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Review

Prescribed safer opioid supply: A scoping review of the evidence

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A B S T R A C T

Background: Safer opioid supply programs provide prescription pharmaceutical opioids, often with supportive services, to people at high risk of experiencing harms related to substance use. However, questions regarding the effectiveness and safety of this practice remain. We conducted a scoping review of literature describing client outcomes from formal opioid supply programs providing prescriptions for pharmaceutical opioids, and the perceptions of involved clients/providers.
Methods: We performed a scoping review of peer-reviewed studies and grey literature published between January 1, 2012, to September 12, 2023. We included articles reporting either safer opioid supply client outcomes or clients/providers perspectives. Extracted data included study objectives, substance use patterns, client outcomes, client/provider perspectives, and estimates of effectiveness and/or harm.
Results: Our search yielded 1,597 articles. Following removal of duplicates and application of exclusion criteria, 24 publications comprising 17 peer-reviewed and seven grey literature publications were included in our study. We generated eight themes summarizing topics in the available literature: opioid-related toxicities, infectious complications, other clinical outcomes, client-reported outcomes, program access barriers, diversion, program retention, and costs to the healthcare system. Specific findings included low rates of opioid toxicities, improved physical and mental health, and improved quality of life among clients. A lack of access to adequate opioid doses and the limited range of opioid options offered within safer opioid supply programs was described by clients and providers as a potential reason for diversion and a barrier to program access.
Conclusions: Generally, evidence suggests that safer opioid supply programs are beneficial to clients through measurable outcomes. However, the available literature has important limitations, including limited inferences about the effectiveness, safety, and potential for diversion within safer opioid supply programs. Further research is needed to support the ongoing evaluation of safer opioid supply programs as one component of a multifactorial response to escalating rates of substance-related harms.

Introduction

The ongoing drug toxicity overdose crisis is a public health emergency driven primarily by illicitly-produced fentanyl (Public Health Agency of Canada, 2023). The magnitude and urgency of this crisis has led to the implementation of various harm reduction interventions across Canada, including supervised consumption sites, drug-checking services, and widespread availability of take-home naloxone. Supervised consumption sites were first implemented in Canada in 2003 (Small et al., 2006), to provide supervised spaces for people to use pre-obtained drugs under the supervision of trained staff after obtaining an exemption from the Controlled Drugs and Substance Act. Despite implementation of these measures, opioid-related toxicities have continued to increase, with 40,642 Canadians losing their lives to an opioid toxicity between January 2016 to June 2023 (Public Health Agency of Canada, 2023).

In response to the ongoing opioid toxicity overdose crisis, the provision of prescribed, pharmaceutical opioids (e.g., immediate-release hydromorphone) as an alternative to the unregulated opioid supply - a practice known as safer opioid supply or prescribed safer supply - was recently introduced as a harm reduction measure (Hales et al., 2020). The goals of prescribed safer opioid supply programs often differ from

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traditional treatment modalities (e.g., opioid agonist treatment) for opioid use disorder. Specifically, prescribed safer opioid supply is not conceptualized as a treatment for opioid use disorder, rather it is implemented as a harm reduction measure to reduce the risk of overdose from fentanyl sourced from unregulated (illicit) markets. Additionally, unlike opioid agonist treatments which have varying requirements for observed consumption, many prescribed safer supply programs provide immediate-release opioids on a daily-dispensed basis for take-home, unobserved use, frequently alongside observed doses of long-acting opioids (methadone and slow-release oral morphine) (Public Health Ontario, 2022). While various program models for the distribution of pharmaceutical opioids have long existed, the term 'safer opioid supply' was first used to describe a program implemented at the London Inter-Community Health Centre in 2016, which provided daily-dispensed, immediate-release hydromorphone tablets for take-home, unobserved use (Gomes et al., 2022). Since then, the number of safer opioid supply programs have rapidly expanded during the COVID-19 pandemic due to the provision of short-term, pilot funding to a small number of prescribed safer supply programs across Canada, as well as publication of emergency Risk Mitigation Guidance in some provinces (British Columbia Centre on Substance Use, B.C Ministry of Health, and Ministry of Mental Health and Addictions., 2022; Canadian Association of People Who Use Drugs., 2019; Glegg et al., 2022; Goyer et al., 2020; Hales et al., 2020), and introduction of a "Prescribed Safer Supply" policy in British Columbia in 2021 (British Columbia Ministry of Mental Health & Addictions, 2021).

Despite the potential benefits of safer opioid supply programs, concerns have been raised regarding the safety implications on individuals and communities, and the effectiveness of these programs relative to more established treatment modalities. Real-world evidence describing the safety and effectiveness of safer opioid supply programs is an urgent priority, particularly as interest in integrating these programs into the suite of harm reduction resources available to people who use drugs has increased. Therefore, we conducted a scoping review of peer-reviewed and grey literature publications that examined health and quality of life related outcomes among clients of safer opioid supply programs and/or the perspectives of clients and their providers pertaining to safer opioid supply programs. We defined safer opioid supply as the provision of prescription opioids to clients, as an alternative to the unregulated toxic drug supply (London InterCommunity Health Centre, 2023). We employed a scoping review approach as this methodology is well suited to address broader topics where several study designs may be considered (Arksey & O'Malley, 2005).

Methods

Search protocol

We conducted a literature search in accordance with the PRISMA extension for scoping reviews (PRISMA-ScR) (Tricco et al., 2018). The protocol for this scoping review was not pre-registered. We developed our full search strategy using Ovid MEDLINE(R) (Supplementary Table 1), which was then adapted for use in Ovid Embase, CINAHL, APA PsycINFO and Scopus (Supplementary Tables 2–5). Additional records were also retrieved through a citation search of peer-reviewed articles and grey literature documents (Atkinson, 2023; Haines et al., 2022; Haines & O'Byrne, 2023b; Kolla & Fajber, 2023; Kolla et al., 2021; McMurchy & Palmer, 2022). We also conducted internet searches using the following search terms (i.e., "safer supply program evaluation" and "prescription safer supply evaluation"). Lastly, we consulted with subject matter experts to retrieve publicly available evaluations of safer opioid supply programs. Specifically, the National Safer Supply Community of Practice, a Canadian network funded by the federal government to support knowledge exchange and capacity building around safer supply maintains a publicly available web page of published safer supply program evaluations. Additionally, co-author GK is involved in independent evaluations of several safer supply programs and has maintained a bibliography of peer-reviewed and grey literature evaluations of safer supply programs, which she acquired by compiling literature from key word alerts running on PubMed, Embase, SCOPUS, Web of Science and Google Scholar since 2020 for the following terms: 1) 'safe supply' and 2) 'safer supply'. These searches were initially run capturing all literature from January 1, 2012, to May 19, 2023. After conducting an initial review and summary of this literature (Ontario Drug Policy Research Network, 2023), we updated our search of the published literature up until September 12, 2023.

Screening and study selection

All records identified were uploaded into Covidence (VeritasHealth Innovation, Melbourne, Australia) for screening, with duplicates removed automatically. We reviewed titles and abstracts to identify published studies that met the following inclusion criteria: 1) published in English and 2) assessed health or quality of life related outcomes following the provision of prescribed safer opioid supply and/or explored the perspectives of safer opioid supply clients or providers (e.g., physicians, nurse practitioners, pharmacists, social workers, program managers/directors, and health authority representatives). We also conducted a search for published research on safer opioid supply programs operating in Quebec, Canada in French, but found no additional results. Our exclusion criteria included: 1) studies only focusing on injectable opioid agonist treatment, heroin assisted treatment, and/or pharmaceutical-grade stimulants, as these interventions did not meet our definition of safer opioid supply; 2) studies describing safer opioid supply program models without reporting outcomes or client/provider perspectives; and 3) commentaries, editorials, and reviews (e.g., did not report original research findings). Four co-authors (SL, RG, CC, TG) screened publications identified through our search strategy. At least two co-authors reviewed each title and abstract. Subsequently, the same two co-authors conducted a full-text review of publications that met our inclusion and exclusion criteria based on the initial assessment of the title and abstract. All discrepancies were resolved by consensus.

Data extraction, synthesis and critical appraisal

To characterize included studies, we extracted information related to the safer opioid supply program, including method of medication delivery (e.g., requirements for observed dosing versus provision of take-home doses), clinical engagement/oversight, and study design. Next, we abstracted the following information: 1) study objective(s); 2) safer opioid supply use patterns; 3) outcomes following enrollment in a safer opioid supply program (e.g., occurrence of drug toxicities, concurrent use of the unregulated drug supply, diversion); and 4) information regarding client and provider perspectives. We summarized descriptive statistics and estimates of safer opioid supply benefit or harm. Additionally, we extracted themes and language used to describe the perspectives of safer opioid supply program clients and providers. Data was extracted from each study by a single co-author and verified by a separate member of the study team. We organized the extracted data into eight themes generated from the synthesis of recurrent phenomena identified across the included studies and pertinent questions raised in the public discourse related to the provision of prescribed opioids as an alternative to the unregulated drug supply (e.g., diversion, risk of infectious complications). Themes were finalized based on consensus between study team members. Finally, we conducted a critical appraisal of the quantitative peer-reviewed and grey literature publications included in our scoping review using the Newcastle-Ottawa Assessment criteria for cohort studies (Peterson et al., 2011) and a modified version for cross-sectional studies (Herzog et al., 2013). We then used previously reported thresholds for converting the Newcastle-Ottawa scales to the Agency for Healthcare Research and Quality standards (Langan et al., 2017). The critical appraisal was conducted independently by two

co-authors (SL and RG), with all discrepancies discussed and resolved by consensus. We did not critically appraise the qualitative and mixed-methods publications given the limitations of available qualitative critical appraisal tools (Eakin & Mykhalovskiy, 2023).

Results

Literature search results

Our search yielded a total of 1597 articles. Following the removal of 537 duplicates, we conducted a title and abstract review for 1060 publications. We excluded an additional 1002 publications, as they were unrelated to the provision of safer opioid supply, descriptive overviews of safer opioid supply programs without outcome data, or commentaries/editorials. Next, we completed a full-text review of 58 publications, which led to the exclusion of 34 publications as they did not study safer opioid supply programs, were conceptual in nature, or did not report on outcomes or perspectives pertaining to safer opioid supply programs (Fig. 1). Thus, 24 publications (17 peer-reviewed and seven grey literature) were retained for the scoping review.

