Safer Opioid Supply:

A Rapid Review of the Evidence

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EXECUTIVE SUMMARY

Safer opioid supply (SOS) programs involve the provision of prescription pharmaceutical opioids (e.g., daily dispensed immediate release hydromorphone) and supportive services (e.g., harm reduction, primary care) to people who are at a high risk of experiencing harms related to substance use. The goals of SOS are to provide a safer alternative to the fentanyl-dominated unregulated drug supply, which is responsible for the overwhelming majority of opioid-related toxicity deaths in Canada, particularly to individuals who have not responded to or do not wish to receive more established treatments, such as opioid agonist treatment (OAT). As SOS programs have expanded in Canada, questions regarding their effectiveness and safety continue to arise. Therefore, we conducted a rapid review of qualitative and quantitative peer-reviewed and grey literature publications that describe the clinical outcomes of SOS programs, as well as the perceptions of clients and providers involved in the provision of these programs. In total, we identified and synthesized evidence from 20 publications.

Key Findings

Clinical Outcomes: Quantitative studies reported a lack of fatal opioid toxicity events among SOS recipients. With regards to non-fatal opioid toxicities, grey-literature publications reported lower event rates among active SOS program clients compared to rates reported at program entry. Additionally, 1 peer-reviewed quantitative study demonstrated that visits to the emergency department and hospitalizations, along with associated healthcare-related costs were significantly reduced among SOS recipients one-year after program entry, while no changes in these outcomes were observed among the matched comparator group. These findings are consistent with grey-literature evaluations of SOS programs, which report fewer emergency department visits and hospitalizations, along with improvements in self-reported physical and mental health among current SOS clients compared to those at program entry.

Qualitative studies from the client perspective described decreased use of unregulated opioids following participation in SOS programs, which led to a perceived decrease in the risk of opioid toxicities. Clients also reported improved stability in drug use patterns due to access to SOS, and reduced experience of opioid withdrawal and cravings, also reducing their vulnerability to toxicities. The perspectives of SOS program providers were consistent with client reported outcomes, as providers noted reduced opioid toxicity events, reductions in injection drug use, and improvements in client health status.

Other Outcomes: Following participation in SOS programs, clients reported greater personal autonomy and reduced stigma. Participation in SOS programs alleviated anxiety and heightened self-perceived safety among SOS clients, as they were aware of the dose and potency of the medications they were accessing. Additionally, clients reported more income for food, shelter and basic needs, and decreased involvement in criminal activities.

Diversion: The diversion of drugs provided through SOS programs was raised as a concern by some clinicians and policy makers. Reasons for diversion were identified in qualitative studies and included compassionate sharing with others unable to access SOS, inadequate doses of opioids obtained through SOS programs, financial needs (e.g., selling hydromorphone to generate income for other drugs, food, and basic needs), and slow titration and/or inadequate doses for withdrawal prevention. It is unknown how commonly diversion occurs. However, population-level analyses of mortality data have found no increases in hydromorphone implicated opioid-related deaths in Ontario and British Columbia during a period of SOS program expansion.

Retention: Factors associated with continued participation in SOS programs included continued use of OAT, co-prescription of mental health medications, increased maximum daily dose of hydromorphone, and receiving SOS from prescribers who treated three or more people with SOS.

SOS Program Barriers: Patient-identified barriers to SOS program participation included inconvenient site hours, regimented check-in requirements, lack of information on program eligibility criteria, insufficient program capacity, and a mismatch between the strength of opioids in the unregulated drug supply and prescribed doses. Specifically, clients of SOS programs felt that the potency of prescribed opioids was low in comparison to the unregulated drug supply and identified a need for a greater range of medication options. Provider identified barriers included uncertainty and lack of training surrounding provision of pharmaceutical-grade hydromorphone as a method of harm reduction, a perception of limited evidence surrounding the effectiveness and safety of SOS, and the need for additional support staff to mitigate provider burnout.

Study Limitations

There are several limitations of the available literature. First, the generalizability of findings is limited as most studies report outcomes among specific patient populations (e.g., shelter residents, people experiencing homelessness), single SOS programs, or highly controlled settings (e.g., COVID-19 isolation hotel). Second, it is difficult to disentangle the specific impacts of providing access to a SOS compared with the wraparound services offered in some SOS programs. Third, many of the publications included in our rapid review rely on small samples (primarily due to the small size and capacity of SOS programs funded across Canada), which introduces challenges studying rare outcomes such as fatal and non-fatal opioid toxicity events. Fourth, quantitative studies included in this rapid review were limited in their ability to directly compare SOS client outcomes to people unexposed to SOS. Finally, evidence related to the prevalence and implications of diversion of safer supply medications was limited, likely due to challenges of capturing diversion and its impacts in regularly collected data.

Future Directions

Provision of SOS is a relatively new intervention in Canada, and as programs expand, there is a need for continued evaluation. Future areas of potential research include examinations of how program delivery characteristics (e.g., composition of staffing and wrap-around services), availability of different medications, and refinement of clinical guidelines may optimize provision of SOS. Additional qualitative research is also needed to broaden our understanding of how different population groups (e.g., Indigenous people, people experiencing homelessness, young adults) access and utilize SOS programs.

INTRODUCTION

The ongoing drug toxicity overdose crisis is a public health emergency driven primarily by the permeation of the unregulated drug supply with clandestinely produced fentanyl.[1] The magnitude and urgency of this crisis has led to the implementation of a broad range of measures across Canada, including harm reduction interventions such as supervised consumption sites, drug-checking services and the widespread distribution of take-home naloxone. Despite these measures, fatal and non-fatal toxicities have continued to increase, with 5,360 Canadians losing their lives to an opioid toxicity in the first six months of 2022. Therefore, additional options are needed to respond to the drug toxicity crisis. The provision of safer alternatives to the unregulated drug supply – a practice known as safer opioid supply (SOS) – is a relatively novel response that began in Ontario in 2016 and expanded during the COVID-19 pandemic following the provision of federal funding for these programs and publication of emergency 'risk mitigation' guidance in some provinces.[2-4] In Canada, SOS programs aim to reduce opioid-related harms among individuals at high risk by providing prescription pharmaceutical-grade opioids (e.g., immediate release hydromorphone) in concert with supportive services that address health and social issues, as well as financial and material insecurity.[3] Consequently, rather than emphasizing abstinence, the main goals of SOS programs are to reduce the use of the unregulated drug supply and the corresponding risk of toxicities, while addressing the conditions that contribute to the socioeconomic and structural marginalization of people who use drugs, including material deprivation and stigma.[5] As such, the goals of clients enrolled in SOS programs often differ from those who receive familiar treatments for opioid use disorder (OUD), such as opioid agonist treatment (OAT).[6]

Despite the potential benefits of SOS 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 SOS programs is an urgent priority, particularly as these programs become increasingly integrated into the suite of harm reduction resources available to people who use drugs. Therefore, we sought to conduct an updated review of the published peer-reviewed and grey literature focused on programs offering a safer supply of pharmaceutical opioids, specifically focused on studies that reported either client perspectives and/or outcomes, along with provider perspectives.

METHODS

Search strategy

We conducted a literature search of Ovid MEDLINE, Ovid Embase, CINAHL, APA PsycINFO and Scopus from January 1, 2012, to May 19, 2023. We employed a broad

search strategy to ensure comprehensive capture of articles that may pertain to the provision of a SOS to people who use drugs, including combinations of Medical Subject Headings (MeSH terms) and keywords (See Appendix Tables 1-5 for an overview of our search strategy). Additional records were also retrieved through a citation search of peer-reviewed articles and grey literature documents. Specifically, we conducted internet searches and consulted subject matter experts to retrieve publicly available evaluations of SOS programs.

Study selection

We reviewed titles and abstracts to identify peer-reviewed studies published in English, which assessed outcomes and/or perspectives of SOS recipients or SOS program provider (e.g., physicians, nurse practitioners, pharmacists, social workers, program managers/directors, health authority representatives) perspectives. We excluded studies which focused their evaluation on injectable OAT, heroin assisted treatment and pharmaceutical grade stimulants, as these interventions did not meet our definition of SOS. We also excluded studies describing SOS program models without outcomes, and commentaries and editorials related to the use of SOS. Four study team members independently reviewed the titles and abstracts of articles identified from our literature search and resolved discrepancies by consensus. A full text-review was conducted for abstracts that met our inclusion criteria by the aforementioned team members who independently reviewed articles based on our study criteria.

Data abstraction and synthesis

To characterize included studies, we extracted information related to the SOS program, including method of medication delivery, clinical engagement/oversight and study design. Next, we summarized study results and abstracted the following information: 1) study objective(s); 2) safer supply use patterns; 3) outcomes following safer supply use (e.g., occurrence of drug toxicities, concurrent use of the unregulated drug supply, diversion); and 4) information regarding the provider perspective. For qualitative studies, we reported themes generated by study team members and for studies which were quantitative, we abstracted statistical results (e.g., descriptive statistics, odds ratios) related to safer supply use outcomes.

RESULTS

Our search yielded a total of 1,005 publications after deletion of duplicates. After title and abstract review, we excluded 964 publications that were not related to the provision of a SOS, were a descriptive overview of SOS programs (no outcome data) and commentaries or editorials. Next, we completed a full text review of 53 publications. Following this review, we excluded an additional 33 publications that did not study SOS programs, were conceptual in nature, did not report on outcomes or perspectives

pertaining to SOS programs, or did not provide pharmaceutical grade hydromorphone to clients of the program (See Figure 1 - PRISMA diagram).

In total, 20 publications comprising 15 peer-reviewed publications and five grey literature publications were selected for inclusion. All publications were published in recent years, with one being published in 2020, two in 2021, 11 in 2022 and six in 2023 (up to May 19, 2023). These publications include report findings related to clients of SOS programs and their providers and were either qualitative and/or quantitative in nature. An overview of the study design, population and SOS model implemented in the included studies can be found in **Tables 1 and 2**. Key study findings are summarized in Appendix table 6.

Summary of Included Studies

Studies Describing Outcomes and Perspectives of SOS Recipients

There were five published peer-reviewed studies[7-11] and four publications in the grey literature[12-14] that reported quantitative analyses of clinical outcomes, health services utilization, engagement in criminal activities, and diversion among recipients of SOS. Additionally, eight peer-reviewed qualitative studies[15-22] described client-reported outcomes related to their self-perceived health status, financial stability, involvement in criminal activity following participation in a SOS program, along with SOS program barriers and facilitators.

