the areas of health and public health, and we will review the first 100 results. If no French records were identified, we will perform a specific search in Google with a French extension and using French terms. This is to ensure we capture lessons learned from the context in France, in which there has been long-term and widespread use of buprenorphine among healthcare professionals.[36] Prior to analysis, searches for the peer-reviewed and grey literature will be re-run to ensure that the most current available information is captured. Third, we will screen the reference lists of all included articles, search PROSPERO for relevant systematic reviews using the term "buprenorphine" and contact registered study authors, and ask knowledge users on the project team for relevant records.[24-26]

Eligibility criteria

English and French-language peer-reviewed and grey literature records will be eligible for inclusion if they: 1) aim to examine barriers and facilitators to buprenorphine use; 2) include study participants (including all age groups) with a diagnosis of OUD, opioid dependence, or currently on buprenorphine, as well as professionals involved in their care; 3) describe barriers or facilitators to buprenorphine use at the patient/caregiver, healthcare professional, organization or system level; and 4) use qualitative (e.g., interviews, focus groups, questionnaires), quantitative (e.g., cohort, case control, randomized controlled trials, questionnaires) or systematic review study designs. There will be no restrictions on the clinical care setting used in the study. Articles with no research method examining barriers and facilitators will be excluded (e.g., narrative reviews, commentary articles, guideline documents without systematic methods for literature synthesis). We will also exclude studies that combine barriers and facilitators for both buprenorphine and methadone together, as we aim specifically to describe those most relevant to buprenorphine.

Study selection

Two reviewers will independently screen search results and apply the eligibility criteria to titles and abstracts. A calibration exercise will be conducted after screening the first 100 results or until sufficient agreement is achieved (80% inter-rater agreement) to ensure reliability of source selection for inclusion, to pilot test the application of the eligibility criteria, and to establish a common understanding of the criteria. We will refine the eligibility criteria if there is low agreement on certain conditions or if limited records are identified for each level.

Both reviewers will independently screen titles and abstracts of eligible articles with the refined criteria, and relevant records will undergo a full-text review that follows the same

process as the title and abstract screening including calibration. Discrepancies will be addressed through consensus discussion or involvement of a third reviewer. We will screen reference lists and relevant records identified by knowledge users in a similar manner. It is likely that the broad inclusion of barriers and facilitators at multiple levels will generate extensive search results that will need to be managed to the scope of our resources and capacity for this project. For example, in preliminary communication with an author of an ongoing systematic review in PROSPERO, the research team expects to include over 100 primary studies [PROSPERO 2018 CRD42018086835; personal communication]. To manage the number and scope of included studies, we will select and use systematic review level evidence, and exclude the primary literature included in the systematic review if there is alignment with our research question and search strategy.

Data charting process

Data will be abstracted into a Microsoft Excel spreadsheet table. The data items are outlined in Table 1.

Table 1. Data items

Data items	**Description**
Reference ID number	ID number in citation management software
Author (s)	First author
Year of publication	Article year
Geographic location	In which country/city was the study conducted
Study design	The study design as defined by authors
Study setting	Where did the study take place
Population and sample size	Number and characteristics of participants of the study
Study aims/purpose	The aims of the study as defined by the author

Intervention description	Characteristics of the buprenorphine intervention described by the author (may include no direct intervention in the study e.g., survey of attitudes)
Outcomes	How the authors measured outcomes and the main results
Barriers to the intervention at different levels	Factors that may have reduced use of buprenorphine at the level of the patient, healthcare professional, organization, and healthcare system level
Facilitators to the intervention at different levels	Factors that may have enabled use of buprenorphine at the level of the patient, healthcare professional, organization, and healthcare systems
Theoretical basis	If applicable, theories and frameworks described in the study for the categorization of barriers and facilitators
Study limitations	Authors' reported gaps and limitations of the study

Two reviewers will independently extract data from 10 records included in the published (n=5) and grey literature search (n=5) to ensure consistency in how the relevant data is extracted and that there is common understanding of the categories and how to use the form. We will sample in sets of five until 80% inter-rater agreement is achieved across all items. Additionally, the principal investigator will review the data, and refine or add categories as needed. Following testing, one reviewer will independently read and extract data from all included records, and a second reviewer will independently verify 20% of the records for reliability. Discrepancies in the extracted information will be resolved through discussion with the principal investigator. Data extraction will be an iterative process whereby the table will be reviewed and revised to include feedback from knowledge users as well as emerging themes from the literature that are not captured in the table. In line with the scoping review methodology and the aims of our project, we will not perform critical appraisal and risk of bias assessment of included records.[29]

Data synthesis

For our second objective, we will code the barriers and facilitators extracted from the literature to the constructs included and defined in the domains of the TDF. Two project team members will analyze and code 10% of the data table into the domains of the TDF using pre-determined definitions. If insufficient detail is provided to map barriers and facilitators to the TDF domains, we will use components of the COM-B model to which the TDF are linked.[37] If the authors of an included study have categorized their findings according to the TDF or COM-B, we will use the author's categorizations, and also note the methodology used by the authors. Codes will be assigned to barriers and facilitators that do not align with the TDF or COM-B. The TDF domains and sub-domains within them, COM-B, and newly generated codes will be used to develop a coding framework. To ensure validity and credibility, the broader project team will be involved in a consensus discussion on the coding framework. Upon reaching consensus, coding will be applied by two team members to the remaining extracted data, and an inter-rater exercise will be completed to achieve 80% agreement. We will provide a descriptive summary highlighting the most frequent themes within each level. When applicable and useful, we will also use frequency analysis to provide a numerical summary of the charted data. For example, study characteristics of the included records (e.g., design, participants, and settings) will largely be described using frequencies. Records drawing from the same study dataset will be treated as one unit of analysis.