An overview of the study design, population, and safer opioid supply model for each included study can be found in Tables 1–3. All studies were conducted in Canada and published between 2020 and 2023. Most studies were conducted in Ontario ($n = 10$) or among residents of British Columbia ($n = 9$), with the remaining studies being conducted in Nova Scotia ($n = 1$) or involved participants from across Canada ($n = 4$). Study

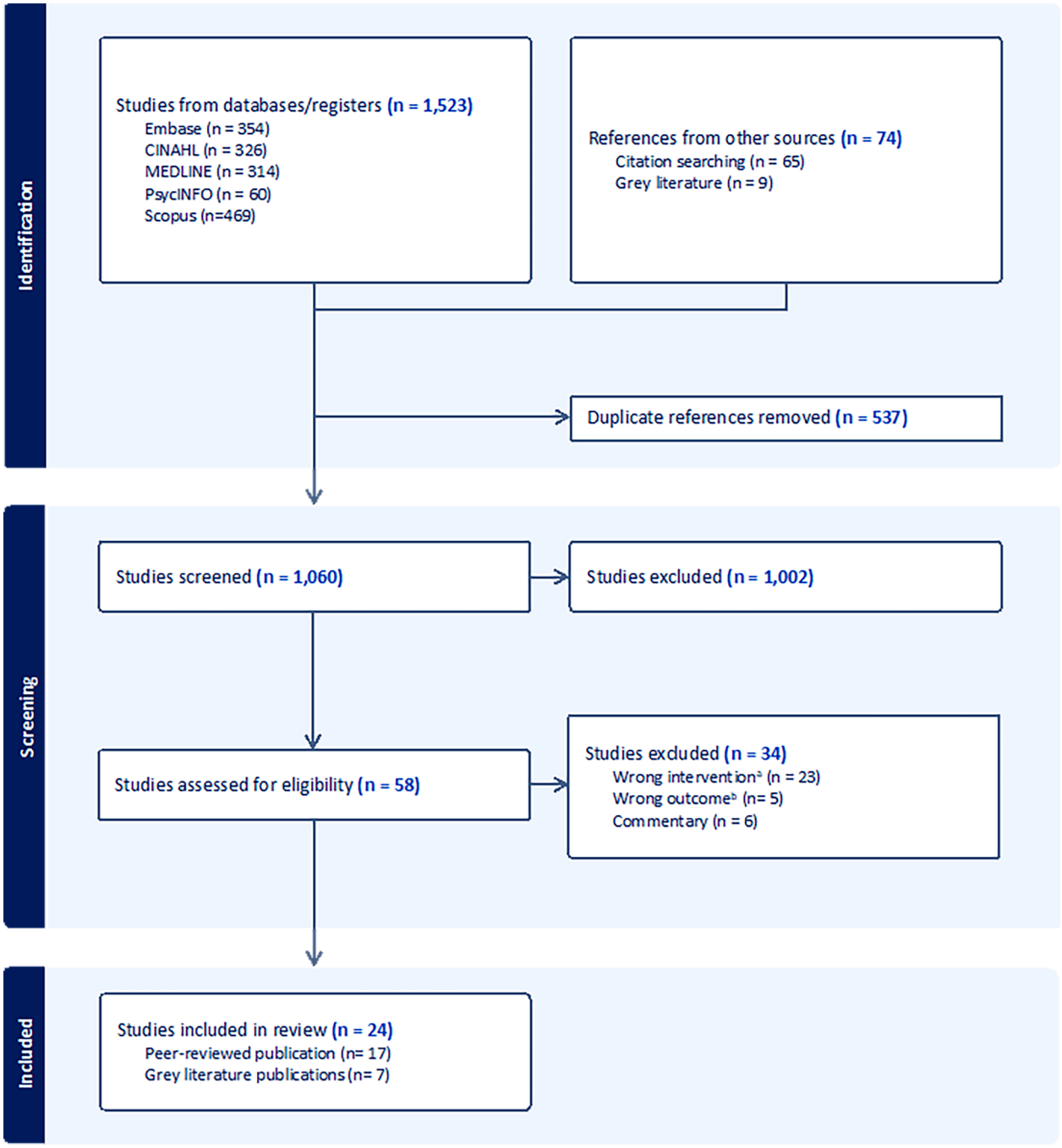

Fig. 1. PRISMA diagram [a] Provision of injectable opioid agonist treatment or heroin-assisted treatments. [b] Assessed the preferences of people who use drugs to inform safer supply programs, did not evaluate provision of a safer supply program itself. TABLES.

Table 1
Overview of peer-reviewed quantitative studies.

Study	Study design	Study Population		Safer Opioid Supply Model	Clinical Engagement/ Oversight
		Inclusion Criteria	Study Size and Demographics		
Brothers et al., 2022	Retrospective case series	Location: Halifax, Nova Scotia, Canada Study period: May 2021 COVID-19 outbreak. Inclusion criteria: All COVID-19 isolation hotel shelter residents during a COVID-19 outbreak in congregate shelter system (May 2021). Safer supply provided during 14-day mandatory isolation.	Participants: $N = 77$ (25 % women; mean age = 42). *Note:* only $N = 27$ were provided with hydromorphone safer opioid supply. Current recipients of opioid agonist treatment: $N = 12$ residents received both opioid agonist treatment and hydromorphone tablets on the same day.	Physicians and NPs prescribed medications following British Columbia's Risk Mitigation Guidance, which covers opioids, stimulants, and benzodiazepines. Opioid specific guidelines: Offer opioid agonist treatment to those with opioid use disorder, oral hydromorphone 8 mg tablets, 1–3 tablets/hour; maximum dose 14 tablets (112 mg); long-acting opioid (e.g., slow-release oral morphine) with short-acting opioid for those not receiving opioid agonist treatment. Provided for 14 days only while isolating. Medications could be taken via any route - guidance provided on safer use within harm reduction framework. All medications/ services provided at no cost.	Clinical engagement: Nurses and/or prescribers assessed residents in person if needed and communicated via mobile secure messaging app. Harm reduction outreach organization provided naloxone kits, sterile drug preparation and injecting equipment and support. Oversight: Medications were delivered daily by community pharmacist. Observed consumption was not required. Prescribers conducted phone follow-ups to adjust dosages daily for first three days, and then as needed.
Gomes et al., 2022	Interrupted time-series analysis using health administrative databases and a matched comparator group.	Location: London, Ontario, Canada Study period: January 1, 2016, and March 31, 2019. Inclusion criteria: Clients of the London Intercommunity Health Centre safer opioid supply Program and matched London residents with opioid use disorder unexposed to safer opioid supply .	Participants: $N = 82$ safer opioid supply clients matched to 303 unexposed London residents with opioid use disorder (40.2 % male, mean age = 41). Current recipients of opioid agonist treatment: 61.0 % (in the prior year). Co-morbidities: safer opioid supply clients had high prevalence of HIV (34.1 %), hepatitis C (69.5 %), and prior infections (28.0 %).	Immediate-release hydromorphone tablets were dispensed daily from a pharmacy of client's choice. Medications can be taken by any route of administration. Slow-release oral morphine often prescribed as long-acting medication alongside hydromorphone; primarily taken as oral, observed dose once daily at pharmacy.S afer opioid supply at the time of the study period was offered to clients with multiple, serious medical complications (i.e., recurrent infective endocarditis, untreated HIV) and was later expanded to others, including those experiencing homelessness or street-involvement.	Clinical engagement: The safer opioid supply program is based in Community Health Centre, so comprehensive primary healthcare was also provided. Health services included comprehensive sexual health care and screening, regular preventative healthcare. Social services include harm reduction education, access to equipment and supplies, assistance accessing food programs and other basic needs. Oversight: Hydromorphone tablets dispensed daily from community pharmacy for take-home dosing; long-acting opioids dispensed daily from pharmacies via observed dosing.
Lew et al., 2022	Case series	Location: Hamilton, Ontario, Canada Study period: January 27 to March 19, 2021. Inclusion criteria: People accessing an emergency adult men's shelter during a COVID-19 outbreak.	Participants: Men residing in a shelter. Comparing those who accessed the shelter during safer supply and safer use space program implementation (total of 1778 occupied beds over 26 days) to those who accessed the shelter in the 28 days prior (total of 2154 occupied beds).	The shelter introduced an integrated emergency safer use space and safer supply program with four components: 1) shelter-embedded space for observed substance use; 2) prescribed opioid agonist treatment and safer opioid supply (hydromorphone tablets aligned with British Columbia's Risk Mitigation Guidance); 3) harm reduction supply distribution; 4) increased overdose response capacity within shelter.	Clinical engagement: On-call physicians provided in-person or phone assessments for opioid agonist treatment and/ or safer opioid supply. Local pharmacy provided naloxone kits to shelter residents, in the safer use space and on shelter premises. Paramedic group provided oxygen; training videos developed for safer use space volunteers. Oversight: Two volunteers or paid peers trained in overdose response were present in the safer use space. Physician available via telephone during open hours (10–16 h/day).
Selfridge et al., 2022	Descriptive chart review	Location: Victoria, British Columbia, Canada Study period: March to August 2020. Inclusion criteria: Clients of the Victoria Cool Aid Society's Community Health Centre, who were prescribed safer opioid supply. Those stable on	Participants: $N = 286$ clients (36.4 % female; mean age = 39). *Note:* Only $N = 274$ received hydromorphone Current recipients of opioid agonist treatment: 90.9 % were co-prescribed opioid agonist treatment at baseline.	BCCSU clinical guidance for tablet hydromorphone and M-Eslon was applied. Oxycodone was added as an option for some clients. All clients were routinely encouraged to start/ continue opioid agonist treatment. Medications were dispensed daily from	Clinical engagement: A multidisciplinary clinical team, including primary care physicians, nurse practitioners, nurses, pharmacists, and allied health professionals. In May 2020, the CHC created a distributed model of care with clinics and on-call services

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Table 1 (*continued*)

Study	Study design	Study Population		Safer Opioid Supply Model	Clinical Engagement/ Oversight
		Inclusion Criteria	Study Size and Demographics		
		opioid agonist treatment (i.e., taking as prescribed without additional illicit opioid use) and those connected with psychiatrist were not eligible for the safer opioid supply program (unless psychiatrist consented).	Co-morbidities: Among clients there was a high prevalence of Hepatitis C (42.0 %), injection drug use (74.8 %), and skin or tissue damage (44.1 %).	community pharmacies (some deliver to shelters and sites supporting self-isolation).	throughout the community including COVID-19 sheltering sites. Oversight: Safer opioid supply was dispensed daily from community pharmacies for unobserved take-home dosing. Provision of opioid agonist treatment was observed. Urine drug screens were regularly conducted.
Young et al., 2022	Retrospective cohort study	Location: Ontario, Canada Study period: January 1, 2016, to March 31, 2020. Inclusion criteria: Individuals with opioid use disorder receiving safer supply with immediate release hydromorphone were identified using health administrative data. Those with a cancer diagnosis in past year were excluded.	Participants: $N = 447$ individuals (60.2 % male; median age = 42). Current recipients of opioid agonist treatment: 69.1 % (in the past year). Co-morbidities: Study participants had a high prevalence of HIV (13.9 %), and prior infective complications (41.6 %).	Safer supply was defined as daily dispensed immediate-release hydromorphone of at least 32 mg on at least two of first three days of prescribing (using 4 mg or 8 mg tablets).	No details of oversight or clinical engagement was provided as this was not an evaluation of a specific program.

design also varied across the included studies. Specifically, 11 studies reported quantitative findings related to client outcomes following enrollment in a safer opioid supply program, 14 publications described the perspectives of safer opioid supply clients, and six publications examined the perspectives of safer opioid supply providers (sum exceeds study sample of 24 because some studies used multiple methods and/or examined the perspectives of both clients and providers). Study objectives and a summary of key study findings are summarized in Supplementary Tables 6–8. We generated eight themes summarizing topics in the available literature: 1) opioid-related toxicities; 2) infectious complications; 3) other clinical outcomes (e.g., hospitalizations); 4) client-reported outcomes (e.g., involvement in criminal activities); 5) program access barriers; 6) diversion; 7) program retention; and 8) costs to the healthcare system. We reported themes ordered by clinical outcomes first, with the remainder based on the highest frequency of reporting between included studies.