Quantitative Findings

Among studies that reported quantitative findings, two of the peer-reviewed publications were conducted among shelter residents, either assessing the impact of expanded SOS and harm reduction services within a shelter setting (Hamilton, Ontario)[10], or assessing outcomes among shelter residents moved to a COVID-isolation hotel in Halifax, Nova Scotia.[9] 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 (LIHC) SOS program, comparing SOS clients (N=82) to a matched group of London, Ontario residents with OUD not accessing the program (N=303), and using health administrative databases to compare rates of clinical outcomes over time.[7] The second study applied an algorithm to health administrative databases to identify all SOS recipients in Ontario, Canada between January 2016 and March 2020 based on dispensing patterns of immediate-release hydromorphone (N=447).[8] This study reported time to SOS discontinuation and a descriptive analysis of the prevalence of all-cause mortality and hospitalization when on treatment. The last peer-reviewed study was conducted at the Victoria Cool Aid Society's community health centre in Victoria, British Columbia (B.C.), where chart reviews were conducted on clients receiving SOS to evaluate 60-day adherence as well as identify factors associated with adherence.[11] Finally, three of the grey literature publications report findings of evaluations of Health Canada-funded SOS programs in Toronto,[13] Ottawa,[14] and London,[12] Ontario. These

reports measured self-reported data on drug-related outcomes at baseline (i.e., SOS program entry) and among ongoing SOS recipients. In all studies described above, there were no direct comparisons with individuals unexposed to SOS, with the exception of Gomes et al., which replicated time-series analyses among a matched unexposed comparator group. Furthermore, the services provided within the SOS programs varied across programs and over time (e.g., before vs. after receipt of Health Canada funding), which means that findings may not be directly comparable between studies or generalizable to all SOS programs in place across Canada.

Qualitative Findings

Qualitative findings surrounding client perspectives related to their physical and mental health, financial stability, involvement in criminal activity and potential for diversion following participation in an SOS program, along with SOS program barriers and facilitators, were also presented in eight peer-reviewed studies[15-24] and four grey literature publications[12-14,253-16] Among the peer-reviewed publications, six publications were conducted using one-on-one semi-structured interviews,[15-17,20-22] one study involved both interviews and ethnographic observation,[19] and one was a case report.[18] The grey literature reports used a combination of one-on-one semi-structured interviews or focus group interviews.

Overall, seven studies were conducted in B.C., Canada and included clients of various SOS programs. Specifically, one study conducted interviews with 46 participants who had been clients of the MySafe program for at least one-month, a program which provides access to SOS through secure biometric dispensing machines.[15] Another study interviewed 30 participants who were clients of the Foundry Vancouver Granville clinic, an SOS program for youth and adolescents under 24 years of age.[16] A total of 42 participants were interviewed regarding barriers and facilitators of engagement with the Molson hydromorphone tablet distribution program, which allows clients to access as much daily SOS as needed within set prescribing parameters.[19,20] One study interviewed 12 supportive housing residents (who first received SOS as part of COVID-19 safety protocols) regarding their experiences with SOS while living in supportive housing.[21] Finally, two studies from B.C. examined access to prescription opioids or stimulants under the provincial risk mitigation guidelines, with one study involving interviews with 40 individuals who use drugs and the other being a case study of an individual receiving SOS while undergoing COVID-19 isolation in a hotel setting.[18,22]

Five studies were conducted in Ontario, Canada. One study interviewed 30 clients enrolled in an SOS program in Ottawa,[17] while the other was part of a broad evaluation of the LIHC SOS program described previously.[12] The qualitative results from the grey-literature program evaluation were based on focus groups conducted with current SOS clients, program staff and people on the SOS waitlist, and summarized themes related to clinical outcomes.[12] Another grey literature report conducted focus-groups with current SOS clients and another conducted 1-on-1 semi-structured interviews with SOS

clients.[13,14] Lastly, the final grey-literature report conducted 15 semi-structured interviews, with clients from seven different SOS programs across Canada.[25]

Studies Describing Provider Perspectives

Three peer-reviewed studies and one dissertation reported on provider perspectives using one-on-one semi-structured interviews and was analyzed using a thematic analysis approach.[16,23,24,26] In the previously described study of the Foundry Vancouver Granville Clinic SOS program, researchers also interviewed 10 addiction medicine physicians to understand their experiences with the implementation of the provincial risk mitigation guidelines.[16] Two studies drew from the same sample of providers involved in the design and implementation of SOS programs in Vancouver, B.C., Victoria, B.C., London, Ontario and Dartmouth, Nova Scotia, with the goals of understanding experiences and perspectives on SOS program design and implementation.[23,24] Finally, the dissertation included interviews of 24 providers across B.C., including clinicians and individuals in leadership roles regarding their SOS program implementation experiences.[26] Additionally, the aforementioned evaluation of the LIHC SOS program conducted focus group interviews with program staff as mentioned above. Finally, one grey literature report presented results from a survey completed by 100 SOS program staff members from across Canada and interviews with SOS program leads.[25]

Clinical Outcomes

Opioid-Related Toxicities

A total of three quantitative studies with follow-up periods of 14 days to one-year examined opioid-related toxicity events, with no fatal toxicities and low rates of non-fatal toxicities observed among SOS recipients. In one study, no opioid toxicities were observed among 27 SOS 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.[9] Similarly, 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 SOS 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).[10] However, the emergency shelter introduced SOS in combination with a Safer Use Space for observed substance use, access to OAT, harm reduction supply distribution, and improved opioid toxicity response capacity, rendering it difficult to isolate the relative impact of each measure.[10] Finally, no significant change in the rate of hospital-treated (emergency department [ED] and/or inpatient) fatal opioid toxicity events was observed after one-year of follow-up among 82 clients of the LIHC SOS program (London, Ontario) (≤5 events compared to 10 events [0.12 per person-year] in the year prior to entering the program; $p>0.05$).[7]

There were three evaluations of SOS programs published in the grey literature that reported outcomes related to non-fatal opioid toxicities, primarily attained by comparing

self-reported toxicity events at time of program entry to those among current SOS clients.[12-14] All of these studies reported lower rates of toxicity events among active clients of the programs compared to rates reported at program entry. Specifically, in the evaluation of the LIHC program during the period in which it was receiving Health Canada funding (i.e., April 2021 – October 2021)[12] Kolla et al. reported a lower prevalence of opioid toxicities over the past six-months (23%) and one-month (11%) among current SOS clients, compared to the prevalence reported among clients entering the program (59% and 33%, respectively).[12] Similarly, in an evaluation of the Parkdale Queen West Community Health Centre's (PQWCHC) SOS program (Toronto, Ontario), 15% of clients enrolled in the program for at least six-months reported having an opioid toxicity in the past three-months compared to 50% reporting an opioid toxicity in the past three-months at program entry.[13] The Ottawa SOS program evaluation reported that among SOS recipients who had experienced a non-fatal opioid toxicity event at the time of program entry (N=255), 81% did not report another toxicity event at their most recent clinical visit according to medical chart records.[17] Similarly, in another evaluation of the Ottawa SOS program, 93% of SOS clients reported an opioid toxicity before starting the program, compared to 20% while on safer supply.[14]

Six peer-reviewed qualitative studies examined opioid-related toxicities. A recurrent finding among all studies was that while many SOS recipients continued to access the unregulated drug supply, their self-reported frequency of use decreased, [15-17,19,21,22] which led to a self-perceived decrease in their risk of an opioid toxicity. Specifically, in the study by McNeil et al., clients expressed that access to SOS increased stability in their drug use patterns, and helped them avoid cycles of withdrawal, cravings, and bingeing, thereby reducing their vulnerability to an opioid toxicity.[22] Further, the LIHC SOS program evaluation in the grey literature reported that a major motivation of clients for joining the program was to reduce their risk of opioid toxicities.[12] The benefits of SOS were also reflected in the perspectives of service providers. A survey of SOS providers at programs across Canada, reported that 99% and 93% of respondents either somewhat or strongly agreed that SOS reduced opioid toxicities and injection drug use, respectively.[25]

Infectious Complications

Only one study reported rates of infectious complications from substance use among SOS clients.[7] Specifically, the rate of serious infections (e.g., endocarditis, osteomyelitis etc.) among 82 LIHC SOS 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)[7]. A similar change was not observed among the 303 matched controls (rate ratio 0.72, 95% CI 0.45-1.17; p=0.2).[7]

Other Clinical Outcomes

Two peer-reviewed publications and four grey literature program evaluations reported quantitative analyses of other clinical outcomes, such as visits to the ED, hospitalizations, and the physical and mental health status of SOS recipients. The peer-reviewed study of

the LIHC SOS program evaluation reported significant reductions in the rate of ED visits (p=0.02), and hospital admissions (p=0.005) among SOS clients one-year after program entry, which were not observed among the matched comparator group (p=0.4 and 0.5, respectively).[7] However, there was no statistically significant change in the rates of mental health-related hospitalizations, substance use-related hospitalizations or all-cause mortality among SOS clients.[7] Lastly, ≤5 deaths from any cause in the one-year follow-up period among the 82 included SOS clients, and seven deaths from any cause in the comparator group (N=303) were reported.[7] A descriptive analysis of all-cause mortality and hospitalization among 534 courses of SOS across Ontario identified ≤5 courses where the individual died while receiving SOS, and ≤5 courses where someone died within a week of discontinuation. In this same study, in 18.4% of courses, individuals were hospitalized for <14 days, and in 3.2% of courses, people were hospitalized for ≥14 days.[8]

Findings from the grey literature and from peer-reviewed qualitative studies were generally consistent and reported improvements in self-perceived health status. Specifically, in an evaluation of 10 SOS programs across Canada, McMurchy and Palmer found that SOS clients reported improved health outcomes and treatment of chronic health illness (e.g., HIV, hepatitis C) following SOS program participation.[25] The follow-up evaluation of the LIHC SOS program during the period when it was receiving Health Canada funding found lower self-reported prevalence of recent ED visits, one-night hospitalizations, poor health and poor mental health among current SOS clients compared to those entering the program.[12] In addition, LIHC clients expressed a desire to improve their health and overall stability through participation in the program.[12] Clients and SOS staff also reported that engagement with the LIHC program improved access to treatment for conditions including HIV and Hepatitis C through the associated wrap-around services.[12] Similarly, the evaluation of the PQWCHC in Toronto reported that 73% of those receiving SOS were able to address a health issue for the first time after starting the program, and 85% reported feeling more connected to healthcare.[13] In the Ottawa SOS program evaluation, improvements in mental and physical health were reported,[14] including healthy weight gain, improved stamina and better self-care.[17] These findings were consistent with those of peer-reviewed qualitative studies where SOS clients reported increased interactions with the healthcare system due to the range of wrap-around services integrated into the various SOS programs[16,17,19] Increased access to and interaction with health services and improved relationships with clients were also described in qualitative studies with SOS providers.[23,25]

Retention

Retention to SOS was reported in two peer-reviewed publications[8,11] and two reports evaluating federally funded SOS programs.[12,13] These publications reported adherence to SOS in BC[11] and Ontario.[8,12,13] In B.C, an evaluation of the SOS program in Victoria (N=286 clients, 275 of whom were receiving hydromorphone) reported that 77.3% of SOS recipients remained adherent at 60 days of follow-up.[11] Factors associated with adherence included continued OAT use, receipt of mental health medications, and

increasing client's maximum daily dose.[11] Similarly, an evaluation of the LIHC SOS program reported 94% retention rates among their clients between April 1, 2020 to September 30, 2021, while the PQWCHC SOS program evaluation reported a one-year retention rate of 80%.[12,13]