For our third objective, the TDF analysis of the barriers and facilitators at different levels will facilitate the process of identifying gaps in the literature. We will examine the domains of the TDF in which there are none or few barriers and facilitators identified. The paucity of identified barriers and facilitators within these domains may represent areas which are not

relevant for buprenorphine use or where a gap in the literature may exist. Non-coded domains will be discussed with the project team to prompt for examples of barriers and facilitators that were not captured in the literature. In addition, we will analyze the charted data on the study limitations, as described by authors, to characterize areas for further research. The proposed data synthesis plan and its alignment with each of the study objectives are presented in Table 2.

Table 2. Synthesis of results

Study objective	Data items	Reporting
To identify the barriers and facilitators to buprenorphine use experienced by patients, healthcare professionals, or within organizations, and healthcare systems	Reported factors that reduced or facilitated use of buprenorphine at the level of the patient, healthcare professional, organization, and healthcare system level	The number of articles identified that report barriers or facilitators at each level.
		The number of articles that report barriers or facilitators by domain of the TDF and COM-B model across the levels.
		Description of the types of barriers or facilitators at each level according to the domains of the TDF and COM-B model, and compare prevalent barriers and facilitators between levels.
		The number of articles that report barriers or facilitators that did not align with the domains of the TDF and a description of these barriers or facilitators.
To identify gaps in the literature	Authors' reported limitations and gaps	Description of existing gaps in the literature and areas for future research and evaluation.
		Description of the domains of the TDF which had none or few coded barriers or facilitators.

Patient and public involvement

The research team includes people with lived experience of substance use and individuals who support people with engagement in treatment for opioid use disorder. Further, several team members work closely with people who use drugs in the context of clinical work or community-based research. These members have provided guidance on designing the scoping review, as part of a larger implementation evaluation study.

Ethics and dissemination

Our protocol follows a rigorous methodology, using a theory-based approach that provides for systematic understanding of the factors contributing to underuse of buprenorphine as an evidence-based treatment for OUD. Our process for analysis will generate a list of barriers and facilitators mapped to the domains of the TDF and COM-B (when applicable) that can be further linked to evidence-based strategies for change to improve use and access. Representation of people who use drugs and practice at all levels on the project team will increase the potential for our findings from the literature and mapping is valid, reliable, and relevant. Although research ethics board is not required for our study, engagement with people who use drugs will also mitigate the potential for our stigmatized beliefs to be reflected in work. Further consultation and understanding of barriers and facilitators in the Canadian context using in-depth interviews and group consultations with representatives from each level will occur in the next phase of this work.

Informed by the Knowledge-to-Action framework,[38] our dissemination strategy will focus on developing tailored activities to meet the needs of diverse knowledge user audiences.

First, dissemination to academic audiences will occur with the preparation of a scoping review manuscript to be submitted to an open-access journal. To supplement the manuscript, we will create summaries using multiple formats that are accessible to a broader set of knowledge users including, online visual and written summaries, webinars, interactive workshops, and conference presentations. All summaries that are developed will contain the link to the open-access journal, and be posted on the Public Health Ontario website and social media page that reaches approximately 27,000 followers.

This scoping review will contribute to the literature the first comprehensive understanding of the multiple levels of barriers and facilitators to buprenorphine use to advance the design and implementation of buprenorphine delivery in various settings. This work will constitute the first step in a multi-phase project aimed at evaluating the implementation of buprenorphine in Canada. Our results can enable healthcare professionals, researchers, organizations, and system leaders to identify population-level strategies that address barriers and enhance facilitators to improve treatment access. Doing so is critical as this evidence-based treatment is a vital component of our response to reduce opioid-related mortality during the largest drug overdose crisis in North America.

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Declarations

Authors' contributions: PL, KC, CS, AMB, ST, EM, KA, EG, MH, HM, SS participated in the development of the protocol for this project. BP developed and conducted the search. PL and TK drafted the manuscript and all authors revised it. All authors read and approved the final manuscript.

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Data availability statement: Data are not available as this manuscript refers to our study protocol which has not yet been completed.

Additional File: Supplement 1 (pdf): Full electronic search strategy for Ovid MEDLINE. This file includes the full search strategy and results for Medline, and adapted for other databases.