Study populations and settings

Studies among safer opioid supply recipients - quantitative findings

Five peer-reviewed studies (Brothers et al., 2022; Gomes et al., 2022; Lew et al., 2022; Selfridge et al., 2022; Young et al., 2022) and six grey literature publications (Atkinson, 2023; Haines et al., 2022; Haines & O'Byrne, 2023b; Kolla & Fajber, 2023; Kolla et al., 2021; McMurchy & Palmer, 2022) reported quantitative analyses of clinical outcomes, health services utilization, engagement in criminal activities, and/or diversion among recipients of safer opioid supply. Please refer to Supplementary Tables 6 and 7 for a full summary of the key quantitative findings from each included study.

Among these studies, two peer-reviewed publications were conducted among shelter residents assessing the impact of expanded access to safer opioid supply and harm reduction services in Hamilton, Ontario (Lew et al., 2022), and outcomes among individuals moved to a COVID-isolation hotel in Halifax, Nova Scotia (Brothers et al., 2022). The other two peer-reviewed publications studied populations in Ontario using health administrative data. The first was an evaluation of the London InterCommunity Health Centre safer opioid supply program before they received Health Canada funding, comparing 82 safer opioid supply clients matched to 303 residents of London, Ontario with opioid use disorder who did not access the program (Gomes et al., 2022). The second study applied an algorithm based on dispensing patterns of immediate-release hydromorphone to health administrative databases, identifying 447 safer opioid supply recipients in Ontario, Canada between January 2016 and March 2020 (Young et al., 2022). This study also reported time to safer opioid supply discontinuation and the prevalence of all-cause mortality and hospitalization while on treatment. The last peer-reviewed study was conducted at the Victoria Cool Aid Society's Community Health Centre in Victoria, British Columbia, and involved chart reviews of safer opioid supply clients to evaluate 60-day adherence and correlates of adherence (Selfridge et al., 2022). The six grey literature publications evaluated Health Canada-funded safer opioid supply programs located in Toronto (Atkinson, 2023), Ottawa (Haines et al., 2022; Haines & O'Byrne, 2023b), and London (Kolla & Fajber, 2023; Kolla et al., 2021), Ontario, while the last study included clients and program staff from 10 different safer opioid supply programs across Canada (McMurchy & Palmer, 2022). Among the grey literature publications, two evaluated the Safer Supply Ottawa program at separate time points. Specifically, the first evaluation used data collected between April 2022 to July 2022 (Haines et al., 2022), whereas the second evaluation used a different data set, as data was collected between December 2022 to March 2023 (Haines & O'Byrne, 2023b). Similarly, two grey literature evaluations of the London InterCommunity Health Centre safer opioid supply program were also conducted using different methodologies and collected data at separate time points, as the first evaluation reported qualitative and survey data collected in fall 2020 and 2021, respectively (Kolla et al., 2021). Whereas, the second publication was a follow-up evaluation, which examined client reported outcomes drawn from surveys collected in 2022 and 2023 (Kolla & Fajber, 2023).

An overview of our critical appraisal of peer-reviewed and grey literature quantitative publications can be found in Supplementary Table 9. Out of the seven quantitative publications included, both cohort studies (Gomes et al., 2022; Young et al., 2022) and one cross-sectional study (Selfridge et al., 2022) were determined to be good quality, with the remaining four cross-sectional studies (Brothers et al., 2022; Haines & O'Byrne, 2023b; Kolla & Fajber, 2023; Lew et al., 2022) classified as poor quality. A recurring limitation observed among cross-sectional studies was the lack of control for significant confounding factors among safer opioid supply clients who experienced different outcomes (e.g., sex and factors associated with OUD severity) and the absence of methods outlining statistical tests.

Table 2
Overview of peer-reviewed qualitative studies.

Study	Study design	Study Population		Safer Opioid Supply Model	Clinical Engagement/Oversight
		Inclusion Criteria	Study Size and Demographics		
Bardwell et al., 2023	One-on-one semi-structured interviews	Location: Vancouver, British Columbia, Canada Study period: November 2021 to April 2022. Inclusion criteria: Participated in one of three MySafe sites in Vancouver, British Columbia for at least one month.	Participants: $N = 46$ (30.4 % female; median age: 41.3 [25–68]). Housing status: Supportive ($N = 36$), private ($N = 3$), apartment ($N = 3$), house ($N = 2$), shelter ($N = 1$), and other ($N = 2$). Current recipients of opioid agonist treatment: Methadone ($N = 15$), extended-release morphine ($N = 4$) and liquid injectable hydromorphone ($N = 1$).	MySafe program recipients accessed pharmaceutical-grade hydromorphone tablets via secure biometric dispensing machines. Clients of this program were dispensed hydromorphone tablets once daily.	Clinical engagement: Clients underwent a medical evaluation before enrolment and were monitored by a healthcare provider at months 1, 6 and 12. The initial dose was determined by the prescribing physician and titrated-up based on the client's need. Oversight: The prescription is filled by a local pharmacy and prescribed doses are inserted into a dispensing machine, which provides daily dispensed hydromorphone tablets by scanning the client's handprint. Doses are not observed, however MySafe staff were available on-site during day-time hours to assist with technical difficulties.
Foreman-Mackey et al., 2022	One-on-one semi-structured interviews coded using a thematic analysis approach	Location: Dartmouth, Nova Scotia; London, Ontario; Victoria, British Columbia; Vancouver, British Columbia Study period: June to September 2021. Inclusion criteria: Professional stakeholders involved in the design, implementation and/or operation of a safer opioid supply programs.	Participants: $N = 17$, including seven program managers/executive directors, three political/health authority representatives, five physicians, one nurse and one pharmacist.	Proposed biometric opioid dispensing machine pilot program locations in Canada.	No details of program oversight or engagement were provided as the interviews were conducted in the pre-implementation stage (at three sites) and early implementation stage (one site) of biometric dispensing machines.
Gagnon et al., 2023	One-on-one semi-structured interviews coded using a thematic analysis approach	Location: Ontario, Canada Study period: February to October 2021. Inclusion criteria: Current safer opioid supply clients and providers across four safer supply programs.	Participants: $N = 52$ safer opioid supply clients (55.8 % male) and $N = 21$ service providers (61.9 % male; 38.1 % less than 35 years old) including nurse practitioners, registered nurses, physicians, and other providers.	The safer supply model across the four programs was not explicitly outlined.	No details of oversight or engagement for each program were provided as the focus of this study was on injection practices.
Giang et al., 2023	One-on-one semi-structured interviews	Location: Vancouver, British Columbia, Canada Study period: April 2020 to July 2021. Inclusion criteria (clients): People aged 19 to 24 years old, who use drugs and were clients of the Foundry Vancouver Granville clinic and eligible for the At-Risk Youth Study (i.e., between 14 and 26 years old, report illicit drug use in the past 30 days, and report accessing health or social services for those experiencing unstable housing and homelessness in Greater Vancouver), and who had accessed safer opioid supply prescription of hydromorphone in the prior six months. Inclusion criteria (providers): Addiction medicine physicians employed by Vancouver Coastal Health Authority and Providence Health.	Participants: 30 young people who use drugs (aged 19 to 24; 47 % identified as women); 10 providers Current recipients of opioid agonist treatment: All participants had an opioid use disorder diagnosis, and most were prescribed opioid agonist treatment.	The safer opioid supply program was based on the 2020 interim Risk Mitigation Guidance, a harm reduction strategy implemented during COVID-19. The Risk Mitigation Guidance allows for the prescription of 12-hour sustained-release oral morphine, hydromorphone tablets, methylphenidate, dextroamphetamine sulfate tablets, and benzodiazepine tablets.	No details pertaining to program oversight or engagement were provided.
Haines & O'Byrne, 2023a	One-on-one semi-structured	Location: Ottawa, Ontario, Canada Study period: Summer of	Participants: $N = 30$ (43.3 % female; median age = 42 [35–50]).	Participants were recruited from three different Ottawa-based safer supply programs: 1) safer	Clinical engagement: Various healthcare services (e.g., primary care) were available to clients at

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Table 2 (*continued*)