Finally, in the lone study using health administrative data in Ontario to assess courses of SOS at the provincial level, among 534 courses of safer supply (447 unique individuals), the median time to discontinuation was 272 days.[8] Furthermore, those receiving SOS from prescribers who treated three or more people with SOS over the study period ('frequent prescribers') had longer retention rates (median 289 days). Retention was also higher among people initiating safer supply in later years (2018-2020, median 309 days).[8]

Costs to the Healthcare System

One study used administrative health records to compare changes in healthcare costs in the one-year following SOS enrollment with costs incurred by the same individuals in the year preceding program enrollment.[7] Overall, statistically significant reductions in healthcare-related costs (excluding costs related to primary care or outpatient medications) (from $15,635/yr to $7310/yr; p=0.002) were observed among SOS clients in the year following program entry relative to the year preceding enrollment. In a subgroup analysis of public drug beneficiaries, medication costs increased among SOS clients following program enrollment (from $12,840 to $21,119/yr; p<0.001), with costs of hydromorphone and OAT accounting for approximately 15% of total medication costs (increase from $1080 to $3128/yr).[7]

Other Client Reported Outcomes

A common theme across included studies was enhanced levels of personal autonomy among clients as they were now able to choose when to use drugs,[15,17,22] the ability to stockpile medications to meet future needs (e.g., going on vacation, requirement for an increased dose),[15,16] and the ability to return to the SOS program after a temporary leave without penalty (e.g., requirements for dose titration).[19] A study of the MySafe SOS program found that clients experienced less stigma and an increased sense of privacy due to not being required to participate in witnessed dosing, which is often a requirement of OAT and some SOS programs.[15] 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.[17,19,21,22]

Two reports evaluating federally funded SOS programs in Canada reported similar findings. In the PQWCHC SOS program evaluation of current SOS 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.[13] Further, clients described improvements in several domains, including mental health, relationships with family and

friends, pain management and overall quality of life.[13] Finally, in the evaluation of initial SOS programs funded by Health Canada, McMurchy and Palmer found that many clients reported multiple ways in which they were receiving support through SOS programs including income, transportation, food, and clothing. However, housing remained an unmet need for many clients.[25]

From a provider perspective, similar findings were reported. Specifically, providers interviewed in the studies by Giang et al.[16] and Foreman-Mackey et al.[23] perceived that SOS provided clients with greater stability and allowed them to carry on with their lives as they were no longer required to spend a substantial portion of their time procuring drugs.

Measures of financial stability were reported in two peer-reviewed qualitative studies,[15,19] and in the PQWCHC SOS program evaluation.[13] In studies in B.C., SOS clients reported that they spent less money on drugs, resulting in the ability to purchase necessities such as food and clothing.[15,19] In the PQWCHC program evaluation, 77% of current SOS 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.[13]

Involvement in criminal activity was evaluated in five peer-reviewed qualitative studies,[17,19-22] and in three of the grey-literature SOS program evaluations.[12-14] In all of the qualitative studies, SOS clients reported decreased involvement in criminal activities following SOS program participation as they no longer needed as much money to purchase unregulated drugs.[17,19-22] The LIHC SOS program evaluation found that, among current SOS 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.[12] In comparison, among a group of individuals entering the SOS program, the respective proportions were much higher at 73%, 86% and 50%.[12] Similar findings were reported by Atkinson et al., with 44% of clients entering the PQWCHC SOS program reporting that they had done something illegal to obtain drugs in the past three months, compared to 19% of current clients.[13] Additionally, among clients enrolled in the PQWCHC SOS program, 27% reported decreased interactions with the police, with the caveat that no differences were noted between current clients and those entering the program in terms of being stopped by the police in the past three months.[13] Finally, the number of Ottawa SOS program clients participating in criminalized behaviour decreased from 93% (N=28) at program entry to 40% (N=12).[14]

Diversion

Only one quantitative study included diversion or medication sharing as an outcome. In this study, investigators described “concerns around diversion/sharing/selling” among people accessing SOS for 14 days during COVID isolation in a hotel setting.[9] This outcome was determined through residents, shelter staff or health professionals reporting, and was described as potential diversion regardless of whether it was confirmed by the resident or another source.[9] Among the 27 residents receiving SOS, there were three documented concerns around diversion.[9] All of these individuals were

provided with supplies of multiple substances, including opioids, stimulants and alcohol, and the investigators did not provide details on which substances were implicated in the diversion-related concerns.[9]

Two peer-reviewed qualitative studies[16,17] and three SOS program evaluations[12,14,25] reported client perspectives on diversion. In all studies, diversion was discussed as a challenge faced by SOS programs. In the evaluation of the 10 federally-funded SOS programs in Canada, some SOS clients reported an increase in immediate release hydromorphone (Dilaudid®) availability on the street and a decrease in price. However, there were no details regarding the frequency with which this was occurring or variations across the sites included in the evaluation.[25] Reasons for diversion have been described in several studies, and included compassionate sharing with others unable to access SOS,[17] inadequate access to opioids through SOS at doses that met their needs,[17] financial needs (e.g. selling hydromorphone to generate income for other drugs, food, and clothing),[16] and slow titration and/or inadequate doses for withdrawal prevention.[25] Furthermore, in the Safer Supply Ottawa and London program evaluations, participants noted that diversion occurs within other substance use programs (e.g. methadone) and therefore is not unexpected.[12,14,17] Clients of this program also indicated that they only shared their medications with people within their networks, and did not provide SOS medications to opioid naive individuals.[17]

There were two peer-reviewed qualitative studies of provider perspectives that reported findings related to diversion.[16,26] In the study by Giang et al., prescribers noted that the early risk mitigation guidelines in BC did not explicitly discuss diversion, with many reporting discomfort in the use of urine drug screens.[16] In contrast, Kalcium reported that SOS providers introduced urine drug screens as a way to increase their comfort regarding diversion, while also recognizing the potential harms of UDS on their patients.[26] Kalcium also reported that providers considered the potential for diversion and its broader public health impacts when making the decisions pertaining to implementation of B.C.'s risk mitigation guidance.[26]

Barriers to Accessing SOS Programs

A number of peer-reviewed studies and grey literature publications described client-identified barriers or limitations to SOS programs. One study of a program in Vancouver, B.C. identified inconvenient site hours and the need for multiple daily visits due to policies that limited the amount of SOS medications dispensed at a time as an access barrier.[19] Additionally, in the Ottawa program evaluation, clients stated that regimented requirements for daily check-ins and supervised consumption was not preferred.[17] However, some clients in the London LIHC program identified the lack of a supervised consumption site as a SOS program barrier.[12] Both the LIHC and PQWCHC program evaluations recommended integration of a supervised smoking site to address the risk of toxicity events among people smoking fentanyl.[12,13]

In the grey literature, SOS clients of programs in Ottawa and London, Ontario, reported problems with accessing their safer supply medications from pharmacies,[12,14] particularly those unfamiliar with SOS programs.[14] The inability to obtain multi-day take-home doses was also identified as a barrier in one report.[13] In the London LIHC program, insufficient program capacity, a lack of information on program eligibility , negative experiences when interacting with health care providers outside of the program, and a lack of continuity of care when entering inpatient care were all identified as barriers to SOS.[12]

Another barrier commonly described by SOS clients is a mismatch between the strength of opioids in the unregulated drug supply and the dose of opioid prescribed within SOS programs.[14-17,19,22] This mismatch was perceived to potentially precipitate symptoms of withdrawal and cravings due to the lower euphoric effect of prescribed opioids provided through SOS programs. [22] Further, findings from three peer-reviewed studies demonstrated that this mismatch led to clients supplementing with drugs from the unregulated supply.[15-17] A similar theme was reported in the report on the PQWCHC SOS Program, as well as at the LIHC program where participants expressed a desire for a greater range of medication options.[12,13]

From the provider perspective, a common barrier identified in peer-reviewed studies and grey literature reports was confusion and uncertainty, particularly regarding the risk mitigation guidelines that were introduced in B.C.[16,24,26] In one report, only 18% of providers surveyed reported that they had sufficient training to prescribe opioids as a form of safer supply.[25] Reasons for the confusion and uncertainty included limited education and training surrounding risk mitigation guidelines,[26] with some providers expressing a lack of confidence in the guidelines or their own knowledge.[16] One study also identified concerns from providers that the guidelines were based on limited evidence (due to the small number of studies that had examined SOS programs at the time),[24] which was consistent with another study where providers reported that SOS prescribing required them to balance the harms of not providing SOS against the unknown risks of this modality.[23] Other barriers included inadequate infrastructure,[26] the need for more staff,[12,25] challenges with recruitment of staff due to high workloads and burnout,[12] as well as a lack of support from regulatory colleges.[24]

While studies on provider perspectives identified a number of barriers to prescribing SOS, some facilitators were also identified. These factors included greater comfort and support from working as part of a team,[23] strong communication between providers,[24] and for some providers, having written guidelines (i.e., the risk mitigation guidelines).[26]

DISCUSSION

The purpose of this review of published peer-reviewed and grey literature was to examine the current evidence base surrounding SOS programs with regards to client outcomes and provider perspectives. We identified 20 publications, all published in Canada since 2020, with 17 published in 2022 and 2023 alone. Many of these studies evaluated a single

SOS program, and quantitative studies had relatively small sample sizes, reflecting the limited scale-up and capacity of SOS programs in place across Canada. Despite variability in SOS programs evaluated in the included studies, findings were largely consistent across these diverse study populations, suggesting that reported benefits of and barriers to SOS apply to a diverse set of SOS programs.

Overall, the currently available evidence regarding health outcomes among SOS clients is generally favorable. Specifically most studies found reductions in opioid toxicity events (fatal and non-fatal)[8-10] and frequency of opioid use among SOS program clients[15-17,19,21,22], with one study finding no change in opioid toxicity events, although these outcomes were generally rare.[7] Other health outcomes also improved among SOS clients, including reductions in any-cause ED visits and hospitalizations,[7,12] infectious complications, and improvements to clients' mental health.[7,12,14] Within the qualitative literature, participants expressed that SOS program participation improved access to health and other wraparound services,[16,17,19,23,25] allowing them to address other health issues such as HIV and hepatitis C.[12] Additionally, both SOS program clients and providers interviewed in qualitative studies expressed that SOS recipients were provided with a greater sense of stability as they were no longer as preoccupied with concerns related to how they would to obtain unregulated drugs,[16,17,19,21-23] or engagement in criminal activity as a means of income generations for drug related purchases.[12-14,17,19-22] Across studies, there was no evidence of negative outcomes from SOS programs, although the evidence base for some outcomes remains limited.

