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Abbreviations: COVID-19, coronavirus disease 2019; PWUD, people who use drugs; CDSA, Controlled Drugs and Substances Act; BCCSU, British Columbia Centre on Substance Use; PWUD-Adcomm, people who use drugs advisory committee; CAPUD, Canadian Association of People Who Use Drugs; BC, British Columbia; OAT, opioid agonist therapies; HAT, heroin-assisted treatment

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ABSTRACT

Background

Safe supply is defined as the legal and regulated provision of drugs with mind and/or body altering properties that have been typically accessible only through the illegal drug market. In response to the coronavirus disease 2019 (COVID-19) pandemic and related social/physical distancing measures, efforts have been made to scale up and increase access to safe supply programs in an effort to reduce overdose and other drug- and drug policy-related risks. However, it remains unclear whether these efforts taken thus far have meaningfully mitigated the barriers to safe supply experienced by People Who Use Drugs (PWUD), both during and beyond the context of COVID-19. We thus undertook a scoping review to identify key concepts, strategies and gaps in evidence with respect to the provision of safe supply during pandemics and other emergencies.

Methods

We conducted three searches across Scopus, Medline, Embase, CINAHL, and The Cochrane Central Register of Controlled Trials (CENTRAL) for peer-reviewed and grey literature articles to understand barriers/facilitators to both accessing and prescribing legal, pharmaceutical-grade drugs, including opioids, benzodiazepines, and/or stimulants during public health emergencies from January 1 2002 to June 30 2020. We also included opioid agonist therapies (OAT) during emergency conditions. All potential sources underwent title/abstract screening and duplicate full-text review to determine eligibility for inclusion. Three reviewers extracted characteristics and barriers/facilitators to accessing or prescribing drugs for each study, and these were then inductively analyzed to identify common themes. Key stakeholders (PWUD, prescribers, and policymakers/regulators) informed the search strategy and validated findings and interpretations. Input from PWUD and prescribers was gathered through Advisory Committee meetings and one-on-one consultations, respectively.

Results

We screened 9,839 references and included 169 studies (135 peer-reviewed articles and 36 grey literature reports). From 119 articles, we identified 35 themes related to barriers/facilitators to prescribing safe supply or OAT. Few studies (n=24) focused on emergency or pandemic contexts. Among the most frequently reported barriers were *restrictive laws or policies* (n= 33; 28%). The most frequently cited facilitator was *temporary legal or regulatory exemptions* (n= 16; 13%). Further stakeholder consultation identified barriers/facilitators to safe supply absent in the reviewed literature: PWUD reported barriers including lack of access to desired substances, concerns about child apprehension, and a lack of cultural competency within safe supply/OAT programs; prescribers reported barriers including regional differences in service delivery, colleague support, and a lack of, or disagreement between, clinical guidance documents.

Conclusion

We identified multiple barriers and facilitators to accessing and/or prescribing safe supply or OAT. With few peer-reviewed studies on safe supply models, particularly in the context of emergencies, input from PWUD and other stakeholders offered crucial insights not reflected in the existing literature. To address the overdose epidemic stemming from the criminalization of an unregulated drug supply, prescribers, regulators, and public health authorities should focus on scaling up, and then evaluating, diverse safe supply frameworks that address the facilitators and barriers we have identified.

INTRODUCTION

"Safe supply" is a terminology that stems from a long history of struggle against limitations and legal sanctions imposed upon people who use drugs (PWUD). It refers to the provision of regulated mind/body altering substances that traditionally have only been available within the illegal market.[1] Safe supply is one harm reduction strategy to reduce fatal and non-fatal harms for PWUD who rely on an increasingly toxic illegal drug supply.[1] Despite global advocacy for safe supply, barriers on multiple levels have limited and continue to constrain its uptake. During the coronavirus disease 2019 (COVID-19) pandemic, public health restrictions have exacerbated the health risks of PWUD who face increased challenges in accessing safe supply.[2]

In Canada, recent regulatory changes have enhanced access to a safe supply of drugs, as well as opioid agonist therapies (OAT). First, in March 2020, new exemptions were introduced under the *Controlled Drugs and Substances Act* (CDSA),[3] which allowed physicians to verbally prescribe and pharmacists to renew, refill, transfer and deliver, take-home doses of controlled substances. According to the exemption, a pharmacist can also assign an individual permission to deliver controlled substances. In turn, colleges regulating physicians and pharmacists have highlighted these exemptions in several provinces to increase awareness of these new flexibilities.[4-6] Second, the British Columbia Centre for Substance Use (BCCSU) developed a clinical guideline[7] to both inform and encourage physicians to prescribe a pharmaceutical alternative during the pandemic to anyone at risk of contracting COVID-19 with ongoing substance use and at high risk of experiencing withdrawal. Third, British Columbia's Provincial Officer of Health issued a public health order authorizing registered nurses to prescribe safe supply in efforts to reduce deaths resulting from the contaminated street drug supply and connect PWUD to needed services.[7]

In theory, these three steps have the potential to improve access to a safe supply of drugs and thus reduce the risks of harms endured by PWUD during the pandemic, and in the post pandemic era. However, the actual impact of these steps remains unclear, even in British Columbia (BC) where most of these efforts originate. In fact, during May-July 2020, British Columbia recorded a record high number of overdose related deaths each consecutive month.[8] The response to COVID-19 coupled with a dangerous illegal drug market created the deadliest wave of British Columbia's overdose crisis which was declared a public health emergency in April 2016.[9] In addition to BC, Ontario experienced increases in overdoses and overdose deaths, where in the first 15 weeks of COVID-19, 695 people died of a confirmed/probable opioid related deaths. This represents a 38% increase relative to the 15 weeks immediately prior to the pandemic.[10]

In order to elaborate upon the multi-dimensionality of safe supply in the COVID-19 pandemic and other emergencies, including the ongoing overdose crisis in Canada and abroad, we sought to understand the barriers and facilitators to the provision of safe supply and in turn, identify relevant policy or regulatory priorities for various stakeholders to address these barriers.

METHODS

We followed an established knowledge synthesis methodology for integrated scoping reviews, incorporating both quantitative and qualitative published sources as well as grey literature.[11] We

partnered with key knowledge holders (PWUD, safe supply prescribers, and policy-makers/regulators) at various stages of the project to inform the search strategy, validate preliminary findings of emerging themes, map priority gaps in the literature, and validate our final interpretations.

Literature search strategy

Three peer-reviewed literature searches were developed in collaboration with an expert librarian (RP) to identify publications relevant to the provision of safe supplies (Appendix A1-A3). These searches were conducted between June 9, 2020 and June 30, 2020. The first strategy was developed to identify publications related to the continued provision of safe supply of various drugs, including opioid agonist therapy (OAT), during emergency pandemic or natural disaster conditions and was implemented in five databases: Scopus, Medline, Embase, CINAHL, and CENTRAL. The search range was defined as January 1st, 2002 to June 7, 2020 to encompass the timeframe of the COVID-19 as well as previous H1N1 and SARS pandemics.

Given that we anticipated a lack of eligible studies in the original search, the search strategy was expanded in scope to capture insights from relevant studies in non-pandemic settings. Due to time and resource limitations, this search was broadly implemented in Medline and Scopus, and limited to January 1st, 2009 to June 13, 2020 to capture the timeframe during which the concept of safe supply and discrete interventions emerged.

Finally, we supplemented the original search by examining studies about heroin-assisted treatment (HAT) given the overlap of this modality with some aspects of safe supply. Again, given time and resource constraints, we undertook this search in a reduced number of databases which included Medline and CENTRAL, beginning January 1st, 2000 to June 30th, 2020. Moreover, we focused on searching the CENTRAL database to capture safe supply clinical trials.

The grey literature was also examined on June 24th, 2020 to identify articles outside of the peer-reviewed literature relevant to accessing safe supply, including emerging guidelines and information reports created by PWUD or community based or non-profit organizations supporting PWUD (Appendix B). No language restrictions were placed on any of the searches, although the implemented searches used only English-language terms.

Eligibility criteria and assessment

For all three searches, we included literature addressing the provision of pharmaceutical grade drugs (opioids, stimulants, and/or benzodiazepines) to people reliant on the unregulated drug supply. For the primary search, the included literature was limited to those that addressed the challenges of providing OAT (buprenorphine, methadone) during COVID-19, natural disasters, or other public health emergencies. We included primary quantitative and qualitative studies of any design, relevant commentaries, clinical guidance, recommended practice, and best practice documents. We chose to include studies that included no primary data to ensure an inductive approach to this review given that safe supply is an emerging modality of care which has encountered barriers to implementation in most settings; as such, we anticipated that evidence on

the topic of safe supply was likely to include frameworks and recommendations as well as real-world data. For all three searches, studies that did not focus on people reliant on the unregulated drug supply were excluded. A two-stage screening process was used to select articles for inclusion. In level 1, three reviewers (BC, EC, MP) independently reviewed titles and abstracts to preliminary assess articles for eligibility before assessing the full-text documents. In level 2, three reviewers (BC, EC, MP) independently assessed the full texts for inclusion. For both screening stages, reviewers needed to be in agreement for articles to be included or excluded. Disagreements were resolved through discussions among the reviewers.

Data extraction and thematic analysis

The study team developed a data extraction form and piloted it on three studies among three reviewers performing data extraction (BC, EC, MP), resulting in minor clarifying changes being made to some extraction field names. Each eligible study was extracted by a single reviewer into an electronic spreadsheet. Extracted data included study characteristics, participant demographic characteristics and recent drug use history, intervention outcomes, barriers and facilitators to safe supply or OAT, and argument for or against safe supply (Appendix C).

An inductive approach was used to assess the extracted data for common themes related to the barriers and facilitators to OAT and safe supply with the goal of developing a variety of context-specific recommendations for addressing barriers to the legal provision of illicit drugs.

Three reviewers (BC, EC, MP) assessed the extracted data for common themes, which were not mutually exclusive, and were circulated to the study team to be collaboratively revised. In addition, members of the team (NT, MB, SW) assessed the themes, as abstracted from the published and grey literature studies included in full-text analysis, against the insights and feedback provided by the members of the PWUD-Adcomm. Although still relevant to understanding the scope of the safe supply literature, not all records fit our barrier/facilitator paradigm. These “themeless” records were still part of our descriptive analyses but were excluded from thematic analyses.

Finally, it is important to note that the term “safe supply” has only recently emerged in the literature and discourse (i.e., in the mid-2000s). Tracing the evolution of the discourse, and identifying relevant sources of knowledge that can speak to and inform our analysis of the barriers and facilitators of safe supply, even if not by name, represents another ongoing point of inquiry for the scoping review.

Stakeholder consultations

We approached this work with the overarching goal to collaborate meaningfully with those with lived/living expertise of drug use. To ensure meaningful engagement of PWUD throughout the project, members of our team with lived/living expertise of drug use (NT and MB) led consultations with a PWUD advisory committee (PWUD-Adcomm) comprised of members across Canada. The PWUD-Adcomm was convened virtually three times throughout the project to guide our search strategy, the analyses and interpretation of our findings, and review of the

draft manuscript. These consultations also served to identify any discrepancies between the literature and PWUD perspectives.

Consultations were also conducted with safe supply prescribers via phone and video calls to further guide the analyses and interpretation of findings. Led by CB, TB, TL, CL, these consultations were conducted with one nurse practitioner and three physicians from British Columbia, Ontario, Quebec, and New Brunswick. Participants were asked to discuss their knowledge of safe supply programs, along with barriers and facilitators to program operation and prescribing safe supply.