Word Count: 2858

Supplement 1. Full electronic search strategy for OVID MEDLINE

The following search was designed by Public Health Ontario (PHO) Library Services in Ovid MEDLINE and then adapted to the Ovid platform databases Embase and PsycINFO, and the EBSCO host databases CINAHL, and SocINDEX, using subject headings and search fields specific to those databases.

Table 1.Search strategy in Ovid MEDLINE (1946 to April 15, 2019)

#	Searches	Results
1	Buprenorphine, Naloxone Drug Combination/	233
2	(buprenorphine or suboxone or subutex).ti.	3667
3	opiate addiction/ or opiate substitution treatment/ or narcotic antagonist/	24746
4	((opioid* or opiate*) adj3 (agonist* or dependen* or disorder* or maintenance or substitut* or treatment* or therap*)).ti,ab,kw.	23800
5	buprenorphine/ or (buprenorphine or suboxone or subutex).ab,kw. or (52485-79-7 or 53152-21-9).rn.	6764
6	5 and (3 or 4)	3846
7	1 or 2 or 6	5508
8	attitude/ or attitude to health/ or awareness/ or consumer health information/ or habit/ or health behavior/ or health education/ or health literacy/ or help seeking behavior/ or motivation/ or perception/ or personal autonomy/ or satisfaction/ or exp self concept/ or social behavior/ or exp "social aspects and related phenomena"/ or self control/ or social discrimination/ or social competence/ or time/ or time factor/	1620486
9	exp "cost"/ or economics/ or pharmacoeconomics/ or exp insurance/ or exp health insurance/ or exp reimbursement/ or fee/	394599
10	exp health care delivery/ or health care organization/ or exp health service/ or economic model/ or resource allocation/	2605283
11	government/ or health care policy/ or medical care/ or exp medicaid/ or exp medicare/ or policy/ or public policy/	101965
12	health personnel attitude/ or medication compliance/ or patient attendance/ or ambulatory care/ or patient attitude/ or patient compliance/ or patient dropout/ or patient education/ or patient participation/ or patient preference/ or patient satisfaction/ or doctor patient relation/ or professional-patient relationship/ or patient referral/ or treatment refusal/	464331
13	(access* or accept* or adverse effect* or afford* or approach* or attitude* or aware* or barrier* or belief* or challenge* or cost* or coverage or denial* or discriminat* or educat* or efficien* or enabl* or facilitat* or fear* or financ* or formularies or formulary or gender or harass* or incarcerat* or induct* or inefficien* or insurance or interaction* or knowledge or law or laws or "lessons learn*" or Medicaid or Medicare or motivat* or office-based or outreach or perception* or perspective* or (pattern* adj3 prescrib*) or pay* or pharmacoeconomic* or polic* or preferen* or promot* or refus* or refer* or regulat* or resource* or side effect* or social or stigma* or support* or	12346029

	sustainab* or threshold or time* or train* or willingness or worry*).ti,ab,kw.	
14	or/8-13	14172121
15	7 and 14	3897
16	(exp Africa/ or exp Asia/ or exp "South and Central America"/ or exp Mexico/ or developing country/) not (North America/ or Canada/ or United States/ or exp "Australia and New Zealand"/ or exp Europe/ or developed country/)	942835
17	15 not 16	3822
18	(exp animal/ or animal experiment/ or nonhuman/) not exp human/	4569638
19	17 not 18	3289
20	limit 19 to (english or french)	3104

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Line and Page No.
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1-2; Pg. 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3; Pg. 5
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	6-46; Pg. 1-3 1-5; Pg. 3
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	2-5; Pg. 25
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	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	6-8; Pg. 25
Sponsor	5b	Provide name for the review funder and/or sponsor	6-8; Pg. 25
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3-16; Pg. 7
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	17-23; Pg. 7
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	1-13; Pg. 11
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	18-22; Pg. 9 1-21; Pg. 10
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	Supplement 1

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	N/A
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)	14-22; Pg. 11 1-11; Pg. 12
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	12-15; Pg. 12 1-13; Pg. 13
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	Table 1; Pg. 12
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	N/A for scoping review
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	N/A for scoping review
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	N/A
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	N/A
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	N/A
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	1-23; Pg. 14 1-6, Table 2; Pg. 15
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	N/A for scoping review
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	N/A for scoping review

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

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Barriers and facilitators to buprenorphine use for opioid agonist treatment: protocol for a scoping review

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TITLE: Barriers and facilitators to buprenorphine use for opioid agonist treatment: protocol for a scoping review

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Abstract

Introduction: In the context of the opioid crisis in North America, the benefits of evidence-based opioid agonist treatments (OAT) such as buprenorphine/naloxone have not been optimized due to low uptake. Numerous factors contribute to the underuse of buprenorphine, and theory-informed approaches to identify and address implementation barriers and facilitators are needed. This scoping review aims to characterise the barriers and facilitators at the patient, healthcare professional, organization, and system level according to the Theoretical Domains Framework (TDF), and identify gaps to inform practice and policy.