Another area of high relevance examined in several publications was the diversion of drugs prescribed through SOS programs, examined in six qualitative studies[12,14,16,17,25,26] and one quantitative study.[9] Although studies included in our rapid review suggest that diversion does occur,[9,12,14,25] the current extent of diversion involving prescription hydromorphone remains unknown. Reasons for diversion identified in the literature include selective compassionate sharing (e.g., clients diverting to others within their networks who are not opioid-naïve),[14,17] inadequacy of the hydromorphone prescribed through SOS programs,[17,25] and financial needs.[16] Furthermore, SOS programs incorporate measures and protocols to prevent and address diversion, including urine drug screens, lock boxes and observed dosing where appropriate.[11-13,25-27] Additionally, despite concerns regarding the diversion of drugs, and in particular hydromorphone, from SOS programs, population-level analyses of mortality data have not found increases in hydromorphone-related deaths in Ontario[28] and B.C[29,30] (where these data are available and most Canadian SOS programs are based). These factors indicate that diversion in the context of SOS requires further study, and that more guidance may be needed for providers on how to mitigate diversion.[16]

A number of client- and provider-reported barriers to SOS program engagement were also identified. For example, clients reported challenges accessing SOS prescribed drugs when program policies mandated frequent check-ins throughout the day to obtain the complete daily dose,[13,17,19] and lack of familiarity with the program by non-SOS

providers.[12,14] The mismatch between the potency of the unregulated drug supply and what was prescribed to SOS clients was also identified as a limitation of SOS programs.[12-17,19,22] In particular, the lack of availability of higher potency opioids, and formulations that allow for safe injection and inhalation may lead to continued use of unregulated drugs which can undermine the effectiveness of SOS programs for prevention of toxicity events. Barriers to SOS programs identified by providers primarily reflected a perceived lack of guidance and training with the introduction of risk mitigation guidelines in B.C.,[16,24,26]concerns about the limited existing evidence base for SOS,[23,24] as well as inadequate staffing[12,25] and infrastructure.[26] For providers, some facilitators to SOS programs were also identified and included belonging to a team,[23] as well as strong communication between providers.[24] Together, these identified barriers and facilitators may help to inform the implementation, scale-up and operation of current and future SOS programs.

Limitations of Reviewed Studies

Despite the rapidly growing body of evidence surrounding safer supply, there are several limitations of the available literature. 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),[11,16] single SOS programs,[7,12,13] or highly controlled settings (e.g., COVID isolation hotel).[9,18] Furthermore, there is considerable variation in the elements of SOS programs across time and geography, meaning that findings from these studies and reports may not be contextually transferable across all parts of Canada or different periods. In addition, it is difficult to disentangle the specific impacts of SOS compared with the wraparound services offered in some SOS programs. However, it is important to note that the LIHC quantitative evaluation[7] was conducted at a time when funding for broad wraparound services was not in place. It is therefore likely that the effects observed in this study reflect the provision of SOS and the associated integration of these clients into the community health center where primary care for physical and mental health comorbidities is available. This aligns with movement towards better integration of OAT into primary care across Canada to better support the broader healthcare needs of people accessing harm reduction and treatment related to substance use in Canada.

Second, many of these studies and reports rely on small samples, which is primarily due to the small size and capacity of SOS programs funded across Canada. This introduces challenges studying rare outcomes (e.g., opioid toxicity events, in particular fatal events) which were either not reported or were censored due to small event rates in the published literature. As SOS programs expand, and more population-based studies are implemented, it is anticipated that the strength of the evidence on these outcomes will improve.

Third, studies pertaining to provider perspectives included participants who were already involved in the implementation and/or provision of SOS, meaning that identified themes

are specific to those who are already familiar with SOS programs, and may not reflect the perspectives of all clinicians.[16,23,24,26] Furthermore, in two studies of provider perspectives,[23,24] interviews with service providers were conducted at the pre-implementation or early implementation stages of the risk mitigation guidelines, such that changing perceptions over time cannot be captured.

Fourth, quantitative evaluations of SOS programs were limited in their ability to directly compare SOS client outcomes to people unexposed to SOS (i.e., either those with similar clinical and demographic characteristics initiating OAT or those unexposed to any treatment or SOS). This was addressed in some studies by either constructing a comparator group of similar individuals living in the same geographic area with OUD not exposed to SOS,[7] or reporting the prevalence of self-reported outcomes among current clients of SOS programs to those described by individuals at intake.[9,11-13,25]

Finally, evidence related to the prevalence and implications of diversion of safer supply medications were limited across studies and reports. This is likely influenced by challenges capturing diversion and its impacts in regularly collected data, meaning that evidence to inform conversations around the prevalence and implications of SOS diversion will require broad engagement with SOS providers, clients and policy-makers.

Future Directions

Given the novelty of SOS programs in Canada, there is a need for their continued evaluation. Studies on more varied SOS programs can help to improve our understanding of the effectiveness of SOS within different contexts, including different client populations, and different levels of integration of wraparound services. In some cases, targeted studies are also warranted, including SOS programs in rural or remote areas where the availability and accessibility to health services may be vastly different from urban areas. Evaluation of rarer outcomes like opioid-toxicity deaths and hospitalizations would also benefit from further research involving larger sample sizes that may require the use of large administrative databases. Additionally, further qualitative research is needed to broaden our understanding of how different population groups (e.g., Indigenous people, people experiencing homelessness, young adults) access and utilize SOS programs and integrated wrap around services (e.g., primary care). Other gaps identified through this review include the scarcity of evidence on cost-effectiveness of SOS programs, as well as on select clinical outcomes like injection-related infectious complications. Further efforts to examine these aspects of SOS will be important to informing these programs as they continue to develop, evolve, and become more established across Canada.

CONCLUSION

The practice of SOS expanded during the COVID-19 pandemic, with the evidence for these programs rapidly evolving in parallel. Generally, evidence from peer-reviewed publications and grey-literature reports suggest that SOS programs are beneficial to

clients through measurable clinical outcomes and improvements in mental health. The prevalence and role of diversion within SOS programs remains understudied, although designing studies to specifically address this concern is challenging. Instead, the ongoing refinement and sharing of protocols to identify and address diversion within SOS programs is likely the most effective response. Importantly, despite limited evidence on diversion, the lack of rising hydromorphone-related deaths at a population-level in the two provinces with most expansive access to SOS is reassuring. Finally, barriers and facilitators to SOS identified by clients and providers may inform the implementation and continued delivery of SOS in the future. In particular, addressing the mismatch in the drugs that are prescribed through SOS programs and drugs that are in the unregulated drug supply may better meet the needs of people who use drugs. With the rapidly expanding evidence-base related to SOS during the COVID-19 pandemic, it is anticipated that research will continue to evolve which will enable program adaptation and refinement with the ultimate goal of improving the physical and mental health of people who use drugs.

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TABLES AND FIGURES

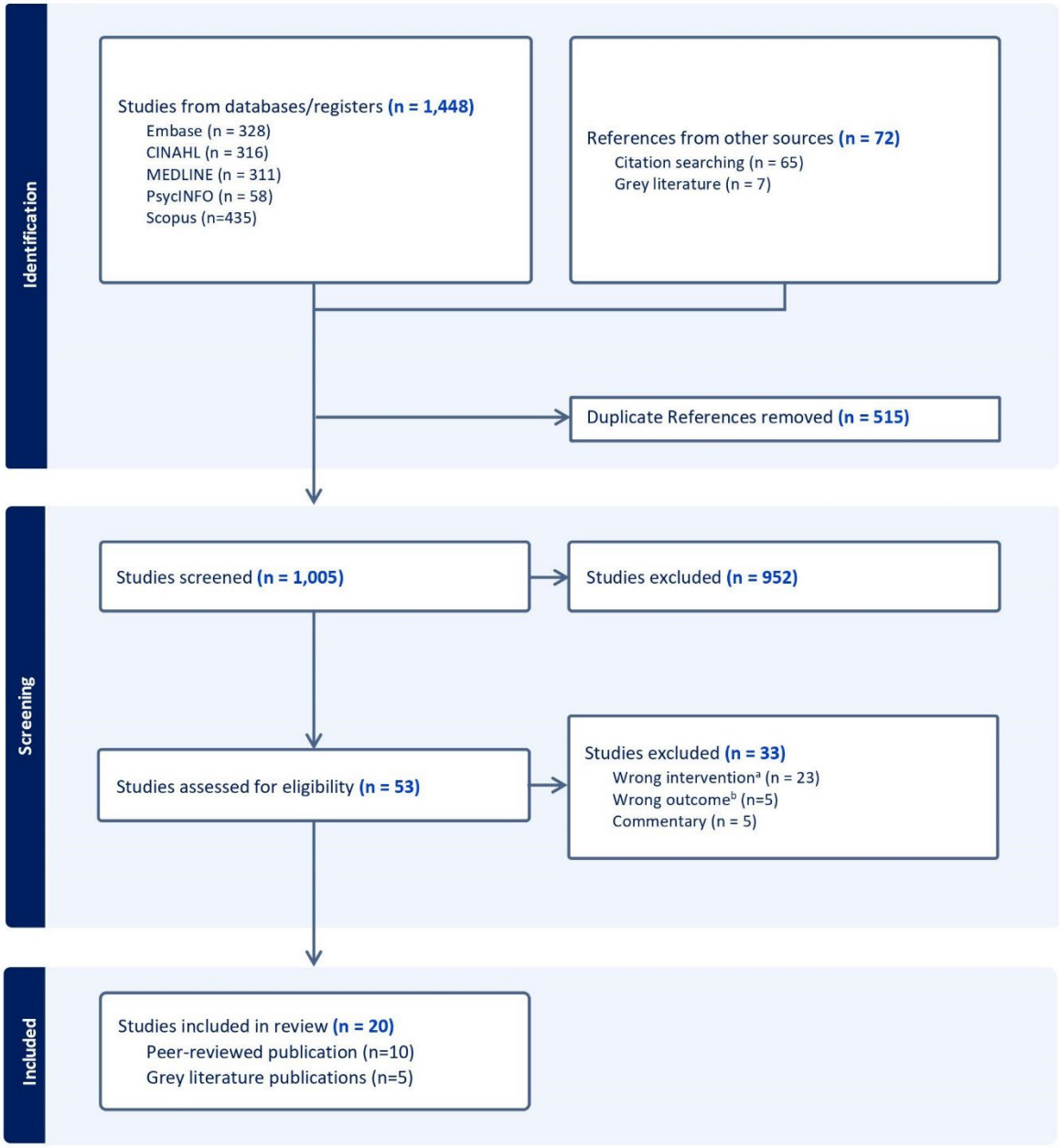

Figure 1. PRISMA Diagram

Footnotes:
[a]Provision of iOAT 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

Table 1. Overview of Peer-Reviewed Studies

Study	Study design	Study Population		Safer Opioid Supply Model	Clinical Engagement/ Oversight
		Inclusion Criteria	Study Size and Demographics		
Bardwell et al., 2023	1-on-1 semi-structured interviews	**Location:** Vancouver, British Columbia, Canada **Study Period:** November 2021 to April 2022 **Inclusion Criteria:** Participated in 1 of 3 MySafe sites in Vancouver, BC for at least 1 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). **Recipients of OAT:** 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 supervised, however MySafe staff were available on-site during day-time hours to assist with technical difficulties.
Giang et al., 2023	1-on-1 semi-structured interviews	**Location:** Vancouver, British Columbia, Canada	**Participants**: 30 young people who use drugs (aged	The SOS program was based on the 2020 interim risk mitigation guidance, a	No details pertaining to program oversight or engagement were provided.