RESULTS

Our scoping review returned 9,785 sources to be screened following deduplication. Additionally, the grey literature search identified 54 potentially relevant sources (Appendix D, Figure 1). Following full-text review, we included 169 studies in our review including 133 academic sources and 36 from the grey literature. We extracted barriers and facilitators to safe supply for 119 of the included sources. In this manuscript, we have opted to provide an overview of findings from all searches disaggregated by theme. Future work with this review will involve distinct analyses of findings from each search.

General study characteristics

A full list of included sources and their characteristics are provided in Table 1 (Appendix E), along with a brief description of their objectives, and key conclusions or summaries. A number of sources were commentaries whose objectives were to outline the challenges of providing OAT treatment during emergency conditions including hurricanes[12-16] and COVID-19.[17-20] The latter of these commentaries also explained how PWUD are at increased risk during COVID-19 due to current service models that require them to leave their homes for treatment or interact with the community to purchase their drugs illegally. In the context of hurricanes, the common conclusion of these sources was that emergency disaster planning procedures are needed to ensure patients are able to continue treatment without interruptions. In the context of COVID-19, the common conclusion was that current treatment models need to adapt to new challenges to ensure patient safety, such as the removal of restrictive laws or policies.[17,21,22] These sources pointed out this is only possible with regulatory change. Another common objective included advocating for safe supply during the COVID-19 pandemic [23,24] or non-pandemic settings.[25,26]

The majority of studies included in our review were published in 2020 (n= 36, 21%), emanate from jurisdictions in Canada (n= 43, 26%), and are randomized control trials (n= 27, 17%) (Appendix E, Table 2). Importantly, 24 (14%) of the studies included in our full-text review follow qualitative research designs, which may report more thematically rich information about barriers and facilitators to safe supply in particular settings compared with quantitative data.

Thematic analysis of barriers and facilitators

We have grouped the barrier and facilitator themes derived from both the academic and grey literature into five levels, ranging from barriers/facilitators at the level of individual users and prescribers to barriers/facilitators observed at program, regulatory, and societal levels. In total, there were seventeen barrier-related sub-themes and eighteen facilitator-related sub-themes identified, which are described further below (Appendix E, Table 3).

Barrier-related themes

1. User-level barriers:

Personal-health barriers among PWUD. One of the barriers to safe supply involved concerns about the health consequences of legalization, such as various adverse side effects[27-29]. One study also identified the challenges of prescribing benzodiazepines for PWUD who are using other substances that increase their risk of overdosing.[30] One article,[31] which centred the perspectives of PWUD, added:

> "In addition to concerns over the potential harms of drug use from increased access, some expressed concern around increasing availability among youth, although views were mixed as to how it would impact the next generation. Several participants thought that the current illicit nature of drugs makes them alluring to youth; proposing that a legal model (with improved access) may make drugs less attractive. 'If people could use it any time they want, they will get sick of it."[31]

Distrust towards institutions. Apart from physicians' unwillingness to prescribe safe supply, PWUD distrust of healthcare providers and institutions as well as government more generally was also reported as a barrier to access. The study in our review that emphasized this barrier relayed how in the course of accessing particular forms of traditional healthcare services, especially addiction medicine physicians engaged in the provision of OAT, PWUD experience stigma and discrimination with respect to active substance use which in enhanced while enrolled in an OAT based program.[26] This has engendered distrust among PWUD and corresponding choices not to seek further care from such providers and institutions. Greer [31] notes:

> "There was a deep sense of suspicion towards the government's role, intentions, and power over the lives of people who use drugs. Two sub-themes related to these views on role of government – corruption and loco parentis [paternalistic control of the government over people's lives]."[31]

Practical barriers. Practical barriers to safe supply were identified in both pandemic and non-pandemic contexts (Appendix E, Table 4). These included transportation-related practical barriers[13,17,32], including limitations placed on persons with physical disabilities seeking access to OAT in pandemics or other emergencies; difficulties receiving quality health services[12,18,33-41], including self-isolation requirements impeding access to treatment; coercive interactions with law enforcement personnel[17,42] and; social or economic-related challenges[43],

such as inadequate income to afford medical services. These practical barriers reflect a larger set of structural issues of oppression and poverty amongst the drug using population. To illustrate the impact of COVID-19 on PWUD, Dunlop[18] explains:

> "Given the need to provide treatment in many countries where home isolation is now very critical, planning alternatives to daily supervised dosing is important and imposes a major challenge. This is the case since daily supervised opiate treatment may involve significant waiting periods for patients, including people having to wait in queues for extended periods of time; and social distancing may not be practical due to the size of waiting areas and the number of patients." [18]

Lack of drug trials or programs reflective of prospective uses and preferences of PWUD. This theme concerns how certain features of HAT trials or programs were perceived negatively by participants, and highlighted the complex needs of some sub-populations (e.g., those involved in sex work) of PWUD that should be considered in study design.[44,45] Participants reported various ways that they did not have their needs for safe supply met due to lack of drug choice,[46] inadequate dosing levels or drug effects, [35,46] the temporary nature of HAT for pilot projects or absence of community programs to ensure continuity of treatment,[47] and not being able to consume drugs via their route of choice.[33,48,49] Studies also reported PWUD who were uncomfortable with various aspects of safe supply injection facilities, such as lack of privacy, adequate lighting, inadequate lighters, or lack of space.[33,35]

2. Prescriber-level barriers.

Limited prescribing power or prescribers. Studies identified the issue of healthcare professionals who are either unable or unwilling to prescribe pharmaceutical grade drugs as a result of regulatory restrictions, as well as real or perceived punishments for providing safe supply options to patients. Studies identified an unbalanced distribution of qualified specialists,[32,50] hesitancy to prescribe due to concerns about diversion or adherence,[39,45,51,52] financial pressures,[45,50] restrictions on the number of pills or refills[53], as well as reluctance to manage treatment programs.[51,54] Other reasons included a perceived lack of clinical competency,[55] and perceived lack of demand.[50,51] Haines[54] attributes this barrier as one reason for the lack of PWUD services in Canada:

> "Managed opioid programs limited implementation Canada-wide may be related to a lack of prescribers who are willing to manage a high-stakes managed opioid programs."[54]

Lack of clinical guidance for/consensus among prescribers. Studies highlighted the absence of adequate and reliable information surrounding safe supply treatment procedures for medical professionals. Specifically, studies suggested that lack of evidence about diamorphine or HAT effectiveness or patient eligibility deterred physicians from prescribing drugs, including benzodiazepines.[51,56-59] One study also mentioned the ambiguities of distributing limited community resources to those who would most benefit.[60] In international contexts, a study reiterated that some physicians chose not to acquire a licence because of lack of evidence.[61] A report from the United Kingdom discussed the need for expanded monitoring alongside

increased heroin prescribing.[50] To illustrate a possible lack of experience or knowledge about administering this treatment, one study discusses the following:

> "There was a surprising lack of agreement about the daily dose-equivalent of 100 mg methadone, ranging from 50 mg to 900 mg...It may be, therefore, that the lower dose equivalent reported by doctors prescribing to nine or less patients reflects a lack of experience in this form of treatment."[51]

3. Program-level barriers.

Ignoring social and cultural aspects of drug use. Another theme identified the role of regional or cultural drug-using differences that may potentially limit or mediate the likelihood of successful retention or treatment satisfaction among some groups. These studies discussed specific drug-culture norms (e.g., inhalation versus injection))[62] that may vary across countries,[63] and overall societal attitudes towards rules that may affect the success of drug treatment programs[63]:

> "One argument advanced against the feasibility of this [HAT] treatment in the United States is that European societies are supposed to be fairly homogeneous and rule-abiding, where program operators can be trusted and even heroin addicts can be expected to follow rules, whereas American addicts would not be capable of meeting the demands imposed by a three times a day clinic attendance."[63]

Small population. Another barrier involved the challenge of having too small of a population density to justify the establishment of a safe supply program. One study[64] discussed the closure of HAT programs in southern Spain due to few participants that inject drugs. Another pilot HAT study[65] discussed program recruitment challenges unique to Montreal due to their low density of PWUD:

> "Further, because Montréal's IDU population is fairly spread out, many would have to travel up to an hour to the clinic up to 3 times per day, which was not seen as very attractive even with the provision of 'free' heroin."[65]

Prohibitive system-level costs. This theme included studies that discussed high healthcare costs that discourage the implementation of safe supply programs. Studies described the high costs of staffing, infrastructure, and drug treatment costs as a deterrent to prescribing or establishing injectable drug treatments or programs, especially compared to methadone treatment.[39,45,51,63,64,66-72]These prohibitive costs may be of particular concern in rural settings or in certain countries.[73] In the context of pilot HAT studies, the financial resources to obtain an appropriate facility space hindered or otherwise constrained program operations and recruitment.[65,74]

Programmatic, administrative, or logistical difficulties to implement program services. Studies described rules or inflexible practices imposed by clinics, limited physical space, human resources, or other pandemic-related disruptions that make it challenging to provide safe supply.[12,14,16,17,19,32,42,65,75-77] Several studies reported difficulties in verifying previous drug treatments.[14,16,65] In pandemic contexts, there were also issues in maintaining continuity of care

due to clinic closures or relocation,[14,16,19] lack of communication to ensure adequate supplies,[76] transportation restrictions that prevented staff from travelling to work,[20,42] and general logistical barriers to dispensing.[32]

Limited safe supply program capacity. Studies also described limited spots for treatment as a barrier to accessing safe supply. Limited clinic capacity prevented or delayed programs from meeting demand,[74] resulting in an overwhelming waitlist.[39] This was an issue even in jurisdictions where safe supply is legally accessible.[47] We note that these findings described by McAdams below were also echoed during consultations with our PWUD-Adcomm:

> "...even in jurisdictions such as Vancouver where community iOAT is available, spots are often extremely limited. As of February 2019, there were approximately 300 iOAT spots in Vancouver, while in most other Canadian provinces iOAT is not available at all. Referrals are therefore made judiciously, often after unsuccessful trials of oral OAT."[47]

Lack of effective pharmacological approaches in the treatment of concurrent cocaine addiction. One study[78] discussed the absence of simultaneous pharmacological treatment for cocaine use, which may affect adherence to opioid addiction treatment given continued involvement in risky activities.