Methods and analysis: We will conduct a scoping review using established methods and follow the Preferred Reporting Items for Systematic Reviews and Meta-analysis extension for scoping reviews (PRISMA-ScR). We will identify English and French-language peer-reviewed literature by searching five electronic bibliographic databases (MEDLINE, Embase, PsycINFO, CINAHL, and SociINDEX), from inception, and use Google, websites of key organizations, and two or more custom search engines to identify relevant grey literature. Eligible records will be quantitative or qualitative studies that examine barriers and facilitators to buprenorphine use at the patient, healthcare professional, organization, and system level, and involve participants with diagnosis of opioid use disorder or professionals involved in their care. Two reviewers will be involved in independently screening, reviewing, and charting the data and calibration exercises will be conducted at each stage. We will conduct descriptive analysis for the charted data, and deductively code barriers and facilitators using the TDF.

Ethics and dissemination: As a scoping review of the literature, this study does not require ethics approval. Our dissemination strategy will focus on developing tailored activities to meet

the needs of diverse knowledge user audiences. Barriers and facilitators mapped to the TDF can be linked to evidence-based strategies for change to improve buprenorphine use and access, and enable practice to reduce opioid-related harms.

Registration: Open Science Framework (osf.io/mwctz; June 4, 2019)

Keywords: opioid agonist treatment; barriers and facilitators, scoping review, buprenorphine

Article summary

Strengths and limitations of the study

- This scoping review aims to understand multiple levels of barriers and facilitators to buprenorphine use to advance the design and implementation of buprenorphine delivery in various settings
- Our methodology will follow the framework developed by Arksey and O'Malley and enhanced by Levac et al. and the Joanna Briggs Institute..
- The Theoretical Domains Framework enables our analysis to comprehensively account for individual, social, and environmental level influences on behavior.
- To manage the number of included studies, we will use systematic review level evidence and exclude overlapping primary literature if there is alignment with our question and search strategy.
- Our search may be limited in capturing newer innovations in practice, such as low-threshold models or recent buprenorphine formulations (e.g., depot buprenorphine)

Introduction

Fatal and non-fatal opioid poisonings continue to escalate in North America, with an estimated 47,600 opioid-related deaths in the United States (U.S.)[1] and more than 10,000 in Canada between January 2016 and September 2018.[2] In response, strategies aimed at preventing and reducing opioid-related deaths have been established, including access to evidence-based treatment options for opioid use disorder (OUD). In the United States, approximately 7% of individuals with OUD receive specialty care with approved medications for OUD,[3] while the extent of the gap in treatment in Canada has not been characterised. Opioid agonist treatments (OAT) such as buprenorphine/naloxone have demonstrated effectiveness in reducing opioid-related morbidity and mortality. Further, the superior safety and side effect profile of buprenorphine and equivalent efficacy compared to methadone has led it to be the preferred first-line treatment for OUD in Canada.[4] Importantly, the superior safety profile of buprenorphine reduces the treatment burden for the patient, with more flexible dosing schedules and earlier provision of take-home prescriptions than methadone.[4] Given the evidence, and continuing opioid overdose crisis, widespread implementation and utilisation of evidence-based buprenorphine for OUD would maximize its benefit in the population. While approved for use in Canada since 2007 without any required exemptions for physicians,[5,6] implementation of buprenorphine including availability, accessibility, and uptake, have not been optimized to achieve higher rates of use among eligible people. In British Columbia and Ontario, more than twice as many patients on OAT receive methadone compared with buprenorphine,[7,8] while many more may need treatment and not be engaged using either medication.

The body of literature relevant to the underuse of buprenorphine for OUD suggests a range of barriers, related to patients, healthcare professionals, organizations, and system level

policies. Numerous factors such as patient preferences,[9,10] insufficient prescriber knowledge,[11-13] inadequate time or resources,[11,12,14,15] institutional support,[16] stigma,[11,12] concern of diversion,[17-19] insurance coverage,[20] geographic barriers,[21] and limited numbers of prescribers[22,23] have been described as causes of limited access and use of buprenorphine. Though several barriers have been identified, there have been few studies that have explored and characterised these factors using theory. Three current systematic reviews of barriers to OAT are registered in PROSPERO,[24-26] of which one focuses on adolescents[25] and two focus on specific professional groups including pharmacists and physicians.[24,26] Furthermore, two of the reviews focus on OAT generally, including methadone.[24,25] To our knowledge, no existing research addresses the barriers and facilitators at multiple levels, and specific to buprenorphine use. Consequently, the literature on barriers and facilitators to buprenorphine use remains narrow in scope and under-theorized. Behaviour change theories and implementation frameworks can be effective tools to identify key behavioural influences related to adoption of evidence-based practices and potential strategies to address them.[27] A theory-informed approach to understanding implementation problems related to buprenorphine use can guide analysis of factors at multiple levels. There is a high potential to expand access to OAT by addressing barriers and leveraging facilitators specific to the context of buprenorphine - it is the preferred first-line treatment due to safety reasons, and considerations may differ between treatments (e.g., initiation protocols, risk of precipitated withdrawal, full- or partial-agonist pharmacology), calling for specific attention to buprenorphine. This information can help to identify effective strategies that address barriers and leverage facilitators, which may ultimately reduce mortality during an opioid crisis. While our research team is based in Canada, this scoping review will be of interest to international

audiences as it includes international literature, and facilitators/ barriers to implementation may be common across jurisdictions (e.g., stigma perceived at the patient level).