Study	Study design	Study Population		Safer Opioid Supply Model	Clinical Engagement/Oversight
		Inclusion Criteria	Study Size and Demographics		
	interviews and surveys	2022. Inclusion criteria: People ≥18 years old, who participated in an Ottawa-based safer supply program.		opioid supply program (open 16 h/day) run at a supervised consumption site (open 24 h/day) attached to a homeless shelter; 2) within an addictions treatment clinic; open Monday to Friday for 8 h/day with oversight from physicians; 3) within a Community Health Center with oversight from nurse practitioners. The three safer opioid supply programs provide clients with hydromorphone and/or slow-release oral morphine and/or methadone or suboxone.	each of the three Ottawa safer opioid supply programs. All clients were required to go through an in-take process and attend weekly check-ins with a healthcare provider. Oversight: Some participants reported observed dosing when beginning the safer opioid supply program; requirements for observed dosing were not specified.
Hong et al., 2022	Case report	Location: British Columbia, Canada Study period: March 2020. Inclusion criteria: N/A	Participant: A 39-year-old man with no fixed address with history of polysubstance use, multiple opioid toxicities, and a COVID-19 diagnosis.	Safer opioid supply was provided based on British Columbia's Risk Mitigation Guidance.	Clinical engagement: Risk mitigation was initiated by an addiction medicine physician. Prescription drugs were delivered daily to the patient's room from nearby pharmacy and included hydromorphone, morphine sulfate extended release, dextroamphetamine, dextroamphetamine sulfate extended release, and nicotine patches. Oversight: Outreach nurses assessed the patient 2–3 times daily during the self-isolation period to monitor for COVID-19 symptoms and collaborated with an addiction medicine physician to monitor for side effects from medications (e.g., oversedation).
Ivsins et al., 2020 Ivsins et al., 2021	One-on-one semi-structured interviews and >100 h of ethnographic observations	Location: Vancouver, British Columbia, Canada Study period: February to December 2019. Inclusion criteria: Clients of the Molson hydromorphone tablet distribution program.	Participants: $N = 42$ (23.8 % female; median age = 44 [26–72]).	Provision of physician prescribed hydromorphone tablets. Required daily visits and onsite, observed consumption. Based on prescribing parameters, clients may access up to five prescribed doses of hydromorphone daily (minimum one-hour interval between 16 mg doses).	Clinical engagement: The program was staffed by a licensed practical nurse. Integration of primary care through an on-site physician, who was available two days a week and a social worker, who was present one day per week. Clients were also provided opioid agonist treatment. Oversight: Program clinic was attached to a supervised injection site where a nurse would observe doses. To prevent diversion, hydromorphone tablets were crushed by the nurse before distribution.
Ivsins et al., 2022	One-on-one semi-structured interviews	Location: Vancouver, British Columbia, Canada Study period: October 2020 to January 2021. Inclusion criteria: Residents of the Bellevue permanent support housing building who were 18 years or older and identified as a person who uses drugs.	Participants: $N = 30$ residents (median age = 48 [34–74]) living in the supportive housing site. *Note:* Only six participants received prescription hydromorphone tablets.	Tenants of the Bellevue permanent support housing building were provided with access to onsite training programs, primary care, and substance use disorder-related services (e.g., opioid agonist treatment, prescribed safer supply).	Clinical engagement: Residents of the Bellevue supporting housing building were provided access to primary care (onsite nurses, physicians), substance use services (opioid agonist treatment, safer opioid supply) and managed alcohol programs. Oversight: The study was conducted while public health restrictions for COVID-19 were in effect. At this time medications were either delivered to client's rooms or available for pick-up from the on-site medical clinic. Participants were free to consume drugs in the privacy of their room or at the supervised consumption site located within

(*continued on next page*)

Table 2 (*continued*)

Study	Study design	Study Population		Safer Opioid Supply Model	Clinical Engagement/Oversight
		Inclusion Criteria	Study Size and Demographics		
					their supportive housing building.
Karamouzian et al., 2023	Progress reports coded using a thematic analysis approach	Location: British Columbia, Ontario, New Brunswick, Canada Study period: February 2020 to March 2022. Inclusion criteria: Performance and progress reports from safer supply pilot programs submitted to Health Canada's Substance Use and Addictions Program as a requirement of their funding.	Participants: $N = 45$ progress reports submitted by 11 safer supply pilot programs. Overall, these programs provided services to $N = 1712$ clients over the study period.	There was variation across the 11 safer supply programs included in the study. At the minimum, each program provided hydromorphone in tablet and/or injection form.	Clinical engagement: All pilot programs provided safer supply integrated with an array of other services (e.g., harm reduction and outreach services, patient advocacy, housing, and legal support, etc.) Oversight: Varied across programs whether or not observed dosing was required.
Mansoor et al., 2023	One-on-one semi-structured interviews coded using a thematic analysis approach	Location: Dartmouth, Nova Scotia; London, Ontario; Victoria, British Columbia; Vancouver, British Columbia Study period: June to September 2021. Inclusion criteria: Professional stakeholders involved in the design, implementation and/or operation of safer supply programs.	Participants: $N = 17$, including seven program managers/executive directors, three political/health authority representatives, and seven clinicians.	Medication is secured by MySafe (a biometric machine that dispenses medication) and allows non-observed use of these medications.	No details of program oversight or engagement were provided as the interviews were conducted in the pre-implementation stage (at three sites) and early implementation stage (one site) biometric dispensing machines.
McNeil et al., 2022	One-on-one semi-structured interviews	Location: British Columbia, Canada Study period: February to July 2021. Inclusion criteria: People who use drugs and accessed/tried to access prescription opioids or stimulants under the British Columbia's Risk Mitigation Guidance.	Participants: $N = 40$ (48 % women; mean age = 39)	Safer opioid supply was provided based on British Columbia's Risk Mitigation Guidance.	Clinical engagement: Participants received a prescription for opioids or stimulants after release of the March 2020 Risk Mitigation Guidance. Oversight: Did not specify whether doses were observed.

Studies among safer opioid supply recipients – qualitative findings

Ten peer-reviewed qualitative studies (Bardwell et al., 2023; Foreman-Mackey et al., 2022; Gagnon et al., 2023; Giang et al., 2023; Haines & O'Byrne, 2023a; Hong et al., 2022; Ivsins et al., 2020, 2021, 2022; McNeil et al., 2022) and four grey literature evaluations of safer opioid supply programs (Atkinson, 2023; Haines et al., 2022; Kolla et al., 2021; McMurchy & Palmer, 2022) described client-reported outcomes related to self-perceived health status, financial stability, involvement in criminal activity following participation in a safer opioid supply program, potential reasons for diversion, along with barriers and facilitators of safer opioid supply program access. Please refer to Supplementary Tables 7 and 8 for a full summary of the key qualitative findings from each included study.

Overall, eight studies evaluated various programs located in British Columbia, Canada (Bardwell et al., 2023; Foreman-Mackey et al., 2022; Giang et al., 2023; Hong et al., 2022; Ivsins et al., 2020, 2021, 2022; McNeil et al., 2022). These included in-depth interviews with clients of the MySafe program (Bardwell et al., 2023), which provides access to prescription opioids through secure biometric dispensing machines, and Foundry Vancouver Granville clinic, a safer opioid supply program for individuals aged 24 and under (Giang et al., 2023). Two studies interviewed clients of the Molson hydromorphone tablet distribution program (Ivsins et al., 2020, 2021). Another study examined the perspectives of supportive housing residents who received access to a safer opioid supply as part of COVID-19 protocols (Ivsins et al., 2022). Finally, two studies examined the provision of prescription opioids or stimulants under the provincial Risk Mitigation Guidance, with one involving participant interviews and the other being a case study of an individual receiving safer opioid supply while undergoing COVID-19 isolation in a hotel setting (Hong et al., 2022; McNeil et al., 2022).

Five studies were conducted in Ontario, Canada (Atkinson, 2023; Gagnon et al., 2023; Haines & O'Byrne, 2023a; Haines et al., 2022; Kolla et al., 2021), which included the aforementioned grey literature evaluations of safer opioid supply programs located in Toronto, Ottawa, and London (Atkinson, 2023; Haines et al., 2022; Kolla et al., 2021), along with two peer-reviewed qualitative studies (Gagnon et al., 2023; Haines & O'Byrne, 2023a). The peer-reviewed study by Gagnon et al., explored the perspectives of safer opioid supply clients and services from different programs across Ontario (Gagnon et al., 2023). The second peer-reviewed qualitative study published by Haines et al., reported findings from semi-structured interviews conducted with clients of the Safer Supply Ottawa program (Haines & O'Byrne, 2023a); some of the findings from this peer-reviewed publication (Haines & O'Byrne, 2023a) were previously published in the 2022 grey literature evaluation of the Safer Supply Ottawa program (Haines et al., 2022). When reporting of findings included in both studies, we explicitly state that findings from both publications were drawn from the same population.

Studies of provider perspectives

Five peer-reviewed studies (Foreman-Mackey et al., 2022; Gagnon et al., 2023; Giang et al., 2023; Karamouzian et al., 2023; Mansoor et al., 2023), one thesis dissertation (Kalicum, 2023) and two grey literature publications (Kolla et al., 2021; McMurchy & Palmer, 2022) examined provider perspectives using in-depth interviews of addiction medicine physicians, other clinicians, individuals in leadership roles and program staff. Additionally, one study reviewed progress reports submitted by providers from 11 safer opioid supply pilot programs (Karamouzian

Table 3
Overview of grey literature publications.

Study	Study design	Study Population		Safer Opioid Supply Model	Clinical Engagement/ Oversight
		Inclusion Criteria	Study Size and Demographics		
Quantitative Studies					
Haines & O'Byrne, 2023b	Evaluation using chart reviews	Location: Ottawa, Ontario, Canada Study period: December 2022 to March 2023 Inclusion criteria: All safer opioid supply clients across three safer opioid supply programs in Ottawa.	Participants (chart review): $N = 460$ (34.0 % female; median age = 40). *Note*: 250 participants used safer opioids, 37 used safer stimulants and 173 used safer opioids and stimulants.	There was slight variation across the three Ottawa based safer opioid supply programs. Typically, each program pairs short-acting hydromorphone tablets (8 mg or 4 mg) and/or injectable hydromorphone (10 mg/mL vials) with a long-acting opioid (slow-release oral morphine, methadone, or buprenorphine/naloxone).	Clinical engagement: Various healthcare services (e.g., primary care; weekly check-ins) were available to safer opioid supply clients at each of the three Ottawa safer opioid supply programs. Oversight: Most clients picked up medications daily from the pharmacy (in some cases receive daily home delivery) and were required to complete weekly check-ins with the safer supply team. Doses were observed when clients first began the program.
Kolla & Fajber, 2023	Evaluation using a survey	Location: London, Ontario, Canada Study Period: February to April 2022 and February 2023 February 2023. Inclusion Criteria: Current clients who had been in the safer opioid supply program for at least four weeks.	Participants: $N = 75$ (44 % women) in 2022 and $N = 95$ (54 % women) in 2023.	The safer opioid supply program is part of the broader health outreach program offered by the London Intercommunity Health Centre. Clients are provided with a prescription for daily-dispensed take-home doses of short-acting hydromorphone tablets (primarily Dilaudid) with or without slow-release oral morphine as a long-acting opioid backbone co-prescribed for observed dosing at a pharmacy.	Clinical engagement: Comprehensive primary care is provided for all safer opioid supply clients, including wrap-around harm reduction services. Clients engage frequently with the health care team. Oversight: Urine screening used to ensure prescribed medications are taken (no consequences for other substances found). Slow-release oral morphine doses were observed, while hydromorphone was provided as take-home doses.
Qualitative Studies					
Kalicum, 2023	One-on-one semi-structured interviews coded using a thematic analysis approach	Location: British Columbia, Canada Study period: October 2020 to August 2021. Inclusion criteria: Service providers involved in safer opioid supply programs in British Columbia.	Participants: $N = 24$, including physicians ($n = 7$), nurse practitioners ($n = 5$), pharmacists ($n = 5$), outreach workers, ($n = 3$), registered nurse ($n = 1$), and individuals in leadership positions within service provider settings ($n = 4$).	The B.C. Centre of Substance Use Risk Mitigation Guidance.	Clinical engagement and oversight were not described in this study as it included providers involved in different programs (but all implementing the Risk Mitigation Guidance).
Mixed Methods Studies					
Atkinson, 2023	Evaluation using a survey and interviews	Location: Toronto, Ontario, Canada Study period: Clients surveyed at program intake: July to November 2022 Survey of current clients: August 2022 to January 2023 Client interviews: November to December 2022 Inclusion criteria (survey): People admitted to the safer opioid supply program and current clients who had been in the safer opioid supply program for at least six months. Inclusion criteria (interviews): Current safer opioid supply clients.	Participants (survey): $N = 10$ people being admitted to the safer opioid supply program and $N = 27$ current clients. Participants (interview): $N = 15$ current clients of safer opioid supply programs	The safer opioid supply program operates as a nurse-led model where registered nurses are the first point of contact. All clients receive daily take-home doses of short-acting hydromorphone usually with a dose of a long-acting opioid backbone observed daily at the pharmacy.	Clinical engagement: Clients have regular contact and follow-ups with registered nurses and see prescribers every few weeks. Additionally, full time case managers and a counselor serve clients on a drop-in and appointment basis. Oversight: Hydromorphone is dispensed from pharmacies as take-home doses, while observed dosing is used for long-acting opioids.
Haines et al., 2022	Evaluation using chart reviews, survey, and interviews	Location: Ottawa, Ontario, Canada Study period: April 2022 to July 2022 Inclusion criteria: Current safer opioid supply clients across three safer opioid supply programs in Ottawa.	Participants (chart review): $N = 425$ (66.0 % male; median age = 40). *Note*: 281 participants used safer opioids, 25 used safer stimulants and 119 used safer opioids and stimulants. Participants (survey & interview): $N = 30$ (57.0 % male; median age = 42).	There was slight variation across the three Ottawa based safer opioid supply programs. Typically, each program pairs short-acting hydromorphone tablets (8 mg or 4 mg) and/or injectable hydromorphone (10 mg/mL vials) with a long-acting opioid (slow-release oral morphine, methadone, or buprenorphine/naloxone).	Clinical engagement: Various healthcare services (e.g., primary care; weekly check-ins) were available to safer opioid supply clients at each of the three Ottawa safer opioid supply programs. Oversight: Most clients picked up medications daily from the pharmacy (in some cases receive daily home delivery)

