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Harm reduction and pharmacotherapeutic interventions for persons with substance use disorders: A protocol for a systematic review of reviews

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INTRODUCTION

Problematic substance use is the harmful use of psychoactive substances such as alcohol and drugs (WHO, 2017). This use can lead to a substance use disorder (SUD): a clinically diagnosed condition where an individual develops a physical or psychological dependence to the particular substance, has difficulties in controlling its use, and causes clinically and functionally significant impairment, such as health problems, disability, and failure to meet major responsibilities (SAMHSA, 2015). Common SUDs include alcohol use disorder, tobacco use disorder, cannabis use disorder, stimulant use disorder, hallucinogen use disorder and opioid use disorder (SAMHSA, 2015). Addressing SUDs may require a multifaceted approach, including harm reductions strategies and pharmacotherapeutic treatment. Harm reduction interventions aim to mitigate the negative consequences of the use of substances on the individual and on public health (Bosque-Pros et al., 2016). Pharmacotherapeutic agents may assist in substitution therapy, maintenance, or in cases of overdose. In order to promote the implementation of harm reduction strategies and pharmacotherapeutic treatment for SUDs into the primary care of vulnerable or marginalized populations, it is important to assess their effects on a range of health and social outcomes.

A systematic review on the effectiveness of interventions for homeless individuals is being conducted to direct the Inner City Health Associates (ICHA) evidence-based guidelines on homeless health (Pottie et al., 2018). Substance use and SUDs are disproportionately high among homeless populations and people who are vulnerably housed (Palepu et al., 2013). Homelessness can lead to, and also be a result of, substance use (Vangeest et al, 2002). While literature exists on harm reduction and pharmacotherapeutic interventions, many of these studies are not specific to homeless populations, and are thus not captured by existing reviews or experimental studies. To better understand the potential impact of harm reduction and pharmacotherapeutic interventions in marginalized populations such as those experiencing homelessness, it is necessary to examine their effectiveness among generalized SUD populations.

This protocol outlines the methodological process of a systematic review of reviews on the effectiveness of harm-reduction strategies and pharmacotherapeutic interventions on the health and social outcomes of people with substance use disorders. Our interventions of interest include supervised consumption facilities, managed alcohol programs (MAPs), and pharmacological interventions for opioid use disorders. The review resulting from this protocol will complement the concurrent review specific to homeless populations to develop the ICHA guidelines for providing social programs and healthcare services to homeless and vulnerable housed persons.

RATIONALE

There is research showing that people with SUDs have worse health and social outcomes compared to those who do not frequently use psychoactive substances (Podymow, 2006). Harm reduction is an approach aiming to reduce the adverse effects of substance use, without requiring abstinence (Tsemberis, 2004). Pharmacological interventions may be used as substitution therapy or in specialized cases such as overdose. In 2017, a systematic review of reviews looking at the effectiveness of interventions that affect health and the social determinants of health among marginalized populations was published (Luchenski, 2017). While this review reported on the effectiveness of pharmacological interventions such as opioid replacement therapy using methadone and buprenorphine, they only assessed a limited number of outcomes. Our review of reviews will analyze and synthesize the effectiveness of different harm-reduction and pharmacotherapeutic interventions on a wide

range of health and social outcomes. The review of these numerous outcomes will enable a better provision of care and implementation of policy in this area. Our systematic review will serve to inform policy and practice for medical and nursing professional organizations as well as health and social service organizations.

In addition to focusing on a broader scope of outcomes, our review is unique in its patient-centered approach. The interventions included in this review were prioritized as part of a national Delphi consensus process that included the views of 84 practitioners and 76 individuals with lived experience of homelessness from across Canada (Shoemaker et al., 2018). Individuals with lived experience, termed 'Community Scholars', form part of the review team, and assist in prioritizing patient-important outcomes in line with the GRADE approach followed in the overarching guideline project.

OBJECTIVES

The objective of this systematic review of reviews is to identify, appraise and synthesize the best available evidence on harm reduction and pharmacotherapeutic interventions to improve health, health services and social outcomes for people with substance use disorders.

METHODS

We will conduct a systematic review of reviews. The methodology for this review was developed based on criteria from the preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) Guidelines (Moher, 2015). This systematic review of reviews aims to inform ICHA guidance for the care of the homeless and vulnerably housed in a Canadian context. This protocol outlines the methods approach of the systematic review.

1. Research question

Our review aims to answer the following key question:

1. What are the effects of harm reduction and pharmacotherapeutic interventions (i.e. supervised consumption facilities, managed alcohol

programs and pharmacological interventions for opioid use disorders) on the health and social outcomes of people with substance use disorders?