4. Societal-level barriers.

Community hesitancy. This theme describes resistance or apprehension among members of the public regarding the establishment of a safe supply program in their community as a barrier to the provision of safe supply. In the context of a pilot trial for HAT, one study discussed difficulty in obtaining a development permit due to the municipal and neighbourhood concerns about increased crime[79]:

> "The goal [of limiting recruitment to a mile of the treatment clinic] was to reassure the local community that the study would not increase crime and public disorder in the neighborhood by drawing people with heroin dependence from other parts of the city (the so-called 'honeypot effect')..."[79]

Profit-driven and/or monopolistic industry practices. A further theme identified in the literature involves monopolistic industry policies or practices that, together with abuse-deterrent logics, prevent people who use drugs from accessing the desired mind/body altering experiences. This theme focuses on the ways that market-level pressures, such as patent expirations, may prevent generic brands from competing with brand-name drugs in such a way that effectively decreases available sources of affordable, regulated supply of drugs. One article[53] suggested that monopolistic incentives may have joined with misguided deterrent logics to spur the introduction (and subsequent market dominance) of "abuse-resistant formulations" of painkillers. This industry move was subsequently shown to have exacerbated risks of harm and increased reliance on illicit sources of supply. Werle[53] writes:

> "Manufacturers faced impending patent expirations, which would have opened their blockbuster painkillers to generic competition. They responded by introducing newly

> patented ADFs and then lobbying the FDA to take pills without these "safety" features off the market, preventing non-ADF generics from competing with brand-name painkillers [. . .] Several years later, economists and public health officials have confirmed that the ADFs backfired and blame them for accelerating users' transitions from pills to powders. Unable to snort the pills, many users turned to injecting them, increasing risks of overdose and disease transmission. Others turned to black-market drugs, buying fentanyl-laced heroin or counterfeit pills."[53]

Discrimination because of stigma of using drugs. A lack of accessible services because of public perceptions and marginalized status as an illegal drug user to be a barrier to safe supply. These studies discussed the influence of negative public perceptions on the establishment or implementation of programs prescribing medical-grade heroin.[49,65,71,80] For instance, Boyd[49] describes:

> "[Participants of the NAOMI research trial] wondered if the failure to create a permanent program had to do with their marginalized status as illegal drug users. The NPA members noted that if a diabetes or cancer treatment proved to be efficacious during a clinical trial, presumably the patients."[49]

5. Policy-level barriers.

Restrictive laws or policies. One of the most prominent themes identified in the academic and grey literature involved laws/policies set by governments or governing bodies that restrict the amount of substances that may be provided, where substances may be used (e.g., not allowing take-home dosing), or that ban substances entirely and thereby prohibit their being prescribed to persons who might benefit from a regulated alternative source relative to an illicit source. Specifically, the insufficient provision of diacetylmorphine was described, which is currently not made available on hospital formularies in Canada.[47] This was similarly described in international studies for diamorphine (in Germany)[63] and diacetylmorphine (in Spain),[64] where national law significantly limits the prescription of these drugs to clinical research settings.

These political and regulatory restrictions appear to persist, even in Canadian jurisdictions where injectable opioid treatments are already approved[81] or are otherwise supported by clinical evidence.[65,82] While most of the studies focused on heroin safe supply, one Canadian study specifically commented on the non-existence of pharmacological treatment options for other drug addiction disorders, such as stimulant use disorders.[83] This reflects the current reality in Canada, and in other countries, where the legal system is not adequately responding to user-identified needs, in spite of strong scientific and public support for the provision of safe supply.

Studies described legal challenges posed by Health Canada that hindered the provision and delivery of safe supply.[48,65,79] Studies cited specific regulations, including the removal of diacetylmorphine from Health Canada's Special Access Programme (SAP) in 2013,[48] the burdensome application process to regularly renew drug licensure,[79] the rejection of heroin clinical trials or prescribing requests[48,79] and the difficulties of transporting legal opioids from abroad to Canada.[48] In the context of a clinical trial (NAOMI), Health Canada also demanded onerous security measures that significantly delayed the establishment of heroin prescribing

clinics.[65] This underscores the need to include PWUD in the co-design of drug policies, given that the perceived requirement for these restrictive policies stemmed in part from Health Canada's erroneous valuation of street heroin, which was approximately twenty-five times more than its actual street value.[65]

Sub-themes in our scoping review also discussed prohibitionist political viewpoints that informed regulations, which further impedes responsive public-health policies to address the continued opioid crisis.[48] In a qualitative research study in Belgium, a PWUD cited incarceration as a reason that prevented their participation in the diacetylmorphine trial.[84]

Combined political opposition, or lack of governance and/or enforcement. This theme describes the lack of governmental capacity to oversee and enforce safe supply program regulations even if they exist. Studies discussed political considerations as a deterrent to safe supply,[80] for instance in countries that have adopted a long-standing abstinence-only approach.[85] Several grey literature records discussed challenges concerning licensing, production and monitoring in countries where there is corruption and distrust of government.[86-88] Other studies highlighted that safe supply is unlikely to be prioritized when faced with austerity measures[66]:

> "Regardless of the medical evidence in favour of injectable opioid therapy, it seems unlikely that there will be much political will to expand this form of expensive and controversial treatment during a time of economic cut-backs."[66]

Concerns about lack of scientific evidence. Several grey literature records discussed the lack of information regarding the benefits and harms of safe supply programs[24] that are needed to inform clear clinical guidelines,[50] and to guide the implementation of interventions that are tailored to communities.[89] One report[24] ultimately concluded that:

> "Safe supply may be a viable option for eligible participants who do not tolerate, use, or desire substitution treatments as well as those who use street drugs in addition to substitution treatments."[24]

As elaborated upon in the discussion below, the insights offered by our PWUD-Adcomm and members of our research team suggest that this call for more evidence may itself constitute a barrier to safe supply; further, the existence of evidence around some forms of safe supply such as HAT has not to date led to an increase in the provision of such safe supply treatments.

Facilitator-related themes

1. User-level barriers.

Health insurance. One study originating from Switzerland discussed the availability of financial resources to cover the costs of participating in a drug treatment/maintenance program.[39]

> "In Switzerland, the costs of participating in a HAT program are covered by the patient's compulsory health insurance, with patients paying a co-pay of approximately 10 Swiss francs a week in addition. If patients are unable to meet the payments, social services will

cover them. In the Netherlands, interviewees reported that the costs are completely covered by mandatory health insurance."[39]

Transportation. Three sources highlighted transportation as a factor enabling access to a safe supply during crises/emergencies.[54,61,90] Door-to-door delivery ensured an uninterrupted access to safe supply for patients located far from clinics with one source noting that during COVID-19 "Huber province in China has provided 398 drug users with door-to-door delivery of their MMT [methadone maintenance treatment]."Compensating for transportation costs may also help to further improve PWUD's access to services.[54] All sources emphasized the need to consider emergency transportation in drug supply policies, especially for rural or large geographic regions who may be removed from centralized services.

2. Prescriber-level barriers.

Availability of medical prescribers. One report in the United Kingdom suggested that increasing the number of physicians who can legally prescribe heroin would facilitate PWUD's access to safe supply.[50] They noted that this should include both general practitioners, as well as specialists with interests in substance use disorders.[50]

3. Program-level barriers.

Understanding the needs and desires of PWUD. Studies highlighted the importance of treating PWUD and their choice to use drugs with respect.[42,77,91] They emphasized the need for an individualized approach to treatment that accounts for PWUD's preferences and current level of substance use,[30,55,92] recognizing the autonomy of PWUD,[93] ensuring multidisciplinary care,[89] and commentary on the quality of the experience (e.g., euphoria, psychological and physical pain reduction) that PWUD are seeking.[91] One guidance document expressed the importance of adopting a non-punitive approach to working with PWUD in the event that doses are missed.[93] Similarly, another study in the context of pandemics captured the idea that treatment should not be withheld because of breakdowns in communication due to emergency conditions or as a form of punishment:

> "When [methadone] dosages could not be verified [for guest patients displaced by 9/11), patients were permitted to attest in writing to their dosage, and on this basis, the State permitted clinics to medicate. [Office of Addiction Services and Supports] staff indicated that no cases of double medicating or over-medicating were reported."[42]

Take-home dosing. Facilitators for safe supply involved situations where PWUD undergoing OAT were given extra take-home doses in response to an emergency situation.[16,77] The extra doses were given so patients could continue their treatment despite barriers to accessing clinics during the emergency. In the context of hurricanes, one study[16] writes:

> "With the impending threat of Hurricane Sandy, approximately 100 patients enrolled in [the program] were asked to come in… to receive several emergency take-home doses of methadone that were anticipated to last for the duration of the storm and its immediate aftermath." [16]

Other studies or guidelines described allowing clinics to supply their patients with additional take-home doses during national security emergencies[42] and the COVID-19 epidemic in response to lockdowns and other restrictions on movements.[59,77,94]Various grey literature records also emphasized the benefits of take-home dosing, such as perceived convenience and increased program retention in HAT programs.[39,91]

Less restrictive dispensing models. This theme relates to alternative dispensing models that could improve the accessibility of safe supply. Studies discussed the provision of drugs without a prescription in supervised settings outside of a medical model, such as at licensed entertainment venues or social settings,[91] or through a members-only cooperative model known as a buyers' club.[95] Another case report explored the positive health and social benefits of drug treatment within a supportive housing environment.[96] One Canadian guideline document outlined the benefits conferred by the prescribing of stimulants during COVID-19.[97]

Flexible eligibility criteria and approaches. This theme encompasses the broadening of safe supply program implementation and/or modifying inclusion criteria to lower access barriers, and thus maximize the number of people who can benefit.[89,93,98,99]Another qualitative study described flexible practices among treatment program staff where, instead of outright rejection, accommodations were made to allow for PWUD to engage safely in services and avoid use of street supplies.[35]

Supervised dispensing models. This theme discusses the use of a supervised administration protocol to improve program adherence and safety. In this medicalized model, PWUD can legally access pharmaceutical-grade drugs under the supervision of healthcare providers, as well as primary care and/or social services.[41,91,100] This model would allow for prompt medical interventions in response to negative side effects[101-103] and to improve adherence.[104]

Reducing stigma or supportive facility environment. Studies also discussed the role of decreased stigma in using drugs to increase interest in or the sustained support of safe supply programs. Two studies pointed to hydromorphone as a more realistic long-term treatment option, given it is less stigmatized than heroin.[39,80] This may be facilitated by consuming drugs via preferred routes, non-judgemental clinicians[34], or familial relationships.[62] In one clinical trial, a participant attributed their ability to express their needs to healthcare providers because of the facility's respectful environment.[40]

Concurrent provision of other therapeutic services. Another facilitator included the provision of drug or therapeutic services to manage discomfort or medical symptoms/conditions alongside treatment. One case report attributed a patient's successful treatment adherence to the combination of both injectable hydromorphone and slow-release oral morphine that they received in the program.[47]

Sufficient infrastructure or human resources to support clinics. The availability of an appropriate physical space and a collection of organizations or individuals was also viewed as conducive to the provision of referrals or services for safe supply.[45]Another case report reinforced this theme, where it described leveraging a network of healthcare clinics and pharmacies as a way to

facilitate access to pharmaceutical-grade drugs despite staff shortages.[68]

4. Societal-level barriers.

Clear communication. There were situations where clear communication between policy makers, people providing treatment, and PWUD improved access to safe supply or treatment during crises/emergencies.[12,14,16,34,90] Clinical trials involved HAT stressed the importance of having up to date contact information, and consistent messaging to foster trust among the public and government stakeholders.[74,85]

Stakeholder engagement or community support. This theme encompasses studies that discuss engagement with all groups who have a stake in safe supply research/implementation including PWUD, policy makers, researchers, medical professionals, law enforcement, and communities to improve understanding of and uptake of safe supply. Studies attributed a region's unique social and political context to widespread public support for heroin-assisted treatment in both national[63] and local settings.[65] A policy case study in Switzerland[85] discussed the role of municipal leadership in convening discussions about harm reduction policies, including a strategy for heroin prescribing. Heroin-prescription trials emphasized the need to work with study participants and local stakeholders to optimize recruitment[62,74] to ensure patient-centred delivery of such drugs[42,93], to foster acceptance of such heroin prescription clinics, including law enforcement personnel[39], and to support drug policy research.[105]