(*continued on next page*)

Table 3 (*continued*)

Study	Study design	Study Population		Safer Opioid Supply Model	Clinical Engagement/ Oversight
		Inclusion Criteria	Study Size and Demographics		
					and are required to complete weekly check-ins with the safer supply team. Doses were observed when clients first began the program.
Kolla et al., 2021	Evaluation using a survey and focus groups	Location: London, Ontario, Canada Study period: Focus group: September to October 2020 Surveys: April to October 2021 Inclusion criteria (survey): People entering the safer opioid supply program for the first time, and current clients who had been in the safer opioid supply program for at least four weeks. Inclusion criteria (focus groups): Current clients of the safer opioid supply program, safer opioid supply program staff, and those on safer opioid supply program waitlist.	Participants (surveys): 19 people (54 % identified as women) being admitted to the safer opioid supply program and 59 (53 % identified as women) current clients. Participants (focus groups): Current clients of the safer opioid supply program (N = 9; 44.4 % female), program staff (N = 14; 71.4 % female) and clients on the waiting list (N = 6; 50 % female). Recipients of opioid agonist treatment: All safer opioid supply clients involved in the focus groups had prior experience with methadone.	The safer opioid supply program is part of the broader health outreach program offered by the London Intercommunity Health Centre. Clients are provided with a prescription for daily-dispensed take-home doses of short-acting hydromorphone tablets (primarily Dilaudid) with or without slow-release oral morphine as a long-acting opioid backbone co-prescribed for observed dosing at a pharmacy.	Clinical engagement: Comprehensive primary care is provided for all safer opioid supply clients, including wrap-around harm reduction services. Clients engage frequently with the health care team. Oversight: Urine screening used to ensure prescribed medications are taken (no consequences for other substances found). Slow-release oral morphine doses were observed, while hydromorphone was provided as take-home doses.
McMurchy & Palmer, 2022	Evaluation using a survey and interviews	Location: Canada Study period: December 2020 to March 2021. Inclusion criteria: Clients and staff at any of the 10 safer supply pilot projects funded by Health Canada's Substance Use and Addictions Program.	Participants (survey): N = 102 staff across eight safer opioid supply programs. Participants (interviews): N = 15 clients (46.7 % male), and N = 15 program staff.	The safer opioid supply program model varied across the different programs. Majority provided hydromorphone tablets, with some also providing injectable hydromorphone, fentanyl patches or oxycodone. Many clients also received slow-release oral morphine as a long-acting backbone. Availability of take-home doses varied by program. Most programs provide daily pick up of hydromorphone tablets at pharmacies, while those receiving injectable hydromorphone have observed dosing.	Clinical engagement: Most clients visited their prescriber and/or nurse once a week - with longer standing clients having increased intervals between appointments. Oversight: Majority of programs require daily pick-up at pharmacies of tablet hydromorphone and observed administration of injectable hydromorphone. Urine samples used differently among programs - some to determine whether to reduce/ remove safer supply and others for surveillance of the content of illegal street drugs.

et al., 2023). Overall, studies examined provider experiences pertaining to safer opioid supply program implementation and design.

Summary of evidence across identified themes

Opioid-Related toxicities

Three peer-reviewed studies, which used administrative data sources (Gomes et al., 2022) and conducted chart reviews (Brothers et al., 2022; Lew et al., 2022), along with five grey literature evaluations of safer opioid supply programs (Atkinson, 2023; Haines et al., 2022; Haines & Haines & O'Byrne, 2023b; Kolla & Fajber, 2023; Kolla et al., 2021) using client-reported survey data, presented quantitative findings related to the occurrence of opioid related toxicity events among safer opioid supply clients. Findings from these eight publications were in consensus, reporting no fatal toxicities and the low occurrence of non-fatal toxicities among safer opioid supply clients (Atkinson, 2023; Brothers et al., 2022; Gomes et al., 2022; Haines et al., 2022; Haines & O'Byrne, 2023b; Kolla & Fajber, 2023; Kolla et al., 2021; Lew et al., 2022).

The evaluation of the London InterCommunity Health Centre safer opioid supply program (before they received Health Canada funding) was the only study which followed clients long-term (i.e., one year of follow-up), reporting no significant change in the rate of hospital-treated (emergency department and/or inpatient) fatal opioid toxicity events after one-year of follow-up among 82 safer opioid supply clients relative to the year prior to program entry ($\leq$5 events compared to 10 events [0.12 per person-year]; p >0.05) (Gomes et al., 2022). These findings align with studies that evaluated temporary, emergency, safer opioid supply programs, with no fatal or non-fatal opioid toxicities observed among 27 safer opioid supply recipients undergoing a mandatory 14-day isolation period at a COVID-19 hotel in Halifax, Nova Scotia, although four cases of intoxication were considered "concerning" (Brothers et al., 2022). Lastly, a study of men accessing an emergency shelter in Hamilton, Ontario found a lower rate of non-fatal opioid toxicities in the 26 days following safer opioid supply program implementation relative to the 28 days prior to implementation (0.17 vs. 0.93 non-fatal opioid toxicities per 100 nights of shelter bed occupancy; odds ratio 5.5, 95 % confidence interval [CI] 1.6–18.6) (Lew et al., 2022). Of note, the emergency shelter introduced provision of safer opioid supply in combination with a safer use space for observed substance use, access to opioid agonist treatment, harm reduction supply distribution, and improved opioid toxicity response capacity, rendering it difficult to isolate the relative impact of each measure (Lew et al., 2022).

Five grey literature publications evaluating safer opioid supply programs (Atkinson, 2023; Haines et al., 2022; Haines & Haines &

O'Byrne, 2023b; Kolla & Fajber, 2023; Kolla et al., 2021) described client-reported episodes of non-fatal opioid toxicities during safer opioid supply program participation, with three studies conducting further comparisons between people at the time of program entry and current clients (Atkinson, 2023; Haines et al., 2022; Kolla et al., 2021). All of these studies reported lower proportions of toxicity events among active clients of the program compared to proportions reported at program entry. Specifically, an evaluation of the London InterCommunity Health Centre program during the period in which it was receiving Health Canada funding (data collected between April 2021 – October 2021) found a lower prevalence of opioid toxicities over the past six-months (23 %) and one-month (11 %) among current program clients compared to clients entering the program (59 % and 33 %, respectively) (Kolla et al., 2021). An updated evaluation of the London InterCommunity Health Centre program found that 100 % and 90 % of clients surveyed in 2022 and 2023, respectively, did not experience an opioid toxicity in the past month (Kolla & Fajber, 2023). Similarly, an evaluation of the Parkdale Queen West Community Health Centre's safer opioid supply program (located in Toronto, Ontario), found that 15 % of clients enrolled in the program for at least six-months reported having an opioid toxicity event in the past three-months, compared to 50 % of individuals at the time of program entry (Atkinson, 2023). Lastly, the 2022 and updated 2023 Ottawa safer opioid supply program evaluations found that among safer opioid supply recipients who experienced a non-fatal opioid toxicity event at the time of program entry, 81 % and 85 % did not report another toxicity event at their most recent clinical visit according to medical chart records, respectively (Haines et al., 2022; Haines & O'Byrne, 2023b).

Seven peer-reviewed qualitative studies examined opioid-related toxicities (Bardwell et al., 2023; Gagnon et al., 2023; Giang et al., 2023; Haines & O'Byrne, 2023a; Ivsins et al., 2020, 2021; McNeil et al., 2022). A recurrent finding among studies was that while many safer opioid supply recipients continued to access the unregulated drug supply, their self-reported frequency of use decreased (Bardwell et al., 2023; Giang et al., 2023; Haines & O'Byrne, 2023a; Ivsins et al., 2020, 2022; McNeil et al., 2022), resulting in a self-perceived decrease in their risk of an opioid toxicity. Specifically, clients expressed that access to a safer opioid supply increased stability in their drug use patterns, and helped avoid cycles of withdrawal, cravings (Hong et al., 2022), and periods of high frequency use, thereby reducing their vulnerability to an opioid toxicity (McNeil et al., 2022). Further, the grey literature London InterCommunity Health Centre safer opioid supply program evaluation reported that a major motivation for clients joining the program was to reduce their risk of opioid toxicities (Kolla et al., 2021).

Two studies examined the perspectives of safer opioid supply service providers. A survey of safer opioid supply providers at programs across Canada reported that 99 % and 93 % of respondents either somewhat or strongly agreed that safer opioid supply programs reduced opioid toxicities and injection drug use, respectively (McMurchy & Palmer, 2022). Another survey reported that safer opioid supply providers agreed that the reduction in fentanyl use helped decrease the number of opioid toxicities experienced by clients (Gagnon et al., 2023).