		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 SOS prescription of hydromorphone in the prior 6 months. **Inclusion Criteria (Providers):** Addiction medicine physicians employed by Vancouver Coastal Health Authority and Providence Health.	19 to 24; 47% identified as women); 10 providers **Recipients of OAT:** All participants had a diagnosis of OUD and most were being prescribed OAT.	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.	
Haines et al., 2023	1-on-1 semi-structured interviews and surveys.	**Location:** Ottawa, Ontario, Canada **Study Period:** Summer of 2022	**Participants:** N=30 (43.3% female; median age = 42 [35-50]).	Participants were recruited from three different Ottawa-based safer supply programs: 1) run at a supervised consumption	**Clinical Engagement:** Various healthcare services (e.g., primary care) were available to clients at each of the three Ottawa SOS

		Inclusion Criteria: People ≥18 years old, who participated in an Ottawa-based safer supply program.		site attached to a homeless shelter that is open 16h/day; 2) within an addictions treatment clinic; open Monday to Friday for 8h/day with oversight from physicians; 3) within a community health center with oversight from nurse practitioners. The three SOS programs provide clients with hydromorphone and/or injectable hydromorphone with SROM and/or methadone or suboxone.	programs. All clients were required to go through an in-take process and attend weekly check-ins with a healthcare provider. **Oversight:** Requirements for witnessed dosing were not specified.
Hong et al., 2022	Case report	**Location:** British Columbia, Canada **Study Period:** Not Reported **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 patient 2-3 times daily during 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. DAD. 2020 Ivsins et al., J Urban Health. 2021	1-on-1 semi-structured interviews and >100 hours 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 consumption. Based on prescribing parameters, clients may access up to five prescribed doses of hydromorphone daily (minimum one-hour interval between 16mg 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. OAT was also provided to clients. **Oversight**: Program clinic was attached to a safe injection site where a nurse would witness doses. To prevent diversion, hydromorphone tablets were crushed by the nurse before distribution.
Ivsins et al., J Urban Health. 2022	>100h of ethnographic observations of study participant	**Location:** Vancouver, British Columbia, Canada **Study Period:** October 2020 to January 2021 **Inclusion Criteria:** Residents of the Bellevue permanent support housing building 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., OAT, prescribed safer supply).	**Clinical Engagement**: Residents of the Bellevue supporting housing building were provided access to primary care (onsite nurses, physicians), substance use services (OAT, SOS) 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 their 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 their supportive housing building.
McNeil et al., 2022	1-on-1 semi-structured interviews	**Location:** British Columbia, Canada **Study Period:** February to July 2021 **Inclusion Criteria:** People who use drugs and accessed prescription opioids or stimulants under the B.C risk mitigation guidelines.	**Participants:** N=40 (48% women; mean age = 39]19–57]	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 guidelines. **Oversight:** Did not specify whether doses were witnessed.
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	**Participants:** N=77 (25% women; mean age = 42). *Note:* only N=27 were provided with hydromorphone SOS. **Recipients of OAT:** 12 residents received both OAT and hydromorphone tablets on the same day.	Physicians and NPs prescribed medications following British Columbia's Risk Mitigation Guidelines, which covers opioids, stimulants, benzodiazepines, alcohol, and tobacco. **Opioid specific guidelines:** Offer OAT to those with OUD, oral	**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

		provided during 14-day mandatory isolation.		hydromorphone 8mg tablets, 1-3 tablets/hr; maximum dose 14 tablets (112mg); long-acting opioid (e.g. SROM) with short-acting opioid for those not on OAT. 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.	delivered daily by community pharmacist. Witnessed consumption was not required. Prescribers conducted phone follow-ups to adjust dosages daily for first 3 days, and then as needed.
Gomes et al. 2022	Interrupted time-series analysis using health administrative databases	**Location:** London, Ontario, Canada **Study Period:** January 1, 2016, and March 31, 2019. **Inclusion Criteria:** Clients of the London Intercommunity Health Centre SOS Program and matched London residents with OUD unexposed to SOS	**Participants:** N=82 SOS clients matched to 303 unexposed London residents with OUD (40.2% male, mean age = 41). **Recipients of OAT:** 61.0% had received OAT in the prior year. **Co-morbidities:** SOS clients had high prevalence of HIV (34.0%), 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. SROM often prescribed as long-acting medication alongside hydromorphone; primarily taken as oral, observed dose once daily at pharmacy. SOS program at the time of study period was offered to clients with multiple, serious medical complications (i.e., recurrent infective	**Clinical Engagement:** SOS program based in Community Health Centre, so comprehensive primary healthcare 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; long-acting opioids dispensed daily

				endocarditis, untreated HIV) and was later expanded to others, including those experiencing homelessness or street-involvement.	from pharmacies via observed dosing.
Lew et al. 2022	Case Series	**Location:** Hamilton, Ontario, Canada **Study Period:** January 27 – March 19, 2021 **Inclusion Criteria:** people accessing an emergency adult men's shelter during a COVID-19 outbreak.	**Participants:** People residing in shelter. Comparing those who accessed the shelter during Safer Use Space 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 OAT 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 OAT and/or SOS. Local pharmacy provided naloxone kits to shelter residents, in SUS and on shelter premises. Paramedic group provided oxygen; training videos developed for SUS 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 (10-16h/day).

Selfridge et al. 2022	Descriptive Chart Review	**Location:** Victoria, British Columbia, Canada **Study Period:** March – August 2020 **Inclusion Criteria:** Clients of the Victoria Cool Aid Society's Community Health Centre, who were prescribed SOS. Those stable on OAT and those connected with psychiatrist were not eligible for the SOS program (unless psychiatrist consented).	**Participants**: N=286 clients (36.4% female; mean age = 39). *Note:* Only N=274 received hydromorphone **Recipients of OAT:** 90.9% were co-prescribed OAT at baseline. **Co-morbidities:** Among clients there was a high prevalence of Hepatitis C (42%), injection drug use (75%), and skin or tissue damage (44%).	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 OAT. Medications were dispensed daily from community pharmacies (some deliver to shelters and sites supporting self-isolation).	**Clinical Engagement:** A Multidisciplinary clinical team, including primary care physicians, nurse practitioner, nurses, pharmacists and allied health professionals. In May 2020, distributed model of care with clinics and on-call services throughout community including COVID-19 sheltering sites. **Oversight:** SOS was dispensed daily from community pharmacies (unwitnessed). OAT doses were witnessed. Urine drug screens were regularly conducted.
Young et al. 2022	Retrospective cohort study	**Location:** Ontario, Canada **Study Period:** **Inclusion Criteria:** Individuals with OUD 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). **Recipients of OAT:** 69% had accessed OAT in the past year. **Co-morbidities:** Study participants had a high prevalence of HIV (14%), and prior infective complications (42%).	Safer supply was defined as daily dispensed immediate-release hydromorphone of at least 32mg on at least two of first three days of prescribing (using 4mg or 8mg tablets).	No details of oversight or clinical engagement was provided as this was not an evaluation of a specific program.
Foreman-Mackey	1-on-1 semi-structured	**Location:** Dartmouth, Nova Scotia; London,	**Participants:** N=17, including 7 program	Proposed biometric opioid dispensing machine pilot	No details of program oversight or engagement were

et al., 2022	interviews coded using a thematic analysis approach	Ontario; Victoria, British Columbia; Vancouver, British Columbia **Study Period:** **Inclusion Criteria:** Professional stakeholders involved in the design, implementation and/or operation of a SOS programs.	managers/executive directors, 3 political/health authority representatives, 5 physicians, 1 nurse and 1 pharmacist.	program locations in Canada.	provided as the interviews were conducted in the pre-implementation stage (at 3 sites) and early implementation stage (1 site) of biometric dispensing machines.
Mansoor et al., 2023	1-on-1 semi-structured interviews coded using a thematic analysis approach	**Location:** Dartmouth, Nova Scotia; London, Ontario; Victoria, British Columbia; Vancouver, British Columbia **Study Period:** **Inclusion Criteria:** Professional stakeholders involved in the design, implementation and/or operation of safer supply programs.	**Participants**: N=17, including 7 program managers/executive directors, 3 political/health authority representatives, 5 physicians, 1 nurse and 1 pharmacist.	Medication is secured by MySafe (a biometric machine that dispenses medication) and allows use non-witnessed use of these medications.	No details of program oversight or engagement were provided as the interviews were conducted in the pre-implementation stage (at 3 sites) and early implementation stage (1 site) biometric dispensing machines.

Table 2. Overview of Grey Literature Publications

Study	Study design	Study Population		Safer Opioid Supply Model	Clinical Engagement/ Oversight
		Inclusion Criteria	Study Size and Demographics		
Kalicum, 2023	1-on-1 semi-structured interviews coded using a thematic analysis approach	**Location:** British Columbia, Canada **Study Period:** **Inclusion Criteria:** Service providers involved in SOS programs in British Columbia.	**Participants**: N=24, including 7 Physicians, 5 Nurse Practitioners, 4 Pharmacists, 3 Outreach Workers, and 1 Registered Nurse, as well as 4 individuals who identified as being in leadership positions within service provider settings.	The B.C. Centre of Substance Use risk mitigation guidance.	Clinical engagement and oversight was not described in this study as it included providers involved in different programs (but all implementing the risk mitigation guidance).
Kolla et al., 2021	Evaluation using a survey and focus groups	**Location:** London, Ontario, Canada **Study Period**: April to October 2021. **Inclusion Criteria (survey):** People admitted to the SOS program being initiated into treatment at intake, and current clients who had been in the SOS program for at least four weeks. **Inclusion Criteria (focus groups):** Current clients of the SOS program and program staff.	**Participants:** N=19 people being admitted to the SOS program and 59 current clients. **Participants (focus groups):** Current clients of the SOS program, program staff and clients on the waiting list. **Recipients of OAT:** All SOS clients involved in the focus groups had prior experience with methadone.	The SOS program is part of the broader 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 SROM as a long-acting opioid backbone co-prescribed for witnessed dosing at a pharmacy.	**Clinical engagement:** Comprehensive primary care is provided for all SOS clients (option of wrap around care). Clients frequently engage with the health care team. **Oversight:** Urine screening used to ensure prescribed medications are taken (no consequences for other substances found). SROM doses were witnessed, while hydromorphone was provided as take-home doses.