This study addresses the question: What are the barriers and facilitators to buprenorphine use at the patient, healthcare professional, organization, and system level, experienced by people with a diagnosis of opioid use disorder or professionals involved in their care? The specific aims of this scoping review are to: (1) characterise the barriers and facilitators to buprenorphine use experienced by patients, healthcare professionals, organizations, and healthcare systems reported in the peer-reviewed and grey literature, and (2) identify gaps in the literature to inform future implementation practice. We will use the Theoretical Domains Framework (TDF)[27] as a behaviour change theory to guide our review and we will apply an integrated knowledge translation (iKT) approach,[28] engaging knowledge users including harm reduction workers and people with lived experience of drug use (including opioid use), health system leaders and educators, primary care and addiction medicine prescribers, health service researchers, implementation science methodologists, and knowledge mobilization specialists throughout the study as members of the project team. Throughout our protocol we use the term OAT as it is consistent with the current national clinical practice guideline for treatment of opioid use disorder opioid use disorder[4]. This term is also used in other jurisdictions, such as Australia, while terms in other jurisdictions vary, including "medications for opioid use disorder (MOUD)" in the United States,[29] and "opioid maintenance treatment" in Europe including the United Kingdom.[30,31]

Methods and analysis

Due to the breadth of the literature on barriers and facilitators of buprenorphine use at multiple levels, a scoping review is an appropriate approach to address the broad aims of this study. [32] Systematic review methods are typically used for understanding outcomes across multiple similar studies; a scoping review can assess the need or feasibility of a systematic review.[32,33] Our scoping review methodology will follow the framework developed by Arksey and O'Malley[32] and enhanced by Levac et al.[34] and the Joanna Briggs Institute,[35] and includes five of the six outlined stages.[32] The optional sixth stage of consultations will be carried out in another phase of our research; however, we will have knowledge user involvement on the project team throughout. Our reporting will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping reviews (PRISMA-ScR) to ensure quality and transparency of the methods and results described in our review;[36] and for the protocol, see the accompanying Research Checklist - Preferred reporting items for systematic review and meta-analysis protocols, PRISMA-P. Our study does not require ethics approval since the proposed methodology consists of a review of publicly available peer-reviewed and grey literature. We have also registered this protocol in Open Science Framework (osf.io/mwctz; June 4, 2019). We will conduct the scoping review between June 2019 and March 2020, with preparation in May 2019 involving an initial assessment of search results and the application of selection criteria between reviewers.

Our objectives are to: 1) systematically scope the literature; 2) map barriers and facilitators at multiple levels according to the 14 theoretical domains of the TDF; and 3) identify gaps in the literature. We selected the TDF to inform our analysis because it has been used extensively in implementation research to identify barriers and facilitators to change (e.g., uptake of new treatments) among healthcare professionals and patients.[37] The TDF is a synthesis of

thirty-three theories relevant to behaviour change into twelve domains, and then revised to fourteen domains, that influence behaviour change: knowledge; skills; social/professional role and identity; beliefs about capabilities; optimism; beliefs about consequences; reinforcement; intentions; goals; memory, attention, and decision processes; environmental context and resources; social influences; emotion; behavioural regulation.[27] The domains of the TDF comprehensively account for individual, social, and environmental level influences on behavior.

Additionally, the fourteen domains of the TDF link to the core dimension of the Behaviour Change Wheel (BCW), in which capability, opportunity, and motivation (COM-B) are conceptualised as the three interacting conditions that generate behaviour. Linkage to the BCW can guide the selection of intervention functions, policy categories, and behaviour change techniques (i.e., the active component on a behaviour change intervention)[38,39] to overcome barriers and enhance facilitators.

Search strategy

First, we will search MEDLINE, Embase, PsycINFO, CINAHL, and SociINDEX electronic databases for peer-reviewed literature using a comprehensive search strategy from inception to 2019. Two research librarians at Public Health Ontario (PHO) developed the search strategy in MEDLINE, which was then peer-reviewed by other members of PHO Library Services (See Supplement 1).Key search concepts included buprenorphine, opioid agonist treatment, and barriers and facilitators. Due to its comprehensive search functions, the search strategy was first developed for MEDLINE, and will be modified for use in the other databases. We will review the first 10 search results per year between 2019 and 2009 to ensure that the search strategy is identifying relevant titles, and captures all sample articles identified prior to the

search. The search strategy will include both English and French language publications, due to long-term experience with buprenorphine prescribing practices in France.[40] Due to limited resources, we are unable to manage publications in other languages, and will not use automated translation tools that could introduce error due to the technical nature of the topic.[41-43] Non-English content represented a small proportion of all results retrieved in Medline (about 5%).