2. Study design

We will include peer-reviewed systematic reviews and meta-analyses of primary studies that include studies with and without control groups. When we identify more than one version of a systematic review, the most recent one will be considered. We will also identify relevant reviews of reviews and will consider their included systematic reviews for eligibility. We will exclude reviews of qualitative studies and reviews which do not follow systematic methodology: research question, search selection and analysis. We will exclude grey literature.

3. Inclusion and exclusion criteria

See Table 1 for complete inclusion and exclusion criteria.

3.1. Population

This review will examine interventions targeting people with substance use disorders. We will include youth aged 16-24 and adults. We will exclude populations in prisons, as the prison setting is not generalizable to the rest of the population. We will only include populations of high-income countries to ensure applicability to the Canadian context.

3.2. Intervention

We will include reviews of three community-based harm reduction and pharmacotherapeutic interventions selected as part of a Delphi consensus process that engaged 76 people with lived experience of homelessness and 84 healthcare workers and researchers with professional experience in Canadian homelessness and health services (Shoemaker et al., 2018).

3.2.1. Supervised Consumption Facilities

Supervised consumption facilities are establishments where people who use drugs can consume privately sourced, pre-obtained drugs under medical supervision. These facilities often serve as a safe space for people who use substances.

3.2.2. Managed Alcohol Programs

Managed alcohol programs (MAPs) are programs where there is regulated provision of alcohol to help residents manage alcohol dependence. MAPs are staffed by healthcare professionals and people with lived experience, and typically also include shelter, medical assistance and social services.

3.2.3. Pharmacological interventions for opioid use disorders

Pharmacological interventions for opioid use disorders are opioid maintenance therapy, opioid substitution therapy, and overdose medications. These include, but are not limited to, buprenorphine/naloxone, naloxone, naltrexone, methadone and injectable diacetylmorphine (heroin). For the purpose of this review, detoxification only medications have been excluded.

3.3 Comparison

We will include systematic reviews that include studies with and without controls. We will compare our interventions to no intervention, standard intervention, alternative intervention or treatment as usual. We will exclude studies comparing different doses of the same medication for opioid use disorders.

3.4. Outcomes

In this protocol, we have identified and ranked all potential patient important outcomes according to GRADE methodology (Guyatt, 2011). Outcomes are ranked as critical, important but not critical, or limited importance for decision making. Only evidence on critical and important outcomes will be considered and reported on.

Studies must use validated measures and must report at least one of the following health and social outcomes in order to be included in this review. We expect to capture any potential benefits and harms within our outcomes.

The following 5 outcomes are those which were ranked as critical or important, and will be reported in our review:

1. **Substance use (critical outcome)**: The use of psychoactive substances including drugs and alcohol.
2. **Mental health (critical outcome)**: Mental health/psychiatric symptoms or diagnoses that affect mood, thinking and behaviour, including attempt or ideation of suicide.
3. **Mortality and morbidity (critical outcome)**: The number of deaths due to overdose and other substance-related causes, as well as any diseased state including comorbid infectious diseases.
4. **Access to care (important outcome):** Access to a range of health and social services. Includes availability of services, affordability of services, and utilization of services.
5. **Retention in treatment (important outcome):** The ability to maintain participants in intervention programs.

3.5. Setting

We will include interventions that take place in settings where the primary care of people with substance use disorders takes place. We also will include community based interventions provided in social service or shelter/supervised consumption locations, private or non-private clinics, hospital emergency rooms, outreach care, street patrols, and mobile care units. We will exclude all studies conducted in low and middle income countries.

4. Search strategy

A librarian will develop and peer-review a search strategy. The following electronic databases will be searched for systematic reviews: MEDLINE, Embase, PsycINFO, Joanna Briggs EBP, Cochrane database of SRs and the Database of abstracts of reviews of effects (DARE). There will be no date or language restrictions set for the search. The literature search results will be uploaded to a reference manager software package to facilitate the study selection process. See Table 2 for example search strategy.

5. Study screening and selection

Two review authors will independently screen titles and abstracts to identify relevant studies for full-text review and will independently screen full texts for final inclusion. Discrepancies will be resolved through discussion or, with help

from a third reviewer if necessary. We will contact authors of reviews once for missing information.

6. Data extraction

We will develop a standardised extraction sheet (see Table 3). Data will be extracted independently by two review authors using standardised extraction sheets. Discrepancies will be resolved by discussion or with help from a third reviewer if necessary. At a minimum we will extract (1) population, intervention, comparison and outcome elements of the research questions for interventional systematic reviews; (2) databases searched; (3) number of studies included in the systematic review; and (4) results.