Advocacy. The efforts of non-profit organizations to raise awareness, dialogue, and/or political action to reduce stigma were identified as an enabler of the establishment of HAT/safe supply treatment programs. Studies attributed the persistent efforts of two peer-led drug use groups (SALOME/NAOMI Association of Patients, and the NAOMI Patients Association) to educate the public and engage decision-makers as a key factor in the expansion or continuation of drug programs.[48,106]

5. Policy-level barriers.

Temporary legal or regulatory exemptions. The most frequently appearing theme concerned the temporary removal of restrictive regulations that may be harming PWUD during crises and/or other non-emergency settings.[13,17,21,37,42,56,61,77,89,107] This included changing clinic policies to accommodate guest-dosing, and virtual prescriber consultations, in light of public health measures implemented during COVID-19.[24,30,55,94] For instance, one article[21] described temporarily waiving a requirement for in-person consultations to initiate buprenorphine treatment, which was instead done through telemedicine:

> "...the Drug Enforcement Administration has waived a requirement that patients who wish to begin buprenorphine treatment have an in-person consultation with the prescriber. This change permits individuals seeking buprenorphine treatment to be prescribed the medication after consulting with a waivered prescriber via telemedicine, without having to physically visit the provider's office."[21]

Another article[61] discussed the opening of "green channels" during COVID-19, which enabled the delivery of methadone to patients requiring methadone maintenance treatment:

> "For those MMT [methadone maintenance treatment] patients who are located far from their MMT clinics, the authorities have opened green channels and required public security departments to ensure that methadone is delivered from the clinics to these MMT patients."[61]

Policy reform. The introduction of policies enabling the study and/or establishment of safe supply programs was identified as another facilitator of safe supply. In the context of HAT clinical trials, one qualitative report mentioned that additional satellite clinics may help to improve study recruitment.[39] In European countries, a study described legal changes that allowed for diacetylmorphine and heroin to be used beyond a research context.[81,85] One report commented that policies should recognize diverse sources of safe supply, including hydromorphone and stimulants, that could be delivered in non-medicalized models.[99] Various briefings commented that these reforms enable a shift from a criminal justice to public health approach[105,108,109], and fosters an environment conductive to drug cooperatives.[95] Several reports also noted that policy reforms would allow physicians to be fairly compensated[55], and prescribe drug treatments in a more coordinated manner, for an increased number of patients.[110,111]

Strong governance. Studies discussed the need to ensure that safe supply programs/regulations can be adequately enforced by a governing body.[85] To optimize program implementation, various reports emphasized the need for all levels of government to collaborate[95], and to consider the local legal context so that conditions allow drug producers and vendors to operate effectively.[89]

Continued accumulation and dissemination of evidence. One case study highlighted the role of research to maintain public support, including the tracking and evaluation of policy reforms to maintain public support.[85]

Stakeholder consultations

PWUD-Adcomm consultations

Further themes relating to barriers to safe supply were identified in discussions with the PWUD-Adcomm. These themes centred on: stigma, discrimination and racism from healthcare providers; over-medicalized safe supply models; lack of access to desired substances; child apprehension (affecting parents, pregnant mothers who may need to access safe supply); and lack of cultural competency (Appendix E, Table 5). They felt that the five themes they identified represented the reality of accessing safe supply or being denied access to safe supply. To facilitate comparisons between PWUD-identified perspectives and the literature, Table 5 also presents sample quotations from qualitative studies for each theme.

The themes from the PWUD-Adcomm overlapped in some respects with those that were identified during the initial review of the academic and grey literature. Theme #1 of *over-medicalization* is closely related to and interconnected with several of the barriers identified through initial inductive analysis, e.g., restrictive laws and policies and distrust towards institutions. Theme #2 of *stigma, discrimination and racism* is also arguably closely associated

with restrictive laws or policies (including criminalization of drug use and over-policing of racialized communities) as well as, again, distrust toward institutions.

When discussing current safe supply programs, advisory committee members consistently mentioned that the restrictive nature of those programs led to the exclusion of some PWUD. For instance, certain eligibility criteria (e.g., method of use) precluded access for some PWUD (e.g., PWUD who do not inject drugs), or if they were otherwise perceived to be ineligible according to the criteria of a typical drug user. Additionally, PWUD reiterated the absence of desired drugs, such as diacetylmorphine and cocaine, which are not typically available in a pharmaceutical-grade formulation. ·

Themes #3-5 regarding *lack of access to desired substances, exposure to child apprehension* and *lack of cultural competency and PWUD representation* were additional themes that extended the foregoing themes of distrust and resistance toward medical and legal authority. Many of these themes are likely directly linked to a lack of PWUD representation -- including lack of equitable and meaningful employment in safe supply program planning, delivery and evaluation -- which consequently limits the capacity of providers to develop programs that fit the needs of clients.

Prescriber consultations

Additional themes were identified through these prescriber consultations, which revealed gaps in the literature regarding barriers and facilitators to safe supply. New barrier themes included regional differences, which emphasized the importance of local context. In conversations about this theme, prescribers identified differences in both safe supply and non-safe supply prescriber beliefs and attitudes, differences in toxicity of drug supply, differences in support (or not) from provincial regulatory authorities, and differences in safe supply models depending on the geographic location. Another barrier theme concerned lack of support from colleagues, where in some places, prescribers are publicly criticized for prescribing safe supply; it can also be hard to find coverage if a prescriber is ill or on vacation or leave.

Finally, both PWUD and prescribers emphasized the need for increased funding for wrap around services and/or infrastructure to expand safe supply programs, or to start safe supply programs where none existed. PWUD and prescribers also identified take-home dosing as an enabling feature in safe supply programs.

DISCUSSION

Our scoping review, co-led by PWUD on our team and advisory committee along with other key stakeholders, identified five broad categories of barriers and facilitators to the provision of safe supply that spanned the user-level, prescriber-level, programmatic-level, policy-level, and societal-level.

Issues of broad agreement in the literature and lessons learned through PWUD expertise

Broadly, there appears to be concordance between the main themes that emerged from the peer-reviewed and grey literature alongside those identified by our PWUD-Adcomm regarding the barriers to, and facilitators of accessing and/or prescribing safe supply. The most frequently

occurring barrier from the literature, restrictive laws and/or policies, was also confirmed when speaking to members of our PWUD-Adcomm, who discussed the inability to access desired substances. We speculate that this observation may in part be borne out by recent trends in opioid prescribing in Canada, which has declined markedly; whereas prescribing rates in 2006 were 72.4/100 people, in 2018 they were at 51.4/100 people.[112]

Literature and PWUD also highlighted how this lack of regulatory support is further reflected at a micro-level, as it filters into the restrictive design and delivery of certain programs. For instance, multiple types of waivers are needed for clinicians to prescribe methadone and buprenorphine in different jurisdictions. This differs from the kind of structured and sustained programs that PWUD envision to provide diacetylmorphine or other desired substances to anyone at risk of overdose and/or to help address other health and social complications.

Consistent with PWUD and prescriber perspectives, funding and practical barriers were consistently identified in the literature as barriers to the implementation and access of safe supply programs. This reflects the trends in low retention rates for PWUD in mental health and addiction treatment services, such as OAT because of logistical barriers,[113,114] which are further exacerbated by socioeconomic disadvantages and public health emergencies such as COVID-19.[115] These barriers suggest a need for safe supply programs to be tailored to the local geographic context and needs of the local PWUD population.

The temporary, if not permanent relaxation, of regulatory restrictions during public health emergencies was identified as a key facilitator of access to safe supply in the literature and through our expert consultations. During the COVID-19 pandemic, this included allowance, at the federal level through exemptions to the CDSA, for verbal prescribing and take-home dosing, which a number of provincial colleges of physicians and pharmacists subsequently echoed in statements to their respective professions. Yet, a significant increase in the provision of safe supply has not been observed since the regulatory exemptions were adopted in March 2020.[116] This suggests that lifting legal restrictions is necessary but insufficient to address the full range of barriers that PWUD face, including with prescribers.

Similarly, the concern about lack of cultural competency reflects the importance of patient-centred care for a stigmatized population. We note that this has implications for medical education and regulatory bodies, who hold responsibilities for ensuring that providers are trained and otherwise equipped to meet diverse patients needs. Besides supporting prescriber competencies to care for this specific sub-population, the healthcare community may also need to consider low barrier community-based models to encourage inclusive program participation among PWUD with various preferred drug consumption methods.

The insights offered by PWUD-Adcomm expanded upon but, in some important respects, diverged from and/or contest the peer-reviewed literature. The theme of stigma and discrimination associated with drug use was identified as a barrier to safe supply in the published and grey literature as well as the members of our PWUD-Adcomm. However, the literature described this issue in general terms. In contrast, the consultation with PWUD-Adcomm went further, emphasizing the intersectionality of this generic kind of stigma/discrimination with

factors such as gender, racialization and/or Indigeneity -- which may further exacerbate the challenges of securing access to safe supply for some PWUD.

A deepening divide between PWUD and prescribers?

There were themes that were agreed upon between PWUD and safe supply prescribers, based on the respective consultations. Prescribers reinforced the view that PWUD preferences regarding drug of choice or dispensing model will need to be prioritized in order for safe supply to be helpful and accepted. However, the PWUD-Adcomm remarked that safe supply should encompass stimulants and other pharmaceutical substances in addition to opioids, and that they would benefit from programs who are more flexible in management and delivery of safe supply.

Further, it appears that the published scientific evidence about the provision of safe supply in the context of an emergency such as COVID-19 is fairly limited. Only three studies in our review highlighted the nascent state of the evidence as a barrier to safe supply implementation, and anecdotal evidence suggests that prescribers and policy-makers may hold the view that the provision of safe supply should wait until the evidence base to inform safe supply prescribing is more established. PWUD participating in this project strongly oppose this interpretation (as do other members of our research team who do not identify as PWUD). Although the scientific evidence about COVID-19's impact on vulnerable populations is evolving,[117] the existing harms associated with illegal sources of drugs warrant a public health approach involving the provision of a regulated, pharmaceutical-grade supply.

In Canada, physicians can prescribe pharmaceutical alternatives to most illegal substances off label, with detailed case notes.[30] Indeed, clinicians in a variety of settings have been prescribing various forms of safe supply such as injectable opioid agonist therapy, tablet injectable opioid agonist therapy, fentanyl assisted treatment, and heroin assisted treatment for some time.[109] Despite this, medical professionals are still reluctant or unable prescribe safe supply due to various anticipated or real challenges reinforced by the literature and our prescriber consultations. Flexibility in legislation, prescribing, and health service delivery are needed to ensure that healthcare providers are equipped to respond to the needs of PWUD.

The leaders in the safe supply prescribing field were practicing prior to COVID-19 and they will continue to provide clinical service delivery once COVID-19 is contained. Further, rigorous scientific evaluation on safe supply is actively taking place in Canada, with strong support from Health Canada's Substance Use and Addictions Program (SUAP).[118] Indeed, the 12 safe supply programs currently funded by SUAP require evaluation, and such evaluations generally engender the development of clinical guidelines and updating of clinical practices as necessary.

However, PWUD access to harm reduction services remains, at best, variable across regions or difficult to access some contexts, such as in rural settings.[119] Despite strong evidence in favour of injectable OAT and diacetylmorphine, these programs remain small and few in number. Including PWUD in the design and delivery of safe supply stands a productive step towards treating PWUD as people first, destigmatizing their existence and creates a chance for authentic patient centred care to take place within the patient's primary care setting.