Second, we will conduct a grey literature search following PHO grey literature standards where fidelity to the academic literature search is maintained within the constraints of our chosen records. The results and strategies for each source will be reported on PHO Grey Literature reporting form. We will search Google, websites of key organizations (e.g., Health Quality Ontario), and two or more custom search engines that capture national and international government and non-government organizations in the areas of health and public health, and we will review the first 100 results. If no French records were identified, we will perform a specific search in Google with a French extension and using French terms. This is to ensure we capture lessons learned from the context in France, in which there has been long-term and widespread use of buprenorphine among healthcare professionals.[40] Prior to analysis, searches for the peer-reviewed and grey literature will be re-run to ensure that the most current available information is captured. Third, we will screen the reference lists of all included articles, search PROSPERO for relevant systematic reviews using the term "buprenorphine" and contact registered study authors, and ask knowledge users on the project team for relevant records.[24-26]

Eligibility criteria

English and French-language peer-reviewed and grey literature records will be eligible for inclusion if they: 1) aim to examine barriers and facilitators to buprenorphine use; 2) include

study participants (including all age groups) with a diagnosis of OUD, opioid dependence, or currently on buprenorphine, as well as professionals involved in their care; 3) describe barriers or facilitators to buprenorphine use at the patient/caregiver, healthcare professional, organization or system level; and 4) use qualitative (e.g., interviews, focus groups, questionnaires), quantitative (e.g., cohort, case control, randomized controlled trials, questionnaires) or systematic review study designs. There will be no restrictions on the clinical care setting used in the study. Articles with no research method examining barriers and facilitators will be excluded (e.g., narrative reviews, commentary articles, guideline documents without systematic methods for literature synthesis). We will also exclude studies that combine barriers and facilitators for both buprenorphine and methadone together, as we aim specifically to describe those most relevant to buprenorphine.

Study selection

Two reviewers will independently screen search results and apply the eligibility criteria to titles and abstracts. A calibration exercise will be conducted after screening the first 100 results or until sufficient agreement is achieved (80% inter-rater agreement) to ensure reliability of source selection for inclusion, to pilot test the application of the eligibility criteria, and to establish a common understanding of the criteria. We will refine the eligibility criteria if there is low agreement on certain conditions or if limited records are identified for each level.

Both reviewers will independently screen titles and abstracts of eligible articles with the refined criteria, and relevant records will undergo a full-text review that follows the same process as the title and abstract screening including calibration. Discrepancies will be addressed through consensus discussion or involvement of a third reviewer. We will screen reference lists

and relevant records identified by knowledge users in a similar manner. It is likely that the broad inclusion of barriers and facilitators at multiple levels will generate extensive search results that will need to be managed to the scope of our resources and capacity for this project. For example, in preliminary communication with an author of an ongoing systematic review in PROSPERO, the research team expects to include over 100 primary studies [PROSPERO 2018 CRD42018086835; personal communication]. To manage the number and scope of included studies, we will select and use systematic review level evidence, and exclude the primary literature included in the systematic review if there is alignment with our research question and search strategy.

Data charting process

Data will be abstracted into a Microsoft Excel spreadsheet table. The data items are outlined in Table 1. To account for differences in health systems, we will extract information available on the jurisdictional context of service delivery to the extent available in the data on geographic location and study setting.

Table 1. Data items

Data items	Description
Reference ID number	ID number in citation management software
Author (s)	First author
Year of publication	Article year
Geographic location	In which country/city was the study conducted (including context)
Study design	The study design as defined by authors
Study setting	Where did the study take place (including context)
Population and sample size	Number and characteristics of participants of the study

Study aims/purpose	The aims of the study as defined by the author
Intervention description	Characteristics of the buprenorphine intervention described by the author (may include no direct intervention in the study e.g., survey of attitudes)
Outcomes	How the authors measured outcomes and the main results
Barriers to the intervention at different levels	Factors that may have reduced use of buprenorphine at the level of the patient, healthcare professional, organization, and healthcare system level
Facilitators to the intervention at different levels	Factors that may have enabled use of buprenorphine at the level of the patient, healthcare professional, organization, and healthcare systems
Theoretical basis	If applicable, theories and frameworks described in the study for the categorization of barriers and facilitators
Study limitations	Authors' reported gaps and limitations of the study

Two reviewers will independently extract data from 10 records included in the published (n=5) and grey literature search (n=5) to ensure consistency in how the relevant data is extracted and that there is common understanding of the categories and how to use the form. We will sample in sets of five until 80% inter-rater agreement is achieved across all items. Additionally, the principal investigator will review the data, and refine or add categories as needed. Following testing, one reviewer will independently read and extract data from all included records, and a second reviewer will independently verify 20% of the records for reliability. Discrepancies in the extracted information will be resolved through discussion with the principal investigator. Data extraction will be an iterative process whereby the table will be reviewed and revised to include feedback from knowledge users as well as emerging themes from the literature that are not

captured in the table. In line with the scoping review methodology and the aims of our project, we will not perform critical appraisal and risk of bias assessment of included records.[32]