Infectious complications

Only one population-based study reported rates of infectious complications among safer opioid supply clients using healthcare administrative data (Gomes et al., 2022). The rate of serious infections (e.g., endocarditis, osteomyelitis) among 82 London InterCommunity Health Centre safer opioid supply program clients declined one year following program entry compared to the year prior (rate ratio 0.51, 95 % CI 0.27–0.96; $p = 0.04$) (Gomes et al., 2022). A similar change was not observed among the 303 matched controls (rate ratio 0.72, 95 % CI 0.45–1.17; $p = 0.2$) (Gomes et al., 2022).

Other clinical outcomes

Two peer-reviewed publications (Gomes et al., 2022; Young et al., 2022) and four grey literature program evaluations (Atkinson, 2023; Haines et al., 2022; Kolla & Fajber, 2023; Kolla et al., 2021) reported quantitative analyses of other clinical outcomes, such as visits to the emergency department, hospitalizations, and the physical and mental health status of safer opioid supply recipients. The peer-reviewed study of the London InterCommunity Health Centre safer opioid supply program reported significant reductions in the rate of emergency department visits (−14 visits per 100; $p = 0.02$) and hospital admissions (−5 admissions per 100; $p = 0.005$) among safer opioid supply clients in the one-year period following program entry, with no significant changes observed among the matched comparator group (Gomes et al., 2022). However, no statistically significant change in the rates of mental health-related hospitalizations or substance use-related hospitalizations among safer opioid supply clients was reported (Gomes et al., 2022). Lastly, although the small number of events precluded calculation of rates, ≤5 deaths from any cause occurred among safer opioid supply clients in the one-year follow-up period, and only seven deaths from any cause in the matched comparator group ($N = 303$; 0.02 per person-year) (Gomes et al., 2022). A descriptive analysis of all-cause mortality and hospitalization among 534 courses of safer opioid supply across Ontario also identified few instances (≤5) where the individual died while receiving safer opioid supply, and where someone died within one week of discontinuation (Young et al., 2022). In this study, a course of safer opioid supply was defined as a period of continuous use of daily dispensed hydromorphone with no gaps in dispensing longer than 14-days (Young et al., 2022). In this same study, 18.4 % of courses involved individuals who were hospitalized for <14 days, while 3.2 % of courses involved individuals who were hospitalized for ≥14 days (Young et al., 2022).

Findings from grey literature and peer-reviewed qualitative studies reported improvements in self-perceived health status. Specifically, in an evaluation of 10 safer opioid supply programs across Canada, McMurchy and Palmer (2022) found that safer opioid supply clients reported improved health outcomes and access to treatment for various chronic health conditions (e.g., HIV, hepatitis C) following safer opioid supply program participation. The initial evaluation of the London InterCommunity Health Centre safer opioid supply program, conducted while it was receiving Health Canada funding, found a lower prevalence of self-reported recent emergency department visits, one-night hospitalizations, poor health, and poor mental health among current safer opioid supply clients compared to those entering the program (Kolla et al., 2021). In addition, clients of the London InterCommunity Health Centre expressed a desire to improve their health and overall stability levels (Kolla et al., 2021). Clients and safer opioid supply staff also reported that engagement with the London InterCommunity Health Centre improved access to treatment for conditions including HIV and hepatitis C through associated wrap-around services (Kolla et al., 2021). The follow-up evaluation of the London InterCommunity Health Centre safer opioid supply program reported similar findings among current clients surveyed in both 2022 and 2023 (Kolla & Fajber, 2023). Similarly, the evaluation of the Parkdale Queen West Community Health Centre in Toronto reported that 73 % of those receiving access to a safer opioid supply were able to address a health issue for the first time after program entry, and 85 % reported feeling more connected to the healthcare system (Atkinson, 2023). Improvements in mental and physical health, including healthy weight gain, improved stamina, and better self-care were also reported by the Ottawa safer supply program evaluation released in 2022 (Haines et al., 2022). These findings were consistent with those of peer-reviewed qualitative studies where safer opioid supply clients reported increased interactions with the healthcare system due to the range of wrap-around services integrated into the various safer opioid supply programs (Giang et al., 2023). Lastly, improved relationships with clients were also described by safer opioid supply

providers (Foreman-Mackey et al., 2022; McMurchy & Palmer, 2022).

Client-Reported outcomes

Other common themes across many included studies were decreased use of fentanyl from unregulated markets (Gagnon et al., 2023; Haines & O'Byrne, 2023a; Ivsins et al., 2021), enhanced levels of personal autonomy among clients regarding the time of day drugs were used (Bardwell et al., 2023; Haines & O'Byrne, 2023a; McNeil et al., 2022), the ability to stockpile medications to meet future needs (e.g., going on vacation, requirements for increased doses) (Bardwell et al., 2023; Giang et al., 2023), and the ability to return to the safer opioid supply program after a temporary leave without penalty (e.g., requirements for dose titration) (Ivsins et al., 2020). A study of the MySafe safer opioid supply program found that clients experienced less stigma and an increased sense of privacy due to the lack of requirements for observed dosing (Bardwell et al., 2023). Participants in four qualitative studies also described reduced levels of anxiety and heightened perceptions of safety due to decreased reliance on the unregulated drug supply, and being informed of the dosages and content of the prescribed opioids they were taking (Haines & O'Byrne, 2023a; Ivsins et al., 2020, 2022; McNeil et al., 2022).

Three grey literature reports evaluating safer opioid supply programs in Canada reported similar findings (Atkinson, 2023; Kolla et al., 2021; McMurchy & Palmer, 2022). The Parkdale Queen West Community Health Centre safer opioid supply program evaluation reported that among current clients, 27 % reported improved housing, 81 % had more time to do the things they wanted, 88 % had a greater sense of safety, and 85 % felt that their life was improved (Atkinson, 2023). Additionally, these clients further described improvements in their mental health, relationships with family and friends, pain management, and overall quality of life (Atkinson, 2023). In the 2021 evaluation of the London InterCommunity Health Centre safer opioid supply programs, clients reported that they had experienced improvements in their sense of safety, housing status, and relationships with family and community members (Kolla et al., 2021). Finally, in the evaluation of safer opioid supply programs funded by Health Canada, McMurchy and Palmer (2022) found that many clients reported multiple ways in which they were receiving support through safer opioid supply program participation including income, transportation, food, and clothing; however, housing remained an unmet need for many clients.

Similar findings were reported among safer opioid supply service providers. Specifically, providers interviewed in the studies by Giang et al. (2023) and Foreman-Mackey et al. (2022) perceived that participation in safer opioid supply programs provided clients with greater stability and improved their quality of life as they were no longer required to spend a substantial portion of their time procuring drugs.

Measures of financial stability were reported in four peer-reviewed qualitative studies, (Bardwell et al., 2023; Ivsins et al., 2020, 2022; McNeil et al., 2022) and in two grey literature safer opioid supply program evaluations (Atkinson, 2023; Kolla & Fajber, 2023). In the two studies conducted in British Columbia, safer opioid supply clients reported that they spent less money on drugs, facilitating their ability to purchase necessities such as food and clothing (Bardwell et al., 2023; Ivsins et al., 2020). In the Parkdale Queen West Community Health Centre program evaluation, 77 % of current safer opioid supply clients interviewed reported that they had more money to do the things they want, although 41 % still felt that they did not have enough money to pay for essential items (Atkinson, 2023). In the updated London InterCommunity Health Centre program evaluation, 71 % of clients interviewed in 2022 and 68 % of clients interviewed in 2023 reported difficulty in paying for basic needs in the past six-months (Kolla & Fajber, 2023).

Qualitative and quantitative findings pertaining to the involvement in criminal activities among safer opioid supply clients were presented in three peer-reviewed studies (Ivsins et al., 2020, 2022; McNeil et al., 2022), and four grey literature program evaluations (Atkinson, 2023; Haines et al., 2022; Kolla & Fajber, 2023; Kolla et al., 2021), respectively. In all of the peer-reviewed qualitative studies, safer opioid supply clients reported decreased involvement in criminal activities following safer opioid supply program participation as they no longer needed as much money to purchase unregulated drugs (Ivsins et al., 2020, 2022; McNeil et al., 2022). The 2021 London InterCommunity Health Centre safer opioid supply program evaluation found that among current safer opioid supply clients, 37 % had a police contact in the past six months, 38 % were involved in criminal activities to obtain drugs, and 20 % engaged in sex work to obtain drugs (Kolla et al., 2021). The respective proportions among individuals entering the safer opioid supply program were 73 %, 86 %, and 50 % (Kolla et al., 2021). In the follow-up London InterCommunity Health Centre program evaluation, 55 % of clients in 2022 and 24 % of clients in 2023 had ceased involvement in criminal activities (Kolla & Fajber, 2023). Similar findings were reported by Atkinson et al., (2023) with 44 % of clients entering the Parkdale Queen West Community Health Centre safer opioid supply program reporting that they had done something illegal to obtain drugs in the past three months, compared to 19 % of current clients. Additionally, among clients enrolled in the Parkdale Queen West Community Health Centre safer opioid supply program, 27 % reported decreased interactions with the police. However, no differences were observed between current clients and those entering the program in terms of being stopped by the police in the past three months (Atkinson, 2023). Finally, the number of Ottawa safer supply program clients participating in criminalized behaviour decreased from 93 % ($N = 28$) at program entry to 40 % ($N = 12$) (Haines et al., 2022).

Program access barriers

Qualitative findings from peer-reviewed and grey literature publications described client-identified barriers or limitations to accessing safer opioid supply programs. Barriers included the need for multiple daily visits due to policies limiting the amount of medication dispensed at one time (Atkinson, 2023; Ivsins et al., 2020; Haines & O'Byrne, 2023a), inconvenient site hours (Ivsins et al., 2020), observed consumption of medications (Haines & O'Byrne, 2023a), difficulties accessing safer supply from pharmacies (Atkinson, 2023; Haines & O'Byrne, 2023a; Kolla et al., 2021), insufficient program capacity (Atkinson, 2023; Kolla et al., 2021), lack of information on program eligibility (Kolla et al., 2021; Mansoor et al., 2023), discontinuity of care upon hospitalization and negative experiences with health care providers outside of safer opioid supply programs (Kolla et al., 2021).