Defining and implementing safe supply

We noted that the published literature used a wide range of terms to refer to safe supply, which highlights how safe supply may be perceived by different actors. Based upon our review to date, use of the phrase 'safe supply' is a relatively recent phenomenon; relevant knowledge can potentially be found in literature that does not adopt this terminology. Other sources, which were captured by our review, used alternative terminologies in place of "safe supply" to refer to the legal provision of illegal drugs, including: "accessible, regulated supply"; "opioid prescriptions intended to treat addiction through maintenance therapy"; "regulated manufacturing"; "legalized-regulated drug supply"; "medically regulated drug supply model"; "medical regulation of opioids"; and, "artisanal version of opioids."

While not highlighted in the literature we analyzed as a barrier *per se*, the inconsistent use of the term has the potential to precipitate confusion, mask division between prescribers and PWUD, and/or otherwise limit support for the uptake of safe supply. Illustrating this point, members of the expert PWUD-Adcomm emphasized a distinction between 'safe' and '*safer*' supply. The latter phrase, intended to acknowledge that the provision of even pharmaceutical-grade opioids and other drugs is not risk-free, originated from prescribing Ontario physicians. However, from the perspective of PWUD (both part of our team and the advisory committee), emphasizing the risks of the regulated supply shifts attention away from the fact that drugs sourced from elsewhere are, by definition, unsafe and contribute to deaths. Reflecting the power dynamics at play, PWUD are forced to adapt or soften their language (i.e., replacing "safe" with "safer supply") to ensure that medical, legal or academic professionals are comfortable with the terminology. The BCCSU guidelines also avoid this language of "safe supply", instead using terms like "pandemic pharmacotherapy" and "risk mitigation".[30]

Study strengths and limitations

This study has several strengths. One of its primary strengths is that it draws upon diverse sources of information to ensure we did not miss any relevant literature, including various academic databases and an extensive list of grey literature sources. The inclusion of PWUD and external healthcare provider perspectives, both through ongoing consultations and as collaborating co-authors, have helped to contextualize our research findings and their implications. Moreover, this study relied on a rigorous two-stage screening method that leveraged simultaneous screening by three reviewers to verify findings and/or discrepancies.

There were also some limitations of this study. Given the lack of programmatic research evaluating safe supply models and the evolving COVID-19 literature, our findings were limited to the available qualitative or clinical studies of pilot treatment programs, as well as OAT programs during similar public health emergencies outside of pandemic contexts. As such, the themes regarding barriers and facilitators were interpreted in this context.

Recommendations

Given the range of barriers and facilitators to the provision of safe supply, we suggest multi-sectoral solutions, spanning different levels of government, programs, and prescribers—led by,

and in meaningful collaboration with, PWUD. To address the overdose epidemic stemming from the criminalization of an unregulated drug supply, prescribers, regulators, and public health authorities should focus on scaling up, and then evaluating, diverse safe supply frameworks that address the facilitators and barriers we have identified. First, to address the diversity of PWUD needs and preferences, as well as the uptake and scale of supportive programs, safe supply models should be tailored to the particular social, and cultural context of the geographic region and that of the local PWUD population. Secondly, barriers that stem from economic and social inequities must be addressed through structural solutions such as basic universal income and universal healthcare to provide the conditions for scale and sustained use. We recommend that stakeholders adopt a health equity approach when responding to the challenges of implementing safe supply, as highlighted by consultations with the PWUD-Adcomm. Thirdly, medical education institutions may consider supporting trainees and physicians with ongoing training about harm reduction and trauma-informed care. Fourthly, policy makers and/or regulatory bodies should support healthcare providers in the provision of low-barrier and/or flexible methods for PWUD to obtain safe supply. Lastly, as a backdrop to all of these changes, the policy and legal sector must recognize the fundamental impact of a decriminalization approach to ensure PWUD receive respectful and timely access to life-affirming substances.

CONCLUSION

We have conducted a scoping review on the impact of pandemics and other conditions on the provision of safe supply. Our investigation was informed by relevant stakeholders, including those who possess lived/living expertise of drug use and their healthcare providers. Our review of the literature revealed key barriers and facilitators ranging from the user-level to societal-level. The barriers and facilitators that we have identified in the course of the review require more critical examination in light of the range of policy contexts where safe supply is to be implemented. The precise strategies and policy mechanisms we recommend in order to overcome various barriers to, and enhance the potential facilitators of, safe supply require further research and development. Further research will enable a comprehensive understanding and refinement of these programs given their potential to address the ongoing and unacceptably high burden of mortality and morbidity stemming from overdoses in Canada and across North America. The urgency of the overdose crisis, and a variety of other harms connected to the unsafe illegal supply of drugs, suggests an immediate need to scale up a safe supply of pharmaceutical-grade drugs and substances.

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APPENDICES

APPENDIX A – Detailed search strategies in peer-reviewed databases

1: Search strategy for safe supply during pandemics and natural disasters among Scopus, Ovid MEDLINE, and Embase databases.

Scopus:

TITLE-ABS-KEY (supply OR supplie* OR access* OR maintain* OR treatment* OR therap* OR safe* OR ((risk OR harm) W/2 (reduc* OR mitigat*))) AND TITLE-ABS-KEY (influenza* OR coronavirus OR covid* OR h1n1 OR sars OR quarantine OR mers OR pandemic OR outbreak*) AND TITLE-ABS-KEY (addict* OR (drug* W/2 (abus* OR misuse* OR user*)) OR opioid* OR opiate* OR methadone OR buprenorphine OR heroin OR hydromorphone OR oxycodone OR morphine OR benzodiazepine* OR cocaine OR crack OR methamphetamine OR oxymorphone OR homeless* OR fentanyl) AND PUBYEAR AFT 2001 = 1703 results

Disaster supplement:

(TITLE-ABS-KEY (supply OR supplie* OR access* OR maintain* OR treatment* OR therap* OR safe* OR ((risk OR harm) W/2 (reduc* OR mitigat*))) AND TITLE-ABS-KEY (disaster* OR earthquake* OR hurricane*) AND TITLE-ABS-KEY (addict* OR (drug* W/2 (abus* OR misuse* OR user*)) OR opioid* OR opiate* OR methadone OR buprenorphine OR heroin OR hydromorphone OR oxycodone OR morphine OR benzodiazepine* OR cocaine OR "crack cocaine" OR methamphetamine OR oxymorphone OR fentanyl) AND PUBYEAR > 2001) added 285 results

Ovid MEDLINE(R) ALL <1946 to June 08, 2020>

Search history sorted by search number ascending

#	Searches	Results
1	coronavirus/ or betacoronavirus/ or coronavirus infections/ or (disease outbreaks/ or epidemics/ or pandemics/)	102605
2	(nCoV* or 2019nCoV or 19nCoV or COVID19* or COVID or SARS-COV-2 or SARSCOV-2 or SARSCOV2 or Severe Acute Respiratory Syndrome Coronavirus 2 or Severe Acute Respiratory Syndrome Corona Virus 2).ti,ab,kf,nm,ox,rx,px.	20721
3	((new or novel or "19" or "2019" or Wuhan or Hubei or China or Chinese) adj3 (coronavirus* or corona virus* or betacoronavirus* or CoV or HCoV)).ti,ab,kf.	7911
4	((coronavirus* or corona virus* or betacoronavirus*) adj3 (pandemic* or epidemic* or outbreak* or crisis)).ti,ab,kf.	1773

5 ((Wuhan or Hubei) adj5 pneumonia).ti,ab,kf. 163

6 SARS virus/ or Severe Acute Respiratory Syndrome/ or Middle East Respiratory Syndrome Coronavirus/ 6949

7 (SARSCOV* or Severe Acute Respiratory Syndrome* or sudden acute respiratory syndrome* or SARS like or MERSCoV* or Middle East Respiratory or camel flu or EMC 2012).ti,ab,kf. 8508

8 ((SARS or MERS) adj5 (virus* or coronavirus* or betacoronavirus* or CoV or CoV2 or HCoV or pandemic or epidemic or outbreak* or infect* or respiratory or pathogen*)).ti,ab,kf. 13295

9 *pandemics/ 5027

10 (influenza* or coronavirus or covid* or h1n1 or sars or mers or pandemic or outbreak*).ti,ab,kf. 243260

11 ((flu or influenza*) adj3 (pandemic* or epidemic*)).ti,ab,kf. 14525

12 quarantine*.ti,ab,kf. 5022

13 or/1-12 287460

14 Harm Reduction/ 3032

15 risk reduction behavior/ 12492

16 exp Health Services Accessibility/ 109967

17 exp "Delivery of Health Care"/ 1070332

18 (supply or supplie* or access* or maintain* or treatment* or therap* or safe* or ((risk or harm) adj2 (reduc* or mitigat*))).ti,ab,kf. 7568788

19 or/14-18 8289618

20 drug users/ 3112

21 exp Substance-Related Disorders/ 276760

22 exp Homeless Persons/ 8848

23 (addict* or (drug* adj2 (abus* or misuse* or user*)) or opioid* or opiate* or methadone or buprenorphine or heroin or hydromorphone or oxycodone or morphine or benzodiazepine* or cocaine or crack or methamphetamine or oxymorphone or homeless* or fentanyl).ti,ab,kf. 324494

24 or/20-23 511276

25 13 and 19 and 24 1144

26 exp Natural Disasters/ 17100

27	(disaster* or earthquake* or hurricane*).ti,ab,kf.	32854
28	26 or 27	44413
29	19 and 24 and 28	199
30	29 not 25	188
31	limit 30 to yr="2002 -Current"	155
32	limit 25 to yr="2002 -Current"	863
33	13 or 28	330016
34	19 and 24 and 33	1332
35	limit 34 to yr="2002 -Current"	1018

Embase (Elsevier)