7. Quality appraisal

Two review authors will independently assess the methodological quality of each review using the Assessment of Multiple Systematic Reviews (AMSTAR-II) tool (Shea, 2009). This will allow us to rate the overall quality of the reviews as high, moderate, low or critically low. Discrepancies in the ratings of the methodological reviews will be resolved by discussion or with help from a third reviewer if necessary. Quality assessment criteria will not be used to include or exclude studies but will be used to assess certainty in the findings. GRADE requires an assessment of the risk of bias. Information on the risk of bias for the individually included studies will be extracted according to the reporting in the included systematic reviews

We will use the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) to rate the certainty of evidence for each relevant outcome (Schünemann, 2017). The rating is based on an assessment of: 1) risk of bias (study limitation), 2) Inconsistency (heterogeneity) in the direction and/or size of the estimates of effect, 3) Indirectness of the body of evidence to the populations, interventions, comparisons and/or outcomes, 4) Imprecisions of results (few participant/ events/ observations and/ or wide confidence intervals), and 5) Other considerations (effect size and publication bias). Discrepancies in the ratings of the certainty of evidence will be resolved by discussion or with help from a third reviewer if necessary. All key data will be entered in the GRADEpro software. This software will be used to produce GRADE evidence profile tables and summary of findings tables (See Table 4)

8. Synthesis and Statistical Procedures

In the final review, the effectiveness of each intervention will be reported based on outcome. Meta-analysis will be conducted where possible, existing meta-analyses will be reported and otherwise narrative synthesis will be used to report results. We will also provide narrative descriptions to explain any heterogeneity between reviews. In the case of overlapping studies in reviews, we will consider the reviews that have the highest methodological ratings.

Continuous outcomes will be expressed as standardized mean differences (SMD) and dichotomous treatment effects will be measured as Relative Risks (RR) or Odds Ratios (OR). In both cases, 95% confidence intervals and exact p-values will be used. Pooled effects will be calculated using random effects models. Statistical heterogeneity will be assessed using I^2 statistics. Clinical heterogeneity will be defined as differences in participant characteristics (e.g., sex, age, baseline disease severity, ethnicity, and comorbidities), types or timing of outcome measurements, and intervention characteristics and will be assessed by clinical experts. Software for statistical analyses will primarily be RevMan 5.0.

Several studies are expected to include outcome data for multiple time points. Comparisons will therefore be carried out separately for 3-months periods after intake: 0-3 months after intake, 4-6 months after intake, 7-9 months after intake, etc. If different measures (e.g. different questionnaire-based indexes) are used to measure of the same outcome (the same construct), then the procedure will depend on the quality of these indexes. The index with higher quality will be preferred to one with lower or unknown quality. If one index is a standardized, validated and internationally well-known index, and the other is a local and not validated indexed developed by the evaluators, then the first index will be chosen and the second will be dropped.

DISSEMINATION

Researchers and Community Scholars (review team members with lived experience of homelessness/substance use) will present the findings at research rounds and related conferences for policy makers, practitioners and lay audience. Community Scholars will also develop and disseminate newsletters for persons with lived experience. The results from this study will be published in a peer-reviewed journal. Eventually the findings of this

systematic review will contribute to an evidence-based guideline for primary care practitioners. This document aims to inform primary care practitioners and build a knowledge network around the recommendations and resources for caring for people who abuse illicit drugs and substances. We plan to publish this guideline in as an open access document in the Canadian Medical Association Journal and develop an easy to use App to increase dissemination.

FUNDING

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AUTHOR CONTRIBUTIONS

KP conceptualized the work. VK, OM and GS drafted the protocol. WD and TH provided content and lived experience expertise. GS and KP provided content expertise. All authors revised and approved the final manuscript.

CONFLICTS OF INTEREST

There are no reported conflicts of interests.

Table 1: Summary of eligibility criteria

Population	Individuals with substance use disorder. We will include youth aged 16-24 and adults who use psychoactive substances such as alcohol and drugs. We will exclude prison populations.
Setting	We will include interventions in high income countries that take place in settings where the primary care of people with substance use disorders takes place.
Interventions	We will include interventions of: Supervised consumption facilities, managed alcohol programs and pharmacological interventions for opioid use disorder, including methadone, naloxone, naltrexone and buprenorphine.
Comparison	No intervention or an alternative intervention (active control).
Outcomes	Substance use, mortality and morbidity, mental health, access to services, retention in treatment programs.
Study design	Systematic reviews of primary studies with and without control groups. We will exclude other review types that do no follow systematic methodology. If we identify reviews of reviews, we will consider their included systematic reviews for inclusion. We will exclude grey literature.
Restrictions	We will exclude populations in prisons, as the prison setting is not generalizable to the rest of the population. We will include interventions that take place in settings where the primary care of people with substance use disorders takes place. No language or date restriction.