Atkinson et al., 2023	Evaluation using a survey and interviews	**Location:** Toronto, Ontario, Canada **Study Period:** July to November 2022 (clients being admitted) and August 2022 to January 2023 (current clients) **Inclusion Criteria (survey):** People admitted to the SOS program and current clients who had been in the SOS program for at least six months. **Inclusion Criteria (interviews):** Current SOS clients.	**Participants (survey):** N=10 people being admitted to the SOS program and N=27 current clients.	The SOS 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 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 witnessed dosing is used for SROM. Urine screenings were used infrequently.
McMurchy et al., 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=100 staff across eight SOS programs. **Participants (interviews):** N=15 clients (46.7% male), and N=15 program staff.	The SOS program model varied across the different programs. Majority provided hydromorphone tablets, with some also providing access to injectable hydromorphone, fentanyl patches or oxycodone. Many clients also received SROM as a longer-acting backbone. Most programs provide daily pick up at pharmacies and observed administration of hydromorphone. Some	**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 and observed administration of 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.

				programs offer carries while others do not.	
Haines et al., 2022	Evaluation using chart reviews, survey, and interviews	**Location:** Ottawa, Ontario, Canada **Study period:** April 1, 2022, to July 31 2022. **Inclusion Criteria:** Current SOS clients across three SOS 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 SOS programs. Typically, each program pairs short-acting hydromorphone tablets (8mg or 4mg) and/or injectable hydromorphone (10mg/mL vials) with a long-acting opioid (SROM, methadone or buprenorphine/naloxone).	**Clinical engagement:** Various healthcare services (e.g., primary care; weekly check-ins) were available to SOS clients at each of the three Ottawa SOS programs. **Oversight:** Most clients picked up medications daily from the pharmacy (in some cases receive daily home delivery) and are required to complete weekly check-ins with the safer supply team. Doses were witnessed when clients first began the program.

APPENDICES

eTable 1. Database: Ovid MEDLINE(R) 2012 to May 19, 2023.

Line	Searches	Results
1	exp Harm Reduction/	4106
2	exp substance-related disorders/ or exp drug overdose/ or exp opioid-related disorders/ or exp substance abuse, intravenous/ or exp substance abuse, oral/	310119
3	safe* opioid supply.mp.	11
4	(pharmaceutical adj2 opioid).mp.	111
5	((diamorphine or diacetylmorphine) adj2 assist*).mp.	6
6	((diamorphine or diacetylmorphine) adj2 prescri*).mp.	32
7	risk mitigation.mp.	2364
8	safe* supply.mp.	158
9	3 or 4 or 5 or 6 or 7 or 8	2669
10	1 or 2	311964
11	9 and 10	262
12	limit 11 to (english language and yr="2012 -Current")	311

eTable 2. Database: Embase 2012 to May 19, 2023.

Line	Searches	Results
1	exp Harm Reduction/	9032
2	exp substance-related disorders/ or exp drug overdose/ or exp opioid-related disorders/ or exp substance abuse, intravenous/ or exp substance abuse, oral/	369203
3	safe* opioid supply.mp.	13
4	(pharmaceutical adj2 opioid).mp.	147

5	((diamorphine or diacetylmorphine) adj2 assist*).mp.	11
6	((diamorphine or diacetylmorphine) adj2 prescri*).mp.	53
7	risk mitigation.mp.	3215
8	safe* supply.mp.	220
9	3 or 4 or 5 or 6 or 7 or 8	3645
10	1 or 2	375135
11	9 and 10	374
12	limit 11 to (english language and yr="2012 -Current")	328

eTable 3. Database: APA Psych Info 2012 to May 19, 2023.

Line	Searches	Results
1	exp Harm Reduction/	4645
2	exp substance-related disorders/ or exp drug overdose/ or exp opioid-related disorders/ or exp substance abuse, intravenous/ or exp substance abuse, oral/	2752
3	safe* opioid supply.mp.	2
4	(pharmaceutical adj2 opioid).mp.	78
5	((diamorphine or diacetylmorphine) adj2 assist*).mp.	2
6	((diamorphine or diacetylmorphine) adj2 prescri*).mp.	19
7	risk mitigation.mp.	469
8.	Safe* supply.mp.	38
9.	3 or 4 or 5 or 6 or 7 or 8	606
10.	1 or 2	7233
11.	9 and 10	65
12.	limit 11 to (english language and yr="2012 -Current")	58

eTable 4. Database: CINHAL 2012 to May 19, 2023.

Line	Searches	Results
1	(MH "Substance Use Disorders+") OR (MH "Substance Use Rehabilitation Programs+") OR (MM "Substance Use Treatment: Overdose (Iowa NIC)") OR (MM "Substance Use Treatment: Drug Withdrawal (Iowa NIC)") OR (MM "Substance Use (Omaha)") OR (MM "Substance Abuse, Perinatal")	188,186
2	TX safe* supply	82
3	TX pharmaceutical opioid*	144
4	TX (diamorphine or diacetylmorphine) and assist*	17
5	TX (diamorphine or diacetylmorphine) and prescri*	50
6	TX risk mitigation	665
7	Limiters - English Language and Published Date: 20120101-20230531	4,814,486
8.	S2 OR S3 OR S4 OR S5 OR S6	946
9.	S1 AND S8 AND S7	316

eTable 5. Database: Scopus 2012 to May 19, 2023.

Line	Searches	Results
1	TITLE-ABS-KEY-AUTH (((substance OR opioid) AND (disorder OR use OR abuse)) AND harm W/2 reduc*) AND (TITLE-ABS (safe* AND supply) OR (safe* AND opioid AND supply) OR (risk AND mitigation)) AND PUBYEAR > 2011 AND PUBYEAR < 2024AND (LIMIT-TO (LANGUAGE , "English"))	435

eTable 6: Overview of Study Results

Article citation	Objective(s)	Key findings
Bardwell et al., 2023	To examine site-specific social, structural and physical contextual factors that affect program access and uptake, assess general satisfaction and determine areas for improvement of the MySafe program; and examine program effects on participants' health and well-being.	**Program Facilitators**: Accessibility and choice: participants preferred the convenience of the My Safer Program relative to programs with set time frames; Non-witnessed use: increased privacy, freedom from judgment of clinicians/others; Ability to use preferred mode of consumption; Contingency planning: able to stockpile their medication in case of future need (vacation, need for a higher dose) **Program Barriers:** Experienced technical difficulties when using biometric machine; Prescribed doses did not match the potency of the unregulated drug supply, which led some to seek additional opioids elsewhere; Inability to use machines at different locations impacted client mobility. **Patient-reported outcomes**: Reduced use of the unregulated drug supply which led to self-perceived decrease in their risk of an opioid toxicity; Decreased spending on drugs – able to prioritize purchasing food and clothes instead; Improvements to overall health and well-being. **Study Limitations:** Results not generalizable to the homeless population; Lack of information regarding how those who stockpiled medications kept them safe/away from diversion.
Giang et al., 2023	To examine how risk mitigation guidance prescriptions of hydromorphone tablets specifically shaped the substance use and care trajectories of young people who use drugs.	**Patient Reported Findings** **Benefits:** Increased interactions with the health system, which also increased likelihood of starting/re-starting and maintaining OAT; Ability to stockpile hydromorphone and use as a "back-up" **Barriers:** Many expressed frustrations because prescribed doses of hydromorphone did not match the potency of the unregulated drug supply, which resulted in continued use of illicit substances, and SOS discontinuation for some. **Diversion:** Reports of selling hydromorphone to generate income to purchase other drugs, food, clothing, and help with experience of poverty. **Study Limitations:** Findings are primarily from youth in poverty and experiencing housing

		instability using fentanyl daily and may not be generalizable to the broader population of young people who use drugs.
		<u>Physician Reported Findings</u> **Provider Perceived Benefits:** Allowing patients to carry on with life without having to spend time buying drugs/making money to buy drugs; Providing hydromorphone tablets alongside OAT helped with easing initial cravings, withdrawal symptoms, titrating therapeutic dose. **Barriers:** Confusion around implementation of guidelines; and Concerns and ethical considerations over diversion and how to monitor for diversion. **Study Limitations:** Provider demographic characteristics were not collected and so it may affect conclusions that may be drawn from provider experiences.
Haines et al., 2023	To better understand the experience of participating in a SOS program, including how the program impacts participants, along with facilitators and barriers to participating in a SOS program.	**Benefits:** Consistency - knowledge of knowing what they were getting and how much they are taking; Improved sense of safety – decreased engagement in criminal activity; Stability - did not need to worry about how/where they would get drugs from next; Structure - regular check-ins and daily witnessed dosing gave them a routine; and Connection with healthcare providers and social workers. **Pre/Post Program Measures**: Decreased criminal activity; Decreased need for fentanyl; Decreased rate of non-fatal overdoses; and Improved mental and physical health status. **Barriers:** Prescribed hydromorphone did not adequately combat opioid cravings and withdrawal; and Restrictive program protocols and policies – did not like supervised dosing, lack of mobility due to regimented requirements for check-ins. **Reasons for Diversion:** Low potency of prescribed hydromorphone in comparison to unregulated fentanyl; and Compassionate sharing with other people who use drugs (participants would not share/sell hydromorphone to opioid naive individuals) **Study Limitations:** Simultaneous provision of prescription stimulants as safe supply; and Unable to disentangle differences between the 3 program sites and impact of SOS versus wrap around services

Hong et al., 2022	Authors presented a patient case of “risk mitigation” prescribing for an individual with a history of polysubstance use disorder and frequent overdoses, who tested positive for SARSCoV-2 virus **Measures:** self-isolation, symptoms of withdrawal or cravings, and post-isolation outcomes.	**During the Self-Isolation Period:** Client was able to self-isolate during the entire period; and Withdrawal symptoms and cravings were well-managed **Upon Return to Community** (after the self-isolation period was completed): Risk mitigation prescribing was continued after return to community (after the self-isolation period ended); OAT was declined (due to poor prior experience); and Client was connected to outreach team focusing on clients with high overdose risk. **Study Limitations:** Lack of long-term results; and Findings were highly specific to a highly restrictive quarantine environment during a pandemic.
Ivsins et al., DAD. 2020	Explore barriers and facilitators to uptake of and engagement with opioid distribution programs.	**Facilitators:** Access to a reliable source of opioids – decreased fear of overdose, better control over the opioid’s effects as they now know the potency of their supply, decreased criminal activity (did not require money to purchase drugs) and decreased use of unregulated fentanyl; Integration of a supervised consumption site; and Agency over opioid use – able to choose how and when they use hydromorphone, may stop and return to SOS program without a penalty (no dose titration – as required for OAT, injectable OAT) **Barriers:** Operating hours and schedule - program opened at 1:30pm, many could not wait until opening and accessed unregulated opioids in the interim; Requirements for multiple check-ins throughout the day to receive full daily dose; Co-location with overdose prevention site - tough being around people who did not participate in the SOS program, at times resulted in missed doses due to the other activities taking place at the overdose prevention site; and Use of generic hydromorphone - difficult to inject, not as potent as the name-brand **Study Limitations:** Results specific to a highly monitored environment, due to requirements for witnessed dosing and provision of part-fills throughout the day.
Ivsins et al., J Urban Health. 2020	Described participant reported outcomes from a hydromorphone tablet distribution program in the Downtown Eastside	**Reduced Use of Street Drugs:** Ability to manage withdrawals without reliance on street opioids; and Decreased use of street fentanyl which led to self-perceived decrease in the occurrence of overdose events. **Improvements to Health and Well-being:** Decreased stress (do not need to worry about

	neighborhood of Vancouver, Canada.	where they will get money for drugs or engage in illegal activity for money); Decreased use of drugs via injection; Improved access to doctors and nurses for wound care and chronic health concerns; and Improvements in co-management of pain. **Economic Stability:** Able to break free from debt cycle (not spending as much money on drugs) **Study Limitations:** Difficult to disentangle whether improvements in health and well-being is due to access to SOS or wrap-around services.
Ivsins et al., J Urban Health. 2022	To explore the drug use practices, including access to and use of prescribed safer supply medications among people living in a permanent supportive housing building in Vancouver, BC	**Experiences Accessing SOS:** Felt safer; Decreased use of unregulated opioids; Improved quality of life; Reduced reliance on criminalized forms of income generation; and Onsite access to safer supply was identified as an important component of supportive housing. **Study Limitations:** Provision of SROM in their definition for safe supply; difficult to disentangle whether improvements in health and well-being is due to access to SOS or wrap-around services.
McNeil et al., AJPH. 2022	To explore the implementation and effectiveness of risk mitigation guidelines among people who use drugs in British Columbia, focusing on how experiences with the illicit drug supply shaped motivations to seek prescription alternatives and subsequent impacts on overdose vulnerability	**Reliable Access to Regulated Drugs:** Ability to exercise greater control over their drug use - allowed for more stable drug use patterns; Reduced use of the unregulated drug supply - reduced self-perceived vulnerability to overdose events; and Reduced involvement in criminal activity - did not need to secure money for drugs. **SOS Program Limitations:** Potency of prescribed hydromorphone did not match the unregulated drug supply – some continued to experience withdrawal symptoms and many supplemented with the unregulated drug supply to experience euphoric effects of drugs use **Study Limitations**: Lack of differentiation between stimulant and opioid safe supply; Evidence specific to the 2020 risk mitigation guidelines which have since been updated.
Brothers et al. DAD. 2022	**Primary Outcome:** Successful completion of a 14-day isolation period **Secondary Outcomes:** Occurrence of adverse	**Daily hydromorphone Dose**: Increased from a median of 32mg (day 1) to 48mg (day 14) per day. Three participants (12%) received dosages exceeding the suggested upper limit recommended by the risk mitigation guidelines (>112mg). **Primary Outcome:** 6 of 77 residents left against public health orders (8%). 4 returned. *[Note: numbers not provided specifically for safer opioid supply recipients]*

	events, including overdose, intoxication, diversion/ sharing, or selling safer supply medications or alcohol (reported by resident, shelter staff or health professionals, regardless of whether confirmed by resident or other source)	**Secondary Outcome:** Zero overdose events during isolation; 4 out of 27 hydromorphone recipients had concerns regarding intoxication documented; 3 documented concerns pertaining to diversion/sharing/ selling (0.003 per person-day), including among 2 with intoxication. All 3 of individuals were provided multiple substances (opioids, stimulants, alcohol). **Study Limitations:** No control group, short-term intervention (i.e., 14 days) in controlled setting (Hotel isolation site) may limit generalizability; conducted in city with low fentanyl use and so dose ranges used may not be generalizable elsewhere in Canada. Specific substances involved in concerns pertaining to diversion/sharing/selling not described.
Gomes et al. CMAJ. 2022	**Primary Outcomes:** Occurrence of emergency department (ED) visits, inpatient hospital admissions, admissions for incident infections, healthcare costs (excluding cost related to primary care or outpatient medications) among those exposed and unexposed to the SOS program. **Secondary Outcomes:** Occurrence of mental health ED visits/ admissions, opioid-related ED visits/ admissions, SUD-related ED visits/ admissions, opioid-related deaths, cost for publicly-funded medication, costs for hydromorphone and OAT among those exposed and unexposed to the SOS program.	**Cohort Description:** 82 of 94 SOS clients linked and matched to at least one unexposed individual (87.2%; N=303 unexposed). After matching, differences between exposure groups remained, including SOS clients having higher prevalence of HIV or hepatitis C, hospital visits for substance use disorder, and skin and soft tissue infections. **Time Series Analysis:** SOS Clients: Significant reductions in ED visits (-13.9 visits per 100 individuals; p=0.02), inpatient hospital admissions (-5.2 admissions per 100 individuals; p=0.005), and healthcare costs unrelated to primary care or outpatient medications (-$922 per person, p=0.008) after entry in program Unexposed: No significant changes. **Annual Outcomes** (during the first year following program entry)**:** SOS Clients*:* ED visits, inpatient) hospital admissions, incident infections, and healthcare costs declined significantly. Among those eligible for public drug benefits, medication costs increase significantly ($12,840 to $21,119 per person-year; p<0.001). No significant changes in any other outcomes. Zero opioid-related deaths and <=5 deaths from any cause. Unexposed: No significant changes in primary outcomes. Significant decreases in number of mental-health related hospital visits, SUD-related hospital visits, and costs for hydromorphone and OAT. There were <=5 opioid-related deaths and 7 deaths from any cause. **Sensitivity Analysis Results:** Generally consistent with main findings. **Study Limitations:** Did not capture overdose events treated in community; Lack data related

		to cost of primary care offered through community health centers; Generalizability limited to London SOS program; and Differences remained between SOS clients and matched residents of London with OUD.
Lew et al. Harm Reduction J 2022	Occurrence of non-fatal overdoses events in shelter spaces before and during the intervention (i.e., SOS program).	**Fatal Overdose Events:** Zero events documented before and during the intervention. **Non-Fatal Overdose Events:** Pre-Intervention Period (4 weeks-prior): 20 non-fatal overdoses; 0.93 non-fatal overdoses per 100 nights of shelter bed occupancy Intervention Period (26 days): Zero overdoses in safer use spaces, 3 non-fatal overdoses responded to in shelter more broadly (0.17 per 100 nights of shelter bed occupancy) Odds Ratio (reference = intervention period): 5.5 (95% CI 1.63 - 18.55) **Study Limitations:** Analyses were not conducted specifically for those receiving SOS, and no details provided on prevalence of SOS uptake. Therefore, cannot disaggregate the impacts of the different services offered by the shelter.
Selfridge et al. Int J Drug Pol 2022	60-day adherence to safer supply medications defined as having received a prescription on average of 4 or more days out of 7 during the 60-day follow-up.	**Cohort Description:** 286 clients were prescribed 1 or more novel opioid alternatives. Majority (N=274) received hydromorphone, 1 received hydromorphone and fentanyl patch. 83% were homeless at baseline. 90.9% were co-prescribed OAT at baseline. **Prescribed Doses:** The mean maximum daily morphine equivalent dose dispensed was 346.59 MME and 3.3% (N=9) were prescribed over 128mg/day hydromorphone. **Adherence to Safer Supply Medications:** 77.3% of clients met criteria for 60-day adherence; 47.6% were still dispensed OAT at 60-days. **Factors Association with 60-Day Adherence:** Continued use of OAT (aOR 6.25, 95% CI 2.67-15.90); Receipt of mental health medications (aOR 3.49, 95% CI 1.26-11.00); and Increased maximum daily dose (aOR 1.03, 95% CI 1.01 to 1.04 [per MME increase]). **Study Limitations:** Short follow-up; Lack of control group; Data not presented separately for hydromorphone recipients, but majority received hydromorphone; and High prevalence of people living in temporary shelter sites - services provided in these settings is unknown.
Young et al.	To investigate the occurrence	**Cohort Description:** Study included 534 courses of safer supply among 447 individuals

IJDP. 2022	of hydromorphone discontinuation (gap in dispensing of 4mg or 8mg tablets extending for 14 days or longer), all-cause mortality, and all-cause hospitalization.	meeting inclusion criteria. There were 155 clinicians who prescribed at least one course of safer supply. Median maximum dose was 88mg/day. **Median Time to Discontinuation:** 272 days was the median time to discontinuation. This differed by prescriber frequency. Patients of prescribers who initiated 3+ courses of safer supply over the study period had longer time to discontinuation (median 289 days) compared to more infrequent prescribers (median 147 days). Retention was also higher in later years (2018-2020; median 309 days). **All-Cause Mortality:** There were <=5 courses of safer supply where someone died in treatment and <=5 courses where someone died within 7 days of discontinuation. **All-Cause Hospitalization:** Hospitalization while on was rare (0.53 per person-year) **Study Limitations:** Used an unvalidated definition of safer supply using health administrative databases; although geographic distribution and characteristics of included patients suggests good specificity; and Study was not designed to look at risk of infectious complications, overdose, or diversion.
Kalcium, 2023 (Thesis Dissertation)	To analyze the perspectives of service providers (MD, NP, pharmD, community workers), whose work was impacted or related to the risk mitigation guidance, to explore facilitators and barriers to risk mitigation guidance implementation.	**<u>Risk Mitigation Guidance (RMG) Implementation Barriers</u>** **Lack of Comprehensive Guidance and Support:** Lack of awareness from the medical community regarding the release of risk mitigation guidance; Prescribers expressed frustrations regarding lack of specific criteria for program eligibility, which resulted in confusion and inconsistencies between prescribers; Some felt they lacked the training and education to implement RMG; Service providers felt unsupported at the institutional and health system levels; lack of infrastructure for risk mitigation prescribing; Lack of robust evidence to support RMG, which made the balance between the benefits and harms of prescribing opioids as harm reduction complex. **Inconsistent Application of RMG:** Differences between implementation of risk mitigation guidelines for rural (as compared to urban areas) areas was noted – in more rural and remote areas, the application of RMG was dependent on the community itself, the comfort level of providers within specific communities, and the historical implementation of harm reduction measures (which many communities have historically been against). A lack of anonymity or privacy for RMG participants was also noted in rural settings.