(((('drug use'/exp OR 'drug abuse'/exp OR 'addiction'/exp OR 'homelessness'/exp OR 'homeless person'/exp) OR (drug* NEAR/2 (abus* OR misuse* OR user*)):ti,ab,kw OR (addict*:ti,ab,kw OR opioid*:ti,ab,kw OR opiate*:ti,ab,kw OR methadone:ti,ab,kw OR buprenorphine:ti,ab,kw OR heroin:ti,ab,kw OR hydromorphone:ti,ab,kw OR oxycodone:ti,ab,kw OR morphine:ti,ab,kw OR benzodiazepine*:ti,ab,kw OR cocaine:ti,ab,kw OR crack:ti,ab,kw OR methamphetamine:ti,ab,kw OR oxymorphone:ti,ab,kw OR homeless*:ti,ab,kw OR fentanyl:ti,ab,kw)) AND (('health care delivery'/exp OR 'health care access'/exp OR 'harm reduction'/exp OR 'risk reduction'/exp) OR ((risk OR harm) NEAR/2 (reduc* OR mitigat*)):ti,ab,kw OR (supply:ti,ab,kw OR supplie*:ti,ab,kw OR access*:ti,ab,kw OR maintain*:ti,ab,kw OR treatment*:ti,ab,kw OR therap*:ti,ab,kw OR safe:ti,ab,kw)) AND ((('coronaviridae'/exp OR 'betacoronavirus'/exp OR 'coronavirus infection'/exp OR 'epidemic'/exp OR 'pandemic'/exp OR 'pandemic influenza'/exp OR 'disaster'/exp OR 'severe acute respiratory syndrome'/exp OR 'sars-related coronavirus'/exp OR 'middle east respiratory syndrome coronavirus'/exp OR 'middle east respiratory syndrome'/exp OR 'quarantine'/exp) OR (influenza*:ti,ab,kw OR coronavirus:ti,ab,kw OR betacoronavirus*:ti,ab,kw OR 'corona virus*':ti,ab,kw OR covid*:ti,ab,kw OR h1n1:ti,ab,kw OR sars:ti,ab,kw OR mers:ti,ab,kw OR pandemic:ti,ab,kw OR outbreak*:ti,ab,kw OR quarantine*:ti,ab,kw) OR (sarscov*:ti,ab,kw OR 'severe acute respiratory syndrome*':ti,ab,kw OR 'sudden acute respiratory syndrome*':ti,ab,kw OR merscov*:ti,ab,kw OR 'middle east respiratory':ti,ab,kw OR 'camel flu':ti,ab,kw OR 'emc 2012':ti,ab,kw) OR ((wuhan OR hubei) NEAR/5 pneumonia):ti,ab,kw OR (ncov*:ti,ab,kw OR 2019ncov:ti,ab,kw OR 19ncov:ti,ab,kw OR covid19*:ti,ab,kw OR covid:ti,ab,kw OR 'sars-cov-2':ti,ab,kw OR 'sarscov-2':ti,ab,kw OR sarscov2:ti,ab,kw OR 'severe acute respiratory syndrome coronavirus 2':ti,ab,kw OR 'severe acute respiratory syndrome corona virus 2':ti,ab,kw)) OR (disaster*:ti,ab,kw OR earthquake*:ti,ab,kw OR hurricane*:ti,ab,kw)) AND [2002-2020]/py) AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) 2655 results

2: Supplemental search strategy for safe supply in both pandemic and non-pandemic settings among Scopus, MEDLINE, and EMBASE databases.

Scopus

TITLE-ABS-KEY ((legal* OR safe* OR barrier* OR facilitat*) W/5 (suppl* OR access*)) AND TITLE-ABS-KEY (addict* OR (drug* W/2 (abus* OR misuse* OR user*)) OR opioid* OR opiate* OR methadone OR buprenorphine OR heroin OR hydromorphone OR oxycodone OR morphine OR benzodiazepine* OR cocaine OR crack OR methamphetamine OR oxymorphone OR homeless* OR fentanyl) AND PUBYEAR > 2009 = 1195

Ovid MEDLINE(R) ALL <1946 to June 08, 2020>

Search history sorted by search number ascending

#	Searches	Results
1	coronavirus/ or betacoronavirus/ or coronavirus infections/ or (disease outbreaks/ or epidemics/ or pandemics/)	102605
2	(nCoV* or 2019nCoV or 19nCoV or COVID19* or COVID or SARS-COV-2 or SARSCOV-2 or SARSCOV2 or Severe Acute Respiratory Syndrome Coronavirus 2 or Severe Acute Respiratory Syndrome Corona Virus 2).ti,ab,kf,nm,ox,rx,px.	20721
3	((new or novel or "19" or "2019" or Wuhan or Hubei or China or Chinese) adj3 (coronavirus* or corona virus* or betacoronavirus* or CoV or HCoV)).ti,ab,kf.	7911
4	((coronavirus* or corona virus* or betacoronavirus*) adj3 (pandemic* or epidemic* or outbreak* or crisis)).ti,ab,kf.	1773
5	((Wuhan or Hubei) adj5 pneumonia).ti,ab,kf.	163
6	SARS virus/ or Severe Acute Respiratory Syndrome/ or Middle East Respiratory Syndrome Coronavirus/	6949
7	(SARSCOV* or Severe Acute Respiratory Syndrome* or sudden acute respiratory syndrome* or SARS like or MERSCoV* or Middle East Respiratory or camel flu or EMC 2012).ti,ab,kf.	8508
8	((SARS or MERS) adj5 (virus* or coronavirus* or betacoronavirus* or CoV or CoV2 or HCoV or pandemic or epidemic or outbreak* or infect* or respiratory or pathogen*)).ti,ab,kf.	13295
9	*pandemics/	5027
10	(influenza* or coronavirus or covid* or h1n1 or sars or mers or pandemic or outbreak*).ti,ab,kf.	243260
11	((flu or influenza*) adj3 (pandemic* or epidemic*)).ti,ab,kf.	14525

12 quarantine*.ti,ab,kf. 5022

13 or/1-12 287460

14 Harm Reduction/ 3032

15 risk reduction behavior/ 12492

16 exp Health Services Accessibility/ 109967

17 exp "Delivery of Health Care"/ 1070332

18 (supply or supplie* or access* or maintain* or treatment* or therap* or safe* or ((risk or harm) adj2 (reduc* or mitigat*))).ti,ab,kf. 7568788

19 or/14-18 8289618

20 drug users/ 3112

21 exp Substance-Related Disorders/ 276760

22 exp Homeless Persons/ 8848

23 (addict* or (drug* adj2 (abus* or misuse* or user*)) or opioid* or opiate* or methadone or buprenorphine or heroin or hydromorphone or oxycodone or morphine or benzodiazepine* or cocaine or crack or methamphetamine or oxymorphone or homeless* or fentanyl).ti,ab,kf. 324494

24 or/20-23 511276

((legal* or safe* or barrier* or facilitat*) adj8 (suppl* or access*)).ti,ab,kf. + Drug concept (line 24) / 2009 limit = 1213 results

3: Supplemental search strategy for clinical trials about pharmaceutical-grade drugs among MEDLINE, Embase, and Cochrane CENTRAL databases.

Ovid MEDLINE(R) ALL <1946 to June 26, 2020>

Search history sorted by search number ascending

Searches Results

1 ((Diacetylmorphine or heroin or diamorphine) adj2 (treatment* or therap* or maintenance or maintain*)).ti,ab,kf. 1183

2 (injectable opioid adj2 (treatment or therapy)).ti,ab,kf. 35

3 (supervised injectable adj1 (heroin or opioid*)).ti,ab,kf. 16

4 ((prescribed or prescription or pharmaceutical or injectoin or injectable or liquid) adj2 (heroin or diacetylmorphine or diamorphine or hydromorphone)).ti,ab,kf. 390

5 *Heroin/tu [Therapeutic Use] 258

6 or/1-5 1642

7 ("19692689" or "27049826" or "20359843" or "16135401" or "20510551" or "21791093" or "20424457" or "19922517" or "12644733" or "18422829" or "16002023" or "17602126").ui. 12

8 6 and 7 12

9 limit 6 to yr="2000 -Current" 1172

Embase = 686 results

(((diacetylmorphine OR heroin OR diamorphine) NEAR/3 (treatment* OR therap* OR maintenance OR maintain*)):ti,ab,kw OR ('injectable opioid' NEAR/3 (treatment OR therapy)):ti,ab,kw OR ('supervised injectable' NEAR/2 (heroin OR opioid*)):ti,ab,kw OR ((prescribed OR prescription OR pharmaceutical OR injectoin OR injectable OR liquid) NEAR/3 (heroin OR diacetylmorphine OR diamorphine OR hydromorphone)):ti,ab,kw OR 'diamorphine'/exp/mj/dd_dt) AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) AND [1-1-2000]/sd NOT [1-7-2020]/sd

Search Name: Heroin assisted therapy

Date Run: 29/06/2020 18:39:02

Comment: Cochrane CENTRAL

ID Search Hits

#1 ((diacetylmorphine OR heroin OR diamorphine) NEAR/3 (treatment* OR therap* OR maintenance OR maintain*)):ti,ab,kw 606

#2 ("injectable opioid" NEAR/3 (treatment OR therapy)):ti,ab,kw 9

#3 ("supervised injectable" NEAR/2 (heroin OR opioid*)):ti,ab,kw 4

#4 ((prescribed OR prescription OR pharmaceutical OR injectoin OR injectable OR liquid) NEAR/3 (heroin OR diacetylmorphine OR diamorphine OR hydromorphone)):ti,ab,kw 122

#5 MeSH descriptor: [Heroin] this term only 308

#6 MeSH descriptor: [Therapeutics] explode all trees 298964

#7 #5 and #6 175

#8 #1 OR #2 OR #3 OR #4 OR #7 743 –> 2000 publication date limit = 545 CENTRAL records

APPENDIX B – List of grey literature search sources

Grey literature source
Abbotsford Drug War Survivors
Alliance for Healthier Communities
British Columbia Centre for Disease Control
British Columbia Centre for Substance Use
CADTH
Canadian Alliance to End Homelessness
Canadian Centre on Substance Use and Addiction
Canadian Drug Policy Coalition
Canadian Research Initiative in Substance Misuse
Canadian Students for Sensible Drug Policy
CAPUD
CATIE
Centre for Addiction and Mental Health
Drug Policy Alliance
European Centre for Disease Prevention and Control
European Monitoring Centre for Drugs and Drug Addiction
Global commission on drug policy
INPUD
International Drug Policy Coalition
Joseph Rowntree Foundation
Manitoba Harm Reduction Network
Metro Vancouver Aboriginal Executive Council
Moms Stop the Harm
Ontario HIV Treatment Network
Pivot
Providence Health Care
Public Health England
RAND

Scottish Drugs Forum
Students for Sensible Drug Policy
Support Don't Punish
Toronto Public Health
Transform Drugs
United Nations Office on Drugs and Crime
Vancouver Coastal Health
Vocal New York

CADTH: Canadian Agency for Drugs and Technologies in Health; CAPUD: Canadian Association of People Who Use Drugs; CATIE: Canadian AIDS Treatment Information Exchange; INPUD: International Network of People who Use Drugs; RAND: Research and development corporation

APPENDIX C – Data extraction fields

Administrative Information:

- Author(s)
- Year of publication
- Country of origin
- Evidence source (name of journal or grey literature source)

Study information:

- Study design: trial, observational, qualitative, guideline/recommendation
- Aims/purpose of study

Participant information

- Brief description of participants
- Safe supply addressed: opioids, stimulants, benzodiazepines, multi/all
- Context: COVID-19, SARS, H1N1, MERS, Hurricane, Earthquake, etc. (specify names of natural disasters where appropriate)
- Intervention and comparator
- Drug use prior to intervention, if no comparator
- Number of participants (initially enrolled)
- Age range of participants
- Gender and sexuality
- Ethno-racial identity
- Financial and housing description
- Opioids used
- Non-opioid drugs used (other than alcohol/tobacco/marijuana)

Geography:

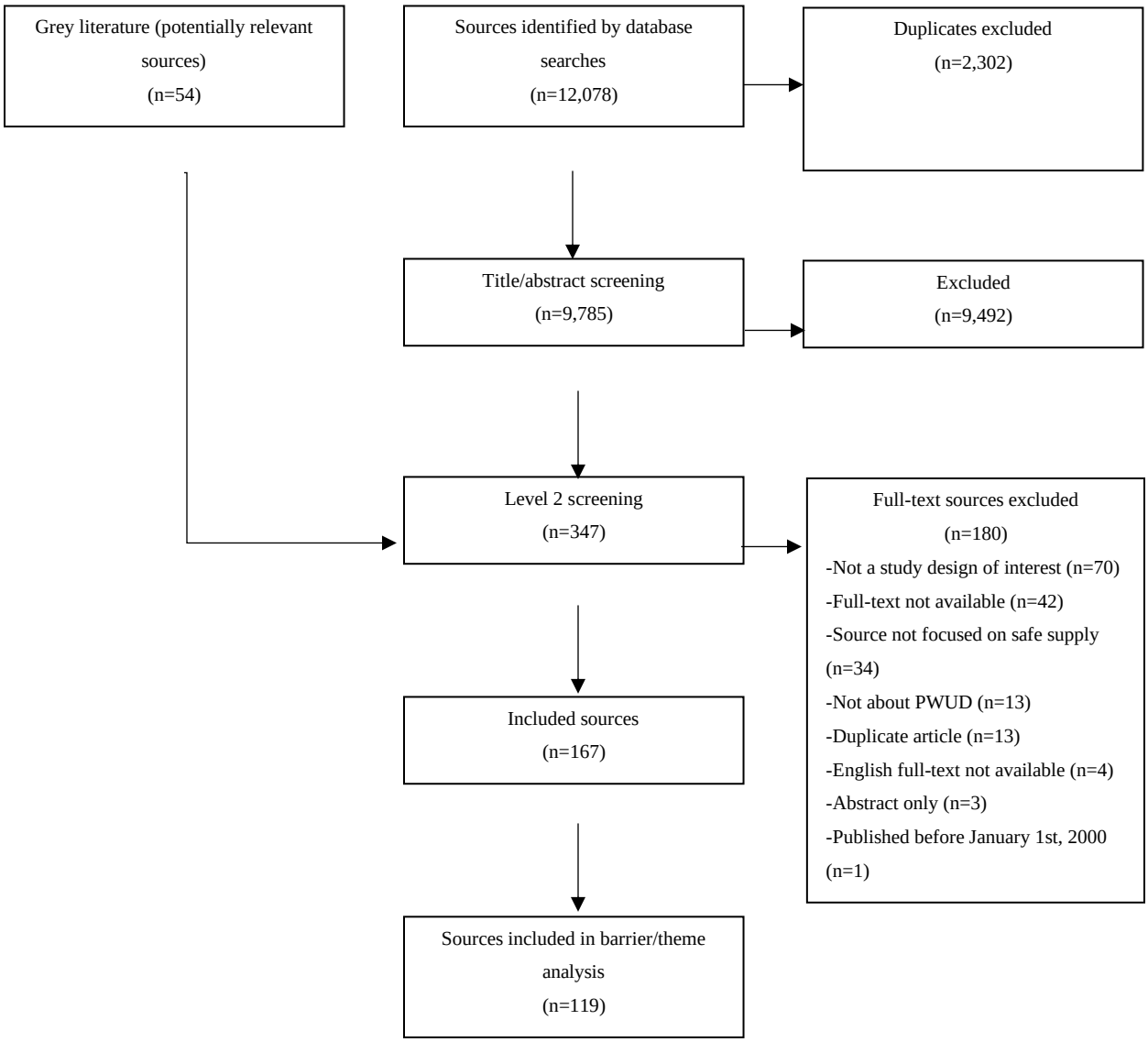
- Participant location (city, state/province, country or countries).
- Rural vs. Urban

Key findings or discussion points:

- Safe supply program outcomes?
    - Were patients retained?
    - Did patients have to turn to street supply?
- Barriers to safe supply
    - Stigma
    - Cultural/language
    - Geographical
    - Financial
- Facilitators to safe supply

    - Operational changes made to ensure safe supply (e.g., guest-dosing)
    - Patient-provider relationships.
    - Legal changes
- Recommendations for addressing barriers to safe supply
- Group or category of safe supply: Heroin assisted treatment, prescription opioid safe supply, or stimulant safe supply
- Terminology (other words used in place of "safe supply")

APPENDIX D – Manuscript figures



APPENDIX E – Manuscript tables

Table 1a. Primary search about barriers and facilitators to accessing or prescribing safe supply in pandemic and non-pandemic contexts (n=32).

First Author	Year	Location	Search source	Design / format	Objective	Population	Type of drug used	Conclusions
Arya[17]	2020	India	Academic journal (pandemic/ disaster search)	Commentary	Outline the challenges expected in managing patients with SUDs during COVID-19's nationwide lockdown	People with SUD	Buprenorphine, methadone	Treatment services need to adapt to daily changing scenarios with emphasis on practical approaches to help people with SUDs
Basu[77]	2020	India	Academic journal (pandemic/ disaster search)	Qualitative	Discuss interim standard operating procedures (SOPs) for running a hospital-based OST service utilizing take-home BNX	People with OUD	Buprenorphine, naloxone	Other institutions may follow or tailor these SOPs to meet the needs and demands of their opioid-dependent patients on OST
Blake[32]	2016	New Zealand	Academic journal (pandemic/ disaster search)	Qualitative	Identify the views of three professional groups working in Aotearoa/New Zealand about OST provision following a disaster	Service providers or managers	Opioids	OST preparedness planning must be multidisciplinary, flexible, and inclusive
Blake[4]	2020	New Zealand	Academic journal (pandemic/ disaster search)	Qualitative	Explores how stigma is experienced as a barrier to engagement with emergency management among people receiving OST	People receiving OST	Buprenorphine, methadone, naloxone	Medications and other necessary treatments should be made accessible to those who need them to maintain health and wellbeing
Darke[120]	2014	USA	Academic journal (supplemental search)	Commentary	Examines whether the provision of regulated and quality-controlled heroin to users in specified doses would reduce heroin overdose rates	PWUD	Opioids	On the basis of the experience with prescription opioids, unregulated legal heroin access would not reduce overdose rates
Davis[21]	2020	USA	Academic journal (pandemic/ disaster search)	Commentary	Describe how people with OUD are at increased risk for COVID-19, and existing policy barriers to evidence-based prevention and treatment for individuals with OUD.	People with OUD	Buprenorphine, methadone	Federal and state governments must reduce barriers to care for individuals with OUD, both during the current crisis and beyond.
Demirjian[42]	2008	USA	Academic journal (pandemic/ disaster search)	Qualitative	Examine effectiveness of clinics' emergency planning policies [post 9/11] and identify transferable lessons to help other programs develop responses to natural and manmade disasters	People with OUD	Methadone	OTP's require individualized disaster plans

Dunlop[18]	2020	Australia	Academic journal (pandemic/ disaster search)	Commentary	Outlines the challenges in maintaining treatment services for people who use drugs during COVID-19	PWUD undergoing treatment	Buprenorphine, methadone	Changes to treatment services for PWUD may be necessary to mitigate their increased risk of infection during COVID-19
Elliott[90]	2017	USA	Academic journal (pandemic/ disaster search)	Qualitative	Generate a set of recommendations from OTP directors, staff, and patients for improving OTP disaster preparedness	People enrolled in an opioid treatment program	Buprenorphine, methadone	The study identified improvements to be made to OTP disaster preparedness.
Fischer[121]	2020	North America	Academic journal (supplemental search)	Commentary	Examines the supply side factors contributing to opioid crisis	PWUD	Opioids	Improved empirical understanding of the causal supply dynamics and structures driving the present opioid mortality crisis are needed
Fleming[25]	2020	Canada	Academic journal (supplemental search)	Commentary	To make an argument for using a safe stimulant supply to address illicit supply quality issues	People using stimulants in North America	Stimulants	Given the success of HAT, there is a need to explore stimulant safe supply treatment to explore possible similar benefits
Green[19]	2020	USA	Academic journal (pandemic/ disaster search)	Commentary	Highlight the role pharmacists in sustaining access to treatment for OUD during COVID-19	PWUD undergoing treatment for OUD	Buprenorphine, methadone	Changes to regulatory barriers for frontline treatment workers are need to improve care for PWUD
Greer[31]	2020	Australia	Academic journal (supplemental search)	Qualitative	To examine the views of PWUD on the effects and role of government in a legalized drug market	PWUD	Multiple	PWUD supported legalization with regulation but with skepticism towards the government's role and intentions
Griffin[16]	2018	USA	Academic journal (pandemic/ disaster search)	Qualitative	Describe the effects of a closure of an OTP from the POV of clinicians and administrators	People enrolled in an opioid treatment program	Methadone	Regulatory controls and structural damage to facilities threatens to disrupt treatment continuity during disasters
Gupta[12]	2017	USA	Academic journal (pandemic/ disaster search)	Qualitative	Describe the emergency merger of opioid treatment programs in response to a hurricane.	People enrolled in an opioid treatment program	Buprenorphine, methadone	The study identified disaster planning measures that clinics could use to facilitate continuity of care
Haines[54]	2020	Canada	Academic journal (supplemental search)	Qualitative	Validate the reality of the unique drug-use culture in Ottawa, and the requirement for harm reduction services to be adapted to the local needs of PWUD	PWUD	Multiple	PWUD are not a homogenous group. Effort needs to be made to tailor harm reduction services to local communities
Harris[38]	2020	USA	Academic journal (pandemic/ disaster search)	Qualitative	Describe video-conference facilitated buprenorphine initiation in 2 people with OUD	PWUD with severe OUD	Buprenorphine	Tele-buprenorphine initiation is an innovative method for lowering barriers to OUD treatment and warrants further investigation

Ivsins[26]	2020	Canada	Academic journal (supplemental search)	Commentary	To make an argument for providing a safe supply to address the overdose crisis	Persons reliant on the unregulated opioid supply in North America	Opioids	Safe supply is urgently needed to save lives given the epidemic of fatal overdoses
Jiang[20]	2020	China	Academic journal (pandemic/ disaster search)	Commentary	Make policy recommendations for how to continue methadone maintenance treatment during COVID-19	PWUD on methadone maintenance treatment	Methadone	New program management measures need to be implemented to improve care for PWUD undergoing treatment during COVID-19
Khatri[43]	2020	USA	Academic journal (pandemic/ disaster search)	Commentary	Summarize innovations that can prevent the opioid epidemic from worsening during COVID-19	Patients with OUD	Buprenorphine, methadone	While innovations have been made to improve care for PWUD during COVID-19 further changes are required to protect PWUD during the pandemic
Leppla[37]	2020	USA	Academic journal (pandemic/ disaster search)	Commentary	Reviews and provides guidance for clinicians regarding 3 prongs of medication treatment of OUD affected by COVID-19 healthcare mandates: methadone take-homes, buprenorphine treatment, and antagonist therapy	People with OUD	Buprenorphine, methadone	Adjustments must be made to dosing and group therapy during pandemic era of social isolation. Provides practical guidance for clinicians regarding optimal approaches to methadone, buprenorphine and naltrexone during the pandemic.
Maghsoudi[122]	2020	Canada	Academic journal (supplemental search)	Commentary	Explores the current state of policy and practice for DAM and hydromorphone as opioid substitution options. Recommends policy changes.	PWUD	Opioids	Given the magnitude of opioid related harms among people reliant on the illicit market, there is a need to remove barriers to safe supplies of DAM and hydromorphone
Marsden[22]	2020	Unclear	Academic journal (pandemic/ disaster search)	Commentary	Summarizes issues to people with addictive disorders as a result of COVID-19 and calls for a coordinated effort to address them.	People with OUD	Multiple	COVID-19 and the measures used to address it exacerbates multiple risk factors for the initiation of addictive behaviors and the maintenance, worsening and relapse of addictive disorders
Matusow[13]	2018	USA	Academic journal (pandemic/ disaster search)	Mixed methods	1) Investigate how OTP staff and administrators anticipated and responded to the disruptions in OTP service (2) Solicit patient and out-of-treatment opioid user perspectives and experiences after Hurricane Sandy, in order to (3) Develop recommendations for OTPs in their ongoing recovery	People with OUD	Multiple	Identified issues with and recommendations for providing continuity of care in Hurricane Sandy-affected opioid treatment communities.