Data synthesis

For our second objective, we will code the barriers and facilitators extracted from the literature to the constructs included and defined in the domains of the TDF. Two project team members will analyze and code 10% of the data table into the domains of the TDF using pre-determined definitions. If insufficient detail is provided to map barriers and facilitators to the TDF domains, we will use components of the COM-B model to which the TDF are linked.[44] If the authors of an included study have categorized their findings according to the TDF or COM-B, we will use the author's categorizations, and also note the methodology used by the authors. Codes will be assigned to barriers and facilitators that do not align with the TDF or COM-B. The TDF domains and sub-domains within them, COM-B, and newly generated codes will be used to develop a coding framework. To ensure validity and credibility, the broader project team will be involved in a consensus discussion on the coding framework. Upon reaching consensus, coding will be applied by two team members to the remaining extracted data, and an inter-rater exercise will be completed to achieve 80% agreement. We will provide a descriptive summary highlighting the most frequent themes within each level. When applicable and useful, we will also use frequency analysis to provide a numerical summary of the charted data. For example, study characteristics of the included records (e.g., design, participants, and settings) will largely be described using frequencies. Records drawing from the same study dataset will be treated as one unit of analysis.

For our third objective, the TDF analysis of the barriers and facilitators at different levels will facilitate the process of identifying gaps in the literature. We will examine the domains of

the TDF in which there are none or few barriers and facilitators identified. The paucity of identified barriers and facilitators within these domains may represent areas which are not relevant for buprenorphine use or where a gap in the literature may exist. Non-coded domains will be discussed with the project team to prompt for examples of barriers and facilitators that were not captured in the literature. In addition, we will analyze the charted data on the study limitations, as described by authors, to characterize areas for further research. The proposed data synthesis plan and its alignment with each of the study objectives are presented in Table 2.

Table 2. Synthesis of results

Study objective	Data items	Reporting
To identify the barriers and facilitators to buprenorphine use experienced by patients, healthcare professionals, or within organizations, and healthcare systems	Reported factors that reduced or facilitated use of buprenorphine at the level of the patient, healthcare professional, organization, and healthcare system level	The number of articles identified that report barriers or facilitators at each level.
		The number of articles that report barriers or facilitators by domain of the TDF and COM-B model across the levels.
		Description of the types of barriers or facilitators at each level according to the domains of the TDF and COM-B model, and compare prevalent barriers and facilitators between levels.
		The number of articles that report barriers or facilitators that did not align with the domains of the TDF and a description of these barriers or facilitators.
To identify gaps in the literature	Authors' reported limitations and gaps	Description of existing gaps in the literature and areas for future research and evaluation.

		Description of the domains of the TDF which had none or few coded barriers or facilitators.

Patient and public involvement

The research team includes people with lived experience of substance use and individuals who support people with engagement in treatment for opioid use disorder. Further, several team members work closely with people who use drugs in the context of clinical work or community-based research. These members have provided guidance on designing the scoping review, as part of a larger implementation evaluation study.

Ethics and dissemination

Our protocol follows a rigorous methodology, using a theory-based approach that provides for systematic understanding of the factors contributing to underuse of buprenorphine as an evidence-based treatment for OUD. Our process for analysis will generate a list of barriers and facilitators mapped to the domains of the TDF and COM-B (when applicable) that can be further linked to evidence-based strategies for change to improve use and access. Representation of people who use drugs and practice at all levels on the project team will increase the potential for our findings from the literature and mapping is valid, reliable, and relevant. Although research ethics board is not required for our study, engagement with people who use drugs will also mitigate the potential for our stigmatized beliefs to be reflected in work. Further consultation and understanding of barriers and facilitators in the Canadian context using in-depth interviews and group consultations with representatives from each level will occur in the next phase of this work.

Informed by the Knowledge-to-Action framework,[45] our dissemination strategy will focus on developing tailored activities to meet the needs of diverse knowledge user audiences. First, dissemination to academic audiences will occur with the preparation of a scoping review manuscript to be submitted to an open-access journal. To supplement the manuscript, we will create summaries using multiple formats that are accessible to a broader set of knowledge users including, online visual and written summaries, webinars, interactive workshops, and conference presentations. All summaries that are developed will contain the link to the open-access journal, and be posted on the Public Health Ontario website and social media page that reaches approximately 27,000 followers.

This scoping review will contribute to the literature the first comprehensive understanding of the multiple levels of barriers and facilitators to buprenorphine use to advance the design and implementation of buprenorphine delivery in various settings. This work will constitute the first step in a multi-phase project aimed at evaluating the implementation of buprenorphine in Canada. Our results can enable healthcare professionals, researchers, organizations, and system leaders to identify population-level strategies that address barriers and enhance facilitators to improve treatment access. Doing so is critical as this evidence-based treatment is a vital component of our response to reduce opioid-related mortality during the largest drug overdose crisis in North America.