		Risk of Destabilizing People on Alternative Treatments: Providers were concerned about possible destabilization of patients if - Risk mitigation guidelines were suddenly withdrawn; and Occurrence of a drug shortage due to COVID-19 related supply chain issues and/or increased prescribing of certain products. **Unknown Harms of Diversion**: Service providers thought it was clear that identification of diversion was needed, leading to use of urine drug screens; and Conflicting feelings of concerns over the effects of diversion on the wider community. **RMG Implementation Facilitators:** Others found the guidelines to be helpful and as something to fall back on; Clear evidence of overdose risk (e.g., positive urine test for fentanyl) and positive COVID-19 test were indicators for risk mitigation prescribing; Some felt more comfortable with the risk mitigation guidelines as a supplement to OAT and helped to engage with those who otherwise would not engage with treatment. **Study Limitations:** Recruitment was targeted towards those expected to be involved in the implementation of risk mitigation, along with use of snowball sampling biases findings towards those supportive of risk mitigation. Participation may also have been limited by the increased workload of service providers during COVID-19.
Foreman-Mackey et al., 2022	Perspectives of service providers including doctors, nurse practitioners, nurses, pharmacists, outreach workers on community-based services pertaining to safer supply, and facilitators and barriers to implementation of SOS programs.	**Benefits of Safer Supply:** Provides safety and stability in people's lives; May reduce exposure to street substances; Ability to build relationships with clients who may not have otherwise engaged with the health system by providing a treatment that a client needs and/or wants (as opposed to OAT) **Facilitators:** Physicians prescribing in teams can help them feel more supported; lower perceived risk of prescribing safer supply; Connecting with clients through community partners. **Barriers:** Prescribers expressed the challenges of balancing the harms of not prescribing safer supply and unknown harms of prescribing it, particularly when the level of benefit to clients may be uncertain and prescribing guidelines are still in their early stages. **Study Limitations:** Participants were from 4 cities and their experiences may not be generalizable, especially to those living in rural locations. All participants were involved in the

		implementation of SOS programs and are likely to be biased
Mansoor et al., 2023	To examine the feasibility and implementation of the MySafe program among professional community partners across Canada.	**Implementation Barriers:** Some providers were hesitant due to concerns regarding their license; Concerns that use of machines could disrupt connections with clients and could lead to them foregoing other prescriptions that require pharmacy dispensing; Concerns regarding feasibility in rural settings; Inconsistent rules (e.g., could not be using OAT) around program eligibility limited access to safer supply; Hydromorphone identified as an inadequate replacement for the unregulated supply. **Implementation Facilitators:** Presence of clinical, regulatory, political, and logistical (e.g., property management) support; Political and community buy-in; adequate funding; and Provision of wraparound services. **Study Limitations:** Experiences of the MySafe program service providers are based on pre-implementation or early implementation stages. Participants were involved in SOS and may have more positive attitudes towards SOS and may not be representative of the entire professional community.
London Intercommunity Health Centre: Safer Opioid Supply Program, 2021 Preliminary Report (Kolla et al., 2021)	To assess use of unregulated substances, use of harm reduction equipment, occurrence of non-fatal toxicities, housing status, income status, criminal activity, involvement in sex work, health service utilization, physical and mental health status, reasons for wanting to join the SOS program, perceived challenges of the SOS program and areas for improvement.	**<u>Survey Results (Patterns of Drug Use)</u>** **Clients Starting SOS reported:** 91% injecting unregulated opioids; 91% smoking/snorting fentanyl; 59% injecting unregulated stimulants; 59% and 33% have had a toxicity in the past six and one-month, respectively; 73% had a police contact in the past-6 months; 86% involved in criminal activities to get drug; 50% involved in sex work to get drugs; 77% had an ED visits in the past six-months; 36% hospitalized for at least one-night in the past six-months; 55% had self-rated poor health; 59% reported poor mental health. **Current SOS Clients reported:** 46% injecting unregulated opioids, 85% smoking/snorting fentanyl, 63% report decreased fentanyl use, 14% no change in fentanyl use, 14% increased fentanyl use, 45% injecting unregulated stimulants, 35% report they no longer inject drugs at all; 23% and 11% have had a toxicity in the past six and one-month, respectively; 37% had a police contact in the past-6 months; 38% involved in criminal activities to get drug; 20% involved in sex work to get drugs; 45% had an ED visits in the past six-months; 11% hospitalized for at least one-night in the past six-months; 27% had self-rated poor health; 43% reported poor mental health. **<u>Clients starting SOS reported:</u>**

		(self-rated poor health (27% vs. 55%), and poor mental health (43% vs. 59%). **<u>Themes from Focus Group Interviews:</u>** **Self-Reported Outcomes:** Improvements in overall health and social wellbeing; Reductions in the self-perceived risk of an opioid toxicity; Reduced use of unregulated fentanyl, which also led to decreased in financial stress; Improved access to HIV and Hepatitis C treatment, Decreased involvement in criminalized methods of income generation; and Improved safety, housing status and relationships with family and community members. **Motivations for Joining the Program:** To avoid opioid toxicities; Reduce involvement in criminal activities; and Improve health and stability. **Program Barriers:** High levels of program demand; Lack of information on admission and eligibility; Limited treatment options; Negative experiences with healthcare professionals who are not affiliated with SOS programs; Lack of care continuity in hospital; Issues accessing prescriptions at pharmacy; Gender-based violence (women forced to give SOS prescriptions to partners); and Diversion (e.g., sharing/selling medications, especially among those highly tolerant to fentanyl). **Suggested Improvements:** Need for onsite supervised consumption site and observed dosing; Removal of urine screenings (perceived as lack of transparency by clients); and Increased staff. **<u>Study Limitations:</u>** Small sample size; Lack of random sampling (convenience sample of those willing to participate); and Limited description of the SOS program.
Parkdale Queen West Community Health Centre, SOS, 2023 Evaluation Report (Atkinson et al., 2023)	To assess several primary and secondary measures including: **Primary:** Risk of opioid toxicities and death; Access to Healthcare services; Involvement in criminalized activities**.**	**Reduced Risk of Toxicities:** 50% of clients had a toxicity in past three-months at program entry vs. 15% among those enrolled in SOS for at least six-months; 78% of clients used fentanyl daily at program entry, compared to 31% among those enrolled in SOS for at least six-months; among those enrolled in SOS, 26% reported decreased fentanyl use and 52% stopped using fentanyl; 92% of those enrolled in SOS reported fewer or better side effects from current opioid use. One-year retention between December 2021 and December 2022 was 80%. **Access to Healthcare Services:** Some clients began Hepatitis C treatment, 33% had an unaddressed health issue at baseline, with 73% of those enrolled in SOS able to address a

	Secondary: Access to social care, housing supports, and harm reduction supports; self-perceived quality of life and safety.	health issue for the 1st time since starting the program; At program entry, 40% had gone to the ED (10% left before issue was addressed), no change among those enrolled. **Involvement in Criminalized Activities:** Among those entering SOS 44% had done something illegal to get drugs in past three-months vs. 19% of those currently enrolled; No change in being stopped by the police in past three months; Among those enrolled in SOS, 27% reported fewer police interactions. **Secondary Outcomes:** 40% met with a case manager/housing worker/counselor before starting SOS vs. 89% of those enrolled in SOS; 56% needed new/better housing at program entry vs. 27% who received improved housing among those enrolled (54% still want a housing improvement). **Outcomes Reported Post-Program Entry:** Improved family/friend relationships, however many noted that daily trips to pharmacy were still limiting (work/travel/etc.); 81% of those enrolled felt that had more time to do things they want; 85% felt more connected to healthcare; 77% had more money to do things they want; 88% have a greater sense of safety, 85% reported life is improved; 41% still do not have enough money to pay for essentials; 92% reported feeling safer in the way they use opioids; 27% report smoking opioids less often; and 58% inject opioids less often. **Client-Identified Needs:** Desire for a greater range of medication options offered through SOS programs; Provision of multi-day take home doses; Scale-up and sustainability of program; and Access to work and volunteer opportunities. **Study Limitations:** Small sample (only 10 at program entry and 27 on-going clients) and comparisons drawn based on unequal sample sizes; On-going clients only represented ⅓ of all clients (results may not be reflective of entire client group); and not a longitudinal survey as they drew two separate cohorts at the same time (but slightly different study periods).
Dale McMurchy Consulting: Assessment of the implementation	To assess key measures including barriers and strategies for establishing and implementing SOS programs.	**Client-Reported Measures:** Reduced use of street drugs; Improvements in overall health status and treatment of chronic issues; Less time and money spent securing unregulated substances; Some clients are now housed or are being supported to find housing; Improved stability in their family life and better relationships.

of Safer Supply Pilot Projects (McMurchy et al., 2022)		**Staff-Reported Measures:** 66% strongly agreed the SOS program helped to reduce toxicities; 57% strongly agreed the SOS program helped to reduce injection drug use; 67% of staff strongly agreed that SOS programs used a collaborative approach; All sites report insufficient staff (in some cases the client-to-staff ratio is 90:1); Reported issues with recruiting staff (high burden and workload on staff); 18% reported that they had sufficient training; 15% strongly agreed that the program worked to prevent staff burnout; 75% strongly agreed the SOS program increased client access to healthcare; and 68% strongly agreed that SOS program participation led to improvements in other health conditions for clients. **Diversion:** Clients reported that there is more Dilaudid on the street and that the price has dropped. Main reason noted was that medications offered were not working for clients due to insufficient doses of hydromorphone, a lack of combination backbone treatment, slow titration, and inadequacy of generic products (many due to drug shortages). **Wrap Around Services:** Clients reported multiple ways in which they were receiving social support (income support, transportation, food, clothing, etc.); Housing identified as a key priority; Many felt that staff provided moral and emotional support; Staff reported collaboration with community partners (HCPs, pharmacists, infectious disease care, social assistance, etc.); and not all clients had access to a supervised consumption site. **Study Limitations:** Reported percentages without the corresponding absolute number of participants who responded to each question; Likert scale offered the following options "strongly agree, somewhat agree, somewhat disagree and strongly disagree" making interpretation difficult; unclear how sample/respondents were selected.
Safer Supply Ottawa Evaluation, Fall 2022 Report (Haines et al., 2022)	To describe fentanyl use and toxicities since enrollment, and experiences with the SOS program.	**Pre/Post Measures:** Among all clients who reported at least one recent opioid toxicity at the time of intake into the safer supply program, 81% did not report another toxicity; Before starting safer supply average mental health score was 1.75 vs. 3.75 on safer supply; Fentanyl use decreased from 10 points per day vs. 1.5 points per day on safer supply; Number of clients living in a shelter decreased from 22 to 14; Those receiving Ontario Disability Support increased from 40% to 77%; Those participating in criminalized behavior decreased from 28 (at program entry) to 12. **Substance Use Patterns:** When describing personal histories of substance use and current experiences of trauma, many reported feelings of hopelessness, constant loss/grief, stigma, and marginalization, etc., related to substance use; Cycle of drug use was often referred to

		(never ending cycle); Many had previously attempted to access support for their substance use. **Client Perspectives Surrounding SOS Programs**: Many heard about the program from word of mouth; some found the weekly check ins to be restrictive; Clients found the safer supply teams to be very supportive and felt they could lean on them for assistance; Several spoke about the integral access to on-site wrap around supports; Deep sense of community in the program and relief associated with no longer needing to participate in criminalized behavior; and Found having a dependable structure to be very helpful. **Client Concerns:** Many found the program to be too restrictive (observed doses, daily pick-up of medication, weekly check-ins); inadequate potency of hydromorphone; Many reported fear of program closure; Repeatedly discussed the difficulty in accessing their medication in settings outside of the community, especially at pharmacies and primary care services unfamiliar with safer supply; increased access is needed (more capacity, mobile services, flexibility in pharmacy pick up) and expanded drug options. **Diversion:** Some approved of diversion as they felt that sharing is a form of caring for other people who use drugs; Many noted that diversions occurs in all substance use programs and should not be considered uncommon or unexpected. **Study Limitations:** Inability to distinguish study results among those who access the stimulant versus opioid safer supply; Little mention of clinical oversight and SOS program description.