Table 2: Search strategy

Database: Embase Classic+Embase <1947 to 2018 July 05>, Ovid MEDLINE(R) ALL <1946 to July 05, 2018>, PsycINFO <1806 to July Week 1 2018>, Joanna Briggs Institute EBP Database - <Current to June 27, 2018>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to July 5, 2018>, EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2016>

Search Strategy:

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1 drug users/
2 exp *substance-related disorders/
3 exp *alcohol-related disorders/
4 alcoholics/
5 exp *opioid-related disorders/
6 exp *substance withdrawal syndrome/
7 ((Illicit or injection or intravenous or iv or parenteral) adj2 drug use$).ti,kf.
8 ((Illicit or injection or intravenous or iv or parenteral) adj2 drug use$).ab.
9 (pwud or pwid).tw,kf.
10 or/1-9
11 substance abuse treatment centers/
12 needle-exchange programs/
13 harm reduction/
14 (supervised adj2 (consumption or drug or injection or treatment)).tw,kf.
15 ((needle? or syringe?) adj2 exchange).tw,kf.
16 or/11-15
17 alcohol drinking/pc
18 *alcoholism/rh, th
19 (managed adj2 (alcohol or drinking)).tw,kf.
20 (supervised adj2 (alcohol or drinking)).tw,kf.
21 (alcohol$ and (manag$ or reduc$ or treat$) and (abus$ or delirium or withdrawal)).tw,kf.
22 ((alcohol or ethanol) adj2 (adminstr$ or administer$ or intravenous or iv or i v or prophyl$ or prescri$ or protocol? or provid$ or provision)).tw,kf.
23 or/17-22
24 exp *opioid-related disorders/dt, pc, rh, th
25 substance abuse, intravenous/dt, pc, rh, th
26 narcotics/rh, tu
27 hydromorphone/ad, tu
28 methadone/ad, tu
29 naloxone/ad, tu
30 naltrexone/ad, tu
31 (((buprenorphine or diacetylmorphine or heroin or hydromorphone or methadone or morphine or opiate? or opioid$) adj (maint$ or replace$ or substitut$)) and (dependen$ or management or therap$ or treatment$)).ti,kf.
32 (((buprenorphine or diacetylmorphine or heroin or hydromorphone or methadone or morphine or opiate? or opioid$) adj (maint$ or replace$ or substitut$)) and (dependen$ or

management or therap$ or treatment$)).ab.
33 or/24-32
34 exp program evaluation/
35 ((effectiveness orimprove$ or initiative? or prevent$ or program$ or reduc$ or strateg$ or treatment?) adj3 (alcohol$ or addict$ or cocaine or drug? or heroin or marijuana or narcotic$ or opioid?)).ti,kf.
36 ((effectiveness or improve$ or initiative? or prevent$ or program$ or reduc$ or strateg$ or treatment?) adj3 (alcohol$ or addict$ or cocaine or drug? or heroin or marijuana or narcotic$ or opioid?)).ab.
37 or/34-36
38 ((overview$ or review or synthesis or summary or Cochrane or analysis) and (reviews or meta-analyses or articles or umbrella)).ti.
39 ((overview$ or reviews) and (systematic or cochrane)).ti.
40 (reviews adj2 meta).ab.
41 (reviews adj2 (published or quality or included or summar$)).ab.
42 (cochrane review* or systematic review*).ab.
43 (evidence and (reviews or meta-analyses)).ti.
44 or/39-43
45 38 or 44
46 animals/ not (humans/ and animals/)
47 45 not 46
48 10 and (16 or 23 or 33) and 37 and 47
49 remove duplicates from 48

Table 3: Data extraction sheet

Bibliographic Details	Author	
	Year	
	Title	
	Publication information	Journal name, volume, issue, page numbers, doi.
Methods	Objective of the review	As reported in the study.
	Search details	Describe databases searched, years and relevant keywords.
	Number of included studies	As reported in the study.
Characteristics of included studies	List of included studies relevant to our intervention and outcomes	List author, year and study design.
	Study methodology	Data collection and analysis methods.
	Population and setting	Description of geographic context (country, city), intervention context (ex: primary care setting), and target population.
	Intervention descriptions	Describe the intervention(s) included in the study. What is implemented, how is it done, by whom, for whom, etc.
	Comparison description	Describe the comparison(s) included in the study. What is implemented, how is it done, by whom, for whom, etc.
	Outcome elements and descriptions	Describe the outcome(s) included in the study. What are they, and how are they measured, etc.

Results	Substance use	Results identified in the study
	Mental Health	
	Mortality and morbidity	
	Access to care	
	Retention in treatment	
	Source of funding	Source of funding and role of the funder.
	Other Information	Other information.

Table 4: GRADE Summary of findings

Outcome:						
N^0 of studies	Study design	N^0 of participants	Relative effect (95% CI)	Absolute effect (95% CI)	Certainty (GRADE)	Importance

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