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Declarations

Authors' contributions: PL, KC, CS, AMB, ST, EM, KA, EG, MH, HM, SS participated in the development of the protocol for this project. BP developed and conducted the search. PL and TK drafted the manuscript and all authors revised it. All authors read and approved the final manuscript.

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Competing interests statement: All authors report a grant from the Canadian Institutes of Health Research during the development of the protocol. PL, TK, EM, BP report employment at Public Health Ontario. PL and CS report non-financial support from Adapt Pharma through in-kind donation of naloxone on an unrelated study.

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Data availability: All data relevant to the study are included in the article or uploaded as supplementary information.

Additional File: Supplement 1 (pdf): Full electronic search strategy for Ovid MEDLINE. This file includes the full search strategy and results for Medline, and adapted for other databases.

Word Count: 3137

Supplement 1. Full electronic search strategy for OVID MEDLINE

The following search was designed by Public Health Ontario (PHO) Library Services in Ovid MEDLINE and then adapted to the Ovid platform databases Embase and PsycINFO, and the EBSCO host databases CINAHL, and SocINDEX, using subject headings and search fields specific to those databases.

Table 1.Search strategy in Ovid MEDLINE (1946 to April 15, 2019)

#	Searches	Results
1	Buprenorphine, Naloxone Drug Combination/	233
2	(buprenorphine or suboxone or subutex).ti.	3667
3	opiate addiction/ or opiate substitution treatment/ or narcotic antagonist/	24746
4	((opioid* or opiate*) adj3 (agonist* or dependen* or disorder* or maintenance or substitut* or treatment* or therap*)).ti,ab,kw.	23800
5	buprenorphine/ or (buprenorphine or suboxone or subutex).ab,kw. or (52485-79-7 or 53152-21-9).rn.	6764
6	5 and (3 or 4)	3846
7	1 or 2 or 6	5508
8	attitude/ or attitude to health/ or awareness/ or consumer health information/ or habit/ or health behavior/ or health education/ or health literacy/ or help seeking behavior/ or motivation/ or perception/ or personal autonomy/ or satisfaction/ or exp self concept/ or social behavior/ or exp "social aspects and related phenomena"/ or self control/ or social discrimination/ or social competence/ or time/ or time factor/	1620486
9	exp "cost"/ or economics/ or pharmacoeconomics/ or exp insurance/ or exp health insurance/ or exp reimbursement/ or fee/	394599
10	exp health care delivery/ or health care organization/ or exp health service/ or economic model/ or resource allocation/	2605283
11	government/ or health care policy/ or medical care/ or exp medicaid/ or exp medicare/ or policy/ or public policy/	101965
12	health personnel attitude/ or medication compliance/ or patient attendance/ or ambulatory care/ or patient attitude/ or patient compliance/ or patient dropout/ or patient education/ or patient participation/ or patient preference/ or patient satisfaction/ or doctor patient relation/ or professional-patient relationship/ or patient referral/ or treatment refusal/	464331
13	(access* or accept* or adverse effect* or afford* or approach* or attitude* or aware* or barrier* or belief* or challenge* or cost* or coverage or denial* or discriminat* or educat* or efficien* or enabl* or facilitat* or fear* or financ* or formularies or formulary or gender or harass* or incarcerat* or induct* or inefficien* or insurance or interaction* or knowledge or law or laws or "lessons learn*" or Medicaid or Medicare or motivat* or office-based or outreach or perception* or perspective* or (pattern* adj3 prescrib*) or pay* or pharmacoeconomic* or polic* or preferen* or promot* or refus* or refer* or regulat* or resource* or side effect* or social or stigma* or support* or	12346029

	sustainab* or threshold or time* or train* or willingness or worry*).ti,ab,kw.	
14	or/8-13	14172121
15	7 and 14	3897
16	(exp Africa/ or exp Asia/ or exp "South and Central America"/ or exp Mexico/ or developing country/) not (North America/ or Canada/ or United States/ or exp "Australia and New Zealand"/ or exp Europe/ or developed country/)	942835
17	15 not 16	3822
18	(exp animal/ or animal experiment/ or nonhuman/) not exp human/	4569638
19	17 not 18	3289
20	limit 19 to (english or french)	3104

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Line and Page No.
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1-2; Pg. 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3; Pg. 5
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	6-46; Pg. 1-3 1-5; Pg. 3
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	2-5; Pg. 25
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	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	6-8; Pg. 25
Sponsor	5b	Provide name for the review funder and/or sponsor	6-8; Pg. 25
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3-16; Pg. 7
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	17-23; Pg. 7
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	1-13; Pg. 11
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	18-22; Pg. 9 1-21; Pg. 10
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	Supplement 1

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	N/A
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)	14-22; Pg. 11 1-11; Pg. 12
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	12-15; Pg. 12 1-13; Pg. 13
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	Table 1; Pg. 12
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	N/A for scoping review
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	N/A for scoping review
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	N/A
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	N/A
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	N/A
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	1-23; Pg. 14 1-6, Table 2; Pg. 15
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	N/A for scoping review
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	N/A for scoping review

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (2015 when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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