					efforts from Hurricane Sandy and for future emergencies			
McClure[14]	2014	USA	Academic journal (pandemic/ disaster search)	Qualitative	Examine advantages and disadvantages of methadone and buprenorphine regulations and dispensing methods in the face of a major disruption of service. Analyze the effects of regulatory differences between methadone and buprenorphine on the continuity of care after Hurricane Sandy.	Providers of opioid maintenance treatment	Buprenorphine, methadone	There is a need for well-defined emergency procedures with flexibility around regulations, the need for a central registry with patient dose information, as well as stronger professional networks and cross-coverage procedures.
O'Dwyer[76]	2020	Australia	Academic journal (pandemic/ disaster search)	Qualitative	Explore the effects of Queensland (QLD) cyclones on opioid treatment programs within Queensland community and hospital pharmacies from three perspectives	Community and public hospital pharmacists, opioid treatment program staff	Buprenorphine, methadone	Continuation of ORT services during and in the aftermath of a cyclone event is complex. To improve continuity of ORT services, stakeholders must coordinate to prepare for and respond to future events.
Peavy[56]	2020	USA	Academic journal (pandemic/ disaster search)	Commentary	Describe (1) measures adopted at the OTP to mitigate spread of COVID-19 while preserving core services to patients; (2) implementation of clinical decision-making strategies aimed at maintaining patient and community safety; and (3) changes in clinic patient flow	People with or high-risk for HIV and OUD	Methadone	Organization-level decisions were made quickly during COVID-19 to ensure uninterrupted access to methadone while balancing efforts to mitigate COVID-19 risk
Pouget[123]	2015	USA	Academic journal (pandemic/ disaster search)	Cross-sectional	Investigate whether Hurricane Sandy affected living circumstances, injection drug use, and helping behavior among PWID	PWUD	Buprenorphine, methadone	PWID served as assets to their respective communities, helping other drug users and non-drug users in the wake
Sun[61]	2020	China	Academic journal (pandemic/ disaster search)	Commentary	Discuss challenges to OUD during COVID-19	People with OUD	Buprenorphine, methadone	People with OUDs require specific consideration in emergency planning and management. The most important issue is to ensure service continuity and accessibility of OAT during the pandemic
Tofighi[15]	2014	USA	Academic journal (pandemic/ disaster search)	Mixed methods	Determine self-reported illicit opioid use (other than illicitly-obtained buprenorphine); self-reported tobacco, alcohol, and drug misuse; coping strategies	Adult, opioid-dependent patients	Buprenorphine	Case study demonstrates relative adaptability of public sector office-based buprenorphine treatment during and after a significant natural disaster

					following buprenorphine supply disruption, and resource loss among opioid-dependent patients enrolled in BHC's office-based buprenorphine clinic immediately following Hurricane Sandy			
Vecchio[124]	2020	Italy	Academic journal (pandemic/ disaster search)	Commentary	Describes novel approaches to enable continuation of care to patients with OUD	People with OUD	Buprenorphine	There is a need for continuing innovation. Access to approved medicines such as the prolonged release buprenorphine products must now be prioritized to further reduce the risk for individuals in care
Werle[53]	2018	USA	Academic journal (supplemental search)	Commentary	Analyzes legal and ideological underpinnings of policies for medication-assisted treatment for opioid addiction	PWUD	Opioids	Decriminalization is a necessary but insufficient response to the opioid crisis. Low-threshold methadone maintenance treatment should be considered as part of comprehensive drug treatment

Table 1b. Grey literature search of barriers and facilitators to accessing or prescribing safe supply (n=36).

First Author	Year	Location	Search source	Design	Objective	Population	Type of drug used	Conclusions/Summary
Advisory Council on the Misuse of Drugs (ACMD)[111]	2016	United Kingdom	Grey literature (second draft)	Report	Explore factors related to the increase in opioid-related harms in the United Kingdom.	PWUD in general	Opioids	There will be an increase in the number of deaths among opioid-users because of increasing vulnerability due to increasing age, increased availability of heroin, polysubstance use, and worsening socio-economic circumstances.
Advisory Council on the Misuse of Drugs (ACMD)[111]	2017	United Kingdom	Grey literature (second draft)	Report	Summarize a national inquiry into factors associated with opioid-related harms.	PWUD in general	Opioids	The UK government is pleased with the detailed inquiry and will work to implement recommendations.
Alliance for Healthier Communities[23]	2020	Canada	Grey literature (first draft)	Commentary	To advocate for expanded access to emergency safe supply in Ontario because of COVID-19.	PWUD in Ontario	Opioids	Safe supply is urgently need during COVID-19. The necessary protocols and professional expertise are already in place to implement safe supply.
British Columbia Centre for Disease Control[99]	2018	Canada	Grey literature (second draft)	Report	Summarize recommendations from a group of multi-disciplinary stakeholders on the current state of the overdose epidemic.	PWUD in general	Opioids	A wide range of stakeholders provided innovative approaches to handle the overdose emergency in BC but action is needed to create measureable change.
British Columbia Centre on Substance Use[125]	2019	Canada	Grey literature (second draft)	Report	Describe a cooperative approach to providing pharmaceutical heroin to compassion club members.	PWUD in general	Opioids	Compassion clubs could provide a safe alternative to dangerously contaminated street drugs by offering opioid-addicted individuals a regulated and controlled supply of their preferred drug.
British Columbia Centre on Substance Use[30]	2020	Canada	Grey literature (second draft)	Guidelines	Provide guidance to healthcare professionals treating people with substance use disorder during a global pandemic.	People with SUD	Multiple	It is recommended to replace both illicit and licit substances with prescribed or regulated substances to reduce risk of withdrawal, exposure to COVID-19, and exposure to a limited and toxic drug supply.
British Columbia Centre on Substance Use[94]	2020	Canada	Grey literature	Guidelines	Provide guidance to OAT prescribers during the COVID-19 pandemic.	People who use opioids	Opioids	Clinics and program administrators should take steps to reduce chances of COVID-19 infection by making sure clinic space is safe and that people have

British Columbia Ministry of Health[126]	2019	Canada	Grey literature	Guidelines	Describe the current state of narcotic therapies and challenges in expanding access.	PWUD in general	Opioids	a supply of safe pharmaceutical grade substances. Health professionals face notable legal and regulatory barriers to providing narcotic-based treatments to patients.
Canada's Drug Futures Forum[127]	2017	Canada	Grey literature	Report	Summary of Canada's Drug Futures Forum presentations and participant recommendations.	PWUD in general	Opioids	Recommendations from stakeholders for policy reform converged into five domains: drug policy reform, criminal justice reform, prevention and treatment, knowledge exchange, and international leadership. Policymakers and stakeholders should take notice of these recommendations.
Canadian Association of People who Use Drugs[91]	2019	Canada	Grey literature	Report	Outline the concept of safe supply including its role in drug policy	PWUD in general	Multiple	Safe supply is a necessary step towards ending the prohibitionist policies that have harmed vulnerable people.
Canadian Centre on Substance Use and Addiction[55]	2020	Canada	Grey literature	Case summary	Share information about complementary measures to increase quality of life for people who use drugs.	PWUD in general	Opioids	Expanding response options to opioid-related harms during COVID-19 can help improve the lives of people who use drugs. Recommendations include sustaining the expanded scope of treatment options after COVID-19 and supporting physician knowledge and decision-making.
Clinical Guidelines on Drug Misuse and Dependence Independent Expert Working Group[52]	2017	United Kingdom	Grey literature	Guidelines	Help providers optimize reach and effectiveness of drug dependence interventions.	People who use heroin	Multiple	The updated guidelines take into account developments in drug treatment including the ageing of the heroin using population, legislative changes affecting treatment, changing patterns of substance use, and the focus on individually defined recovery journeys.
Danish National Board of Health[128]	2009	Copenhagen	Grey literature	Guidelines	Outline guidelines for prescription heroin as a treatment for opioid dependence.	People with heroin dependence	Opioids	Guidelines will be updated every six months as necessary on the basis of treatment monitoring.
de Villa[129]	2019	Canada	Grey literature	Report	Recommendations for scaling up opioid dependence programs.	PWUD in general	Opioids	The implementation of managed opioid programs should be expanded to include

								pharmaceutical heroin and rapidly scaled up to fight the opioid poisoning crisis.
Drug Policy Alliance[130]	2016	USA	Grey literature	Report	To give an overview of HAT research	People who use heroin	Opioids	There is evidence supporting HAT, federal laws should be amended so trials can begin in US cities.
Global Commission on Drug Policy[131]	2019	Switzerland	Grey literature	Report	Summarize the Global Commission of Drug Policy's recommendations for mitigating the opioid crisis.	PWUD in general	Opioids	The Commission recommends making harm reductions strategies and treatment widely available and ending drug prohibition in favor of responsible regulation.
Global Commission on Drug Policy[105]	2018	Switzerland	Grey literature	Report	Describe effective regulatory strategies that take into account the reality of world-wide drug use.	PWUD in general	Multiple	Legal regulation of drugs is needed to reduce the harms of drug prohibition. Legal regulation is complex and requires a cautious, incremental implementation backed by evidence.
Hales[93]	2020	Canada	Grey literature	Guidelines	Provide guidelines based on clinical experiences and current evidence to help combat overdose deaths.	PWUD in general	Opioids	Safer opioid supply programs are a harm reductive, clinician-experience driven, community-based approach that can be implemented to reduce the risk of overdose and death.
House of Commons Health and Social Care Committee[132]	2019	United Kingdom	Grey literature	Policy briefing	Recommendations for changing drug policy in the UK to better protect PWUD.	PWUD in general	Multiple	There is a clear need for an evidence-based harm reduction approach to mitigating drug-related harms.
International Network of People Who Used Drugs[133]	2020	United Kingdom	Grey literature	Recommendations	Recommendations for protecting the human rights of people who used drugs during the COVID-19 pandemic.	PWUD in general	Multiple	The international community needs to take urgent action to protect the rights and dignity of people who use drugs during COVID-19. Failure to do so could have disastrous consequences because of this population's vulnerability.
Jesseman[89]	2018	Canada	Grey literature	Briefing	Inform stakeholders about the applications of drug decriminalization.	PWUD in general	Multiple	There is growing evidence supporting decriminalization as a means of reducing drug-related harm. However, decriminalization needs to be rigorously evaluated to improve supporting evidence.

Mexico Unido: Contra la Delincuencia Transform Drug Policy Foundation[87]	2019	Mexico	Grey literature	Briefing	Describe the challenges of legally producing opium for medical use in Mexico.	People who use opioids	Opioids	Mexico could legally produce opium for domestic use and export it to support harm reduction strategies as part of a wider social development program.
National Treatment Agency for Substance Misuse[57]	2003	United Kingdom	Grey literature	Report	Provide guidance to practitioners in drug treatment services on the role of injectable heroin and injectable methadone.	Patients unresponsive to oral maintenance treatments	Opioids	Injectable treatments should only be considered for patient unresponsive