Another common barrier described by safer opioid supply clients is a mismatch between the potency of opioids in the unregulated drug supply and the dose of opioid prescribed within safer opioid supply programs (Bardwell et al., 2023; Giang et al., 2023; Haines & O'Byrne, 2023a; Ivsins et al., 2020; Mansoor et al., 2023; McNeil et al., 2022). This mismatch was perceived as a possible source of withdrawal symptoms and cravings due to the lower euphoric effect of prescribed opioids provided through safer opioid supply programs (McNeil et al., 2022), potentially resulting in clients supplementing with drugs from the unregulated supply (Bardwell et al., 2023; Giang et al., 2023; Haines & O'Byrne, 2023a). A similar theme was reported by the Parkdale Queen West Community Health Centre and London InterCommunity Health Centre safer opioid supply program evaluations, where participants expressed a desire for a greater range of medication options, particularly opioid formulations that would allow for consumption by either injection or inhalation (Atkinson, 2023; Kolla et al., 2021).

From the provider perspective, a common barrier to prescribing safer opioid supply was confusion and uncertainty, particularly regarding the Risk Mitigation Guidance that was introduced in British Columbia (Foreman-Mackey et al., 2022; Giang et al., 2023; Kalicum, 2023; Karamouzian et al., 2023; Mansoor et al., 2023). Reasons for the confusion and uncertainty included limited education and training surrounding

opioid prescribing for the purposes of risk mitigation (Kalicum, 2023), a lack of confidence in their knowledge, a limited evidence base for the guidelines and balancing the harms of not prescribing opioids supply against the unknown risks of this modality (Foreman-Mackey et al., 2022). Logistical barriers identified by providers included inadequate infrastructure (Kalicum, 2023; Karamouzian et al., 2023), the need for more staff (Karamouzian et al., 2023; Kolla et al., 2021; McMurchy & Palmer, 2022), challenges with staff recruitment in light of high workloads and burnout (Karamouzian et al., 2023; Kolla et al., 2021; McMurchy & Palmer, 2022), and lack of support from regulatory colleges (Mansoor et al., 2023). Finally, a qualitative study of the progress reports from all pilot safer opioid supply programs in Canada found that many providers had concerns about the limited and short-term nature of program funding and the impact this had on clients and program staff and their ability to build meaningful relationships (Karamouzian et al., 2023).

While studies on provider perspectives identified a number of barriers to provision of a safer opioid supply, some facilitators were also identified. These factors included greater comfort and support from working as part of a team (Foreman-Mackey et al., 2022), strong communication between providers (Mansoor et al., 2023), and for some providers, having written guidelines (i.e., the Risk Mitigation Guidance) (Kalicum, 2023).

Diversion

In the only quantitative study examining diversion, investigators documented "concerns around diversion/sharing/selling" among people accessing safer opioid supply for 14 days in a COVID-19 isolation hotel (Brothers et al., 2022). This outcome was ascertained through reports from residents, shelter staff or health professionals and was defined as potential diversion regardless of whether it was confirmed by the resident or another source (Brothers et al., 2022). Among the 27 residents provided access to a safer opioid supply, there were three documented concerns for diversion (Brothers et al., 2022). All of these individuals were provided with supplies of multiple substances, including opioids, stimulants, and alcohol. Details regarding which substances were implicated in the diversion-related concerns were not provided (Brothers et al., 2022).

Qualitative findings from one peer-reviewed study (Giang et al., 2023) and three grey literature safer opioid supply program evaluations (Haines et al., 2022; Kolla et al., 2021; McMurchy & Palmer, 2022) described that diversion was a challenge faced by safer opioid supply programs. In the evaluation of the 10 federally-funded safer opioid supply programs in Canada, some clients reported an increase in immediate release hydromorphone (Dilaudid®) availability on the street and a decrease in price (McMurchy & Palmer, 2022). However, there were no details regarding the frequency with which this was occurring or variations across the sites included in the evaluation (McMurchy & Palmer, 2022). Reasons for diversion were provided in several studies, and included compassionate sharing with others unable to access a safer opioid supply (Haines & O'Byrne, 2023a), financial needs (e.g., selling hydromorphone to generate income for food, clothing) (Giang et al., 2023), and slow titration and/or inadequate doses of opioids provided through safer opioid supply programs, resulting in clients selling their hydromorphone to purchase more potent opioids from the unregulated supply (Haines et al., 2022; McMurchy & Palmer, 2022). Furthermore, participants in the Ottawa and London program evaluations noted that diversion is not unexpected, given that it occurs within other treatment (e.g., methadone) programs (Haines et al., 2022; Kolla et al., 2021). Clients of the Ottawa program also indicated that they only shared their medications with people within their networks and not opioid-naïve individuals (Haines et al., 2022).

There were two qualitative studies from the provider perspective that reported findings related to diversion (Giang et al., 2023; Kalicum, 2023). In the study by Giang et al. (2023) prescribers noted that the early Risk Mitigation Guidance in British Columbia did not explicitly discuss diversion, with many reporting discomfort in the use of urine drug screens. In contrast, (Kalicum, 2023)reported that safer opioid supply providers introduced urine drug screens as a way to increase their comfort regarding diversion, while also recognizing the potential harms this practice may have on their patients.(Kalicum, 2023) also reported that providers considered the potential for diversion and its broader public health impacts when making decisions regarding implementation of British Columbia's Risk Mitigation Guidance.

Program retention

Retention was evaluated in five peer-reviewed and grey literature publications, with one study using administrative health datasets to identify safer opioid supply recipients across Ontario (Young et al., 2022), along with evaluations of safer opioid supply programs located in British Columbia (Selfridge et al., 2022), and safer opioid supply programs across Ontario (Atkinson, 2023; Kolla & Fajber, 2023; Kolla et al., 2021). Specifically, the Victoria Cool Aid Society's safer opioid program ($N = 286$ clients, 275 of whom were receiving hydromorphone) reported that 77.3 % of safer opioid supply clients remained adherent at 60 days of follow-up (Selfridge et al., 2022). Factors associated with adherence included continued use of opioid agonist treatments, receipt of mental health medications, and increasing client's maximum daily dose (Selfridge et al., 2022). Similarly, the initial grey literature evaluation of the London InterCommunity Health Centre safer opioid supply program reported that 94 % of clients were retained in the program between April 1, 2020 to September 30, 2021 (Kolla et al., 2021), while the Parkdale Queen West Community Health Centre safer opioid supply program evaluation reported that 80 % of clients were retained in the program for one year (Atkinson, 2023). Lastly, the 2023 evaluation of the London InterCommunity Health Centre program reported that 16 % of clients took a break from the program for more than one month after starting safer opioid supply in 2022, increasing to 20 % of clients in 2023 (Kolla & Fajber, 2023).

Finally, Young et al. (2022) reported a median time-to-discontinuation of 272 days among 534 courses (447 unique individuals) of safer opioid supply identified using Ontario's administrative data. Furthermore, retention was longer (median time-to-discontinuation of 289 days), among those who received safer opioid supply from prescribers who treated three or more individuals with safer opioid supply compared to people receiving safer opioid supply from infrequent prescribers (median time-to-discontinuation of 147 days) (Young et al., 2022). Retention in this study was also higher among people initiating safer supply between 2018 and 2020 (median time-to-discontinuation of 309 days) relative to those initiating safer supply between 2017 and 2019 (median time-to-discontinuation of 179 days) (Young et al., 2022).

Costs to the healthcare system

One study used administrative health records to compare changes in healthcare costs in the first year following safer opioid supply enrollment with costs incurred by the same individuals in the year preceding program enrollment (Gomes et al., 2022). Overall, statistically significant reductions in healthcare-related costs (excluding costs related to primary care or outpatient medications) were observed among safer opioid supply clients, decreasing from $15,635 to $7310 ($p = 0.002$) in the year following program entry relative to the year preceding enrollment. In a subgroup analysis of public drug beneficiaries, medication costs increased among safer opioid supply clients following program enrollment (from $12,840 to $21,119/year, $p<0.001$), with costs of hydromorphone and opioid agonist treatment accounting for approximately 15 % of total medication costs (increasing from $1080 to $3128/year) (Gomes et al., 2022).

Discussion

The purpose of this review was to examine the current evidence base surrounding safer opioid supply programs with regards to client outcomes and client/provider perspectives. Overall, we identified 24 publications, which evaluated various safer opioid supply programs across Canada, with 21 published in 2022 and 2023 alone. Many of these studies evaluated a single safer opioid supply program, with considerable variability in the availability and nature of wrap around services offered at each program. Furthermore, quantitative studies included in our scoping review generally had small sample sizes, reflecting the limited capacity of safer opioid supply programs currently in place across Canada. Despite variability in safer opioid supply programs evaluated across included studies, findings were largely consistent across these diverse study populations, suggesting that reported benefits of and barriers to safer opioid supply program participation apply to a diverse set of programs and clients.

Overall, the currently available evidence regarding health outcomes among safer opioid supply clients is generally favorable. Specifically, when reported, most studies found reductions (Brothers et al., 2022; Haines & O'Byrne, 2023a; Lew et al., 2022) or a lack of change (Gomes et al., 2022) in the occurrence of opioid toxicity events, along with a reduction in the frequency of unregulated opioid use among clients of safer opioid supply programs (Bardwell et al., 2023; Giang et al., 2023; Haines & O'Byrne, 2023a; Ivsins et al., 2020, 2022; McNeil et al., 2022). Other health outcomes were also shown to improve among safer opioid supply clients, including increased access to the healthcare system (Gomes et al., 2022; Kolla & Fajber, 2023; Kolla et al., 2021), infectious complications (Gomes et al., 2022), and improvements to clients' mental health (Gomes et al., 2022; Haines et al., 2022; Kolla & Fajber, 2023; Kolla et al., 2021). Also, participants of qualitative studies expressed that safer opioid supply program participation improved their access to healthcare and other wraparound services (Foreman-Mackey et al., 2022; Giang et al., 2023; Haines & O'Byrne, 2023a; Ivsins et al., 2020; McMurchy & Palmer, 2022), allowing them to address health issues such as HIV and hepatitis C (Kolla et al., 2021). Additionally, safer opioid supply program clients and providers interviewed in qualitative studies expressed that safer opioid supply recipients were afforded a greater sense of stability as clients were less preoccupied with concerns related to drug procurement (Foreman-Mackey et al., 2022; Giang et al., 2023; Haines & O'Byrne, 2023a; Ivsins et al., 2020, 2022; McNeil et al., 2022), or engagement in criminal activity as a means of income generation for drug related purchases (Atkinson, 2023; Haines & O'Byrne, 2023a; Haines et al., 2022; Ivsins et al., 2020, 2021, 2022; Kolla et al., 2021; McNeil et al., 2022).

Diversion of safer opioid supply drugs was examined in six qualitative studies (Giang et al., 2023; Haines & O'Byrne, 2023a; Haines et al., 2022; Kalicum, 2023; Kolla et al., 2021; McMurchy & Palmer, 2022) and one quantitative study (Brothers et al., 2022). These studies found that diversion does occur (Brothers et al., 2022; Haines et al., 2022; Kolla et al., 2021; McMurchy & Palmer, 2022), although the extent of diversion remains unknown. Importantly, safer opioid supply programs include measures and protocols to prevent and address diversion, including urine drug screens, lock boxes and observed dosing (Atkinson, 2023; Kalicum, 2023; Kolla et al., 2021; McMurchy & Palmer, 2022; Selfridge et al., 2022; Waraksa et al., 2022). Despite concerns regarding the diversion of hydromorphone from safer opioid supply programs, unregulated fentanyl remains the largest contributor of death in both Ontario (Public Health Ontario, 2023) and British Columbia (British Columbia Centre for Disease Control, 2021; Owens, 2023), Canada with no substantial changes in occurrence of deaths related to prescription opioids use, including hydromorphone. These factors indicate that diversion in the context of safer opioid supply requires further study, and ongoing refinement and sharing of protocols to address diversion within safer opioid supply programs is likely the most effective response.

Several client- and provider-reported barriers to safer opioid supply program engagement were also identified. Provider identified barriers to prescribing opioids for the purposes of safer supply primarily reflected a perceived lack of guidance and training with the introduction of the Risk Mitigation Guidance in British Columbia (Giang et al., 2023; Kalicum, 2023; Mansoor et al., 2023), and the limited evidence base regarding the effectiveness and safety of safer opioid supply. For providers, some facilitators to safer opioid supply programs were also identified and included belonging to a team (Foreman-Mackey et al., 2022), as well as strong communication between providers (Mansoor et al., 2023). Barriers reported by clients included challenges accessing safer opioid supply prescribed drugs when program policies mandated multiple visits throughout the day to obtain the complete daily dose (Atkinson, 2023; Haines & O'Byrne, 2023a; Ivsins et al., 2020), and lack of familiarity with the program by non-safer opioid supply providers (Haines et al., 2022; Kolla et al., 2021). The mismatch between the potency of the unregulated drug supply and what was prescribed to safer opioid supply clients was also identified as a limitation of safer opioid supply programs (Atkinson, 2023; Bardwell et al., 2023; Giang et al., 2023; Haines & O'Byrne, 2023a; Haines et al., 2022; Ivsins et al., 2020; Karamouzian et al., 2023; Kolla et al., 2021; McNeil et al., 2022). In particular, the lack of availability of higher potency opioids and multiple formulations that allow for consumption by either injection or inhalation was described in some studies as leading to continued use of unregulated drugs, which may undermine the effectiveness of safer opioid supply programs for prevention of toxicity events. This aligns with a recent study conducted in Ontario, which found a shift in the mode of drug use toward inhalation, contributing significantly to opioid toxicity deaths (MacDonald et al., 2023). A survey conducted among people who use drugs in British Columbia also found that half of respondents would prefer smokeable options if they were provided by safer opioid supply program. Kamal et al., 2023). Furthermore, as the opioid toxicity crisis continues to evolve across North America, polysubstance use is increasingly associated with substance-related deaths (Konefal et al., 2022; Park et al., 2022). In addition to the availability of higher potency opioids, provision of non-opioid prescription medication should continue to be implemented. This is supported by findings generated from interviews conducted with people who use drugs highlighting the need for access to a regulated supply of stimulants and benzodiazepines for people currently accessing these substances from the unregulated supply and to help prevent non-opioid related withdrawal symptoms when transitioning to safer supply programs (Canadian Community Epidemiology Network on Drug Use., 2021; Xavier et al., 2023). Together, identified barriers, facilitators, and suggestions for the improvement of safer supply programs may help to inform the implementation, scale-up and operation of current and future safer supply programs.

Despite the rapidly growing body of evidence surrounding safer opioid supply, several limitations of the available literature were also identified. First, the generalizability of findings is limited as most studies report outcomes among a highly specific client population (e.g., shelter residents, people experiencing homelessness) (Giang et al., 2023; Selfridge et al., 2022), single safer opioid supply programs (Atkinson, 2023; Gagnon et al., 2023; Gomes et al., 2022; Kolla et al., 2021), or highly controlled settings (e.g., COVID isolation hotel) (Brothers et al., 2022; Hong et al., 2022). Furthermore, there is considerable variation in the programmatic structure and service offerings in different safer opioid supply programs across time and geography, meaning that findings may not be directly comparable between studies or contextually transferable across all parts of Canada or different time periods. In addition, it is difficult to disentangle the specific impacts of safer opioid supply provision compared with the wraparound services offered in some safer opioid supply programs. However, the London InterCommunity Health Centre peer-reviewed quantitative evaluation (Gomes et al., 2022) was conducted at a time when funding for broad wraparound services was not in place, in comparison to the grey literature evaluations which were conducted during a period they received Health Canada funding (Kolla

& Fajber, 2023; Kolla et al., 2021). Wrap around services were also not provided by clients who accessed safer supply through British Columbia's Risk Mitigation Guidance (Giang et al., 2023; McNeil et al., 2022), or secure biometric dispensing machines (Bardwell et al., 2023). It is therefore likely that the effects observed in the aforementioned study reflect the provision of safer opioid supply and the associated integration of these clients into the Community Health Center. This aligns with movement towards integration of treatment and care for substance use into primary care across Canada to better support the broader healthcare needs of people accessing harm reduction and treatment for substance use. Third, many of these studies and reports rely on small samples, which is primarily due to the small size and capacity of safer opioid supply programs funded across Canada. This introduces challenges studying rarer outcomes (e.g., fatal opioid toxicities) which were either not reported or were censored due to small event rates in the published literature. Fourth, studies pertaining to provider perspectives included individuals already involved in the implementation of safer opioid supply programs, and may not reflect the perspectives of clinicians with less familiarity with safer opioid supply or those with program-related concerns (Foreman-Mackey et al., 2022; Gagnon et al., 2023; Giang et al., 2023; Kalicum, 2023; Karamouzian et al., 2023; Mansoor et al., 2023). Furthermore, in the two studies that explored provider perspectives (Foreman-Mackey et al., 2022; Mansoor et al., 2023), interviews with service providers were conducted at the pre-implementation or early implementation stages of the Risk Mitigation Guidance, such that changes in perspectives over time could not be studied. Fifth, quantitative evaluations of safer opioid supply programs were limited in their ability to directly compare safer opioid supply client outcomes to people unexposed to safer opioid supply (i.e., individuals with similar clinical and demographic characteristics who are either initiating opioid agonist treatment or unexposed to treatment, including safer opioid supply), with only a single quantitative study including a comparator group (Gomes et al., 2022). Additionally, while grey literature evaluations did include data from pre/post safer supply program participation surveys these studies were often limited in their ability to make direct comparisons due to the lack of longitudinal (i.e., use of cross-sectional study design) and control for systematic differences (e.g., clinical and demographic characteristics) between those current program clients versus clients at program entry. Sixth, a majority of quantitative evaluations were either self-reported cross-sectional studies or used shorter follow-up times (e.g., 14 to 28 days) to assess for study outcomes. The limited data from quantitative studies, along with heterogeneity in reported outcomes precluded us from conducting a meta-analysis across studies. Future research with the standardized reporting of key outcomes among clients enrolled in safer opioid supply programs is required to enable further synthesis of data in this important research area. Finally, evidence related to the prevalence and implications of the diversion of safer supply medications was limited across studies and reports. This is likely influenced by challenges of capturing diversion and its impacts in regularly collected data, meaning that evidence to inform conversations around the prevalence and implications of safer opioid supply diversion will require broad engagement with safer opioid supply providers, clients, and policymakers.

The literature surrounding the provision of safer opioid supply has continued to rapidly evolve, including the recent publication of a large population-based retrospective cohort study of the implementation of Risk Mitigation Guidance dispensing in British Columbia that used administrative databases and integrated an unexposed comparator group (Slaunwhite et al., 2024). This study was published after the completion of our data extraction and was therefore not included in our scoping review; however, the findings were consistent in demonstrating improved clinical outcomes among people receiving safer opioid supply. In this quantitative analysis, one day or more of prescription opioids dispensed under British Columbia's Risk Mitigation Guidance was associated with significant reductions in all-cause mortality (adjusted hazard ratio= 0.39, 95 % CI: 0.25–0.60) and overdose related mortality (adjusted hazard ratio= 0.45, 95 % CI: 0.27–0.75) in the subsequent week (Slaunwhite et al., 2024). There is a continued need for additional quantitative research with large sample sizes from administrative databases, a range of outcomes and sufficient follow-up is needed to strengthen the evidence of the risks and benefits of safer opioid supply. In some cases, targeted studies are also warranted, including safer opioid supply programs in rural or remote areas where the availability and accessibility to health services may be vastly different from urban areas. Moreover, as safer opioid supply programs continue to expand across Canada, theoretically informed qualitative research examining client and provider perspectives, including of those with contrasting experiences of safer opioid supply programs, is needed to better understand the context for program implementation including which types of interventions work best and how overlapping client and provider identities influence access to and experiences with safer opioid supply. Given the importance of local context on program implementation, scale-up and delivery, future research using implementation science approaches to understand which intervention elements of safer opioid supply programs are most effective in different contexts would also be useful.

Conclusions

In summary, our scoping review summarized existing literature regarding safer opioid supply programs and highlights where gaps in the evidence exist given the novelty of safer opioid supply in Canada. Evidence from peer-reviewed publications and grey literature reports suggest that safer opioid supply programs result in improved clinical outcomes. However, gaps in evidence remain, particularly long-term safety and effectiveness evaluations, comparisons with traditional treatments (e.g., opioid agonist treatment), along with the prevalence and impacts of diversion within safer opioid supply programs. The barriers and facilitators of access to safer opioid supply programs, as identified by both clients and providers, can inform the implementation and ongoing delivery of these programs to better meet the needs of people who use drugs. With the rapidly expanding safer opioid supply evidence-base, it is anticipated that research will continue to evolve across North America in multiple settings to enable program adaptation and refinement as part of the multifactorial response to escalating rates of substance-related harms.

CRediT authorship contribution statement

Shaleesa Ledlie: Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing. **Ria Garg:** Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing. **Clare Cheng:** Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing. **Gillian Kolla:** Conceptualization, Methodology, Writing – review & editing. **Tony Antoniou:** Conceptualization, Methodology, Writing – review & editing. **Zachary Bouck:** Conceptualization, Methodology, Writing – review & editing. **Tara Gomes:** Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

G. Kolla, T. Antoniou, and T. Gomes are co-authors on some of the literature summarized in this review. T. Gomes has received funding to support her research program from the Ontario Ministry of Health. G. Kolla has received funding from London Intercommunity Health Centre's Substance Use and Addictions Program grant to conduct independent program evaluations of their SOS program. No other authors have conflicts to declare.

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Ethics approval

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.drugpo.2024.104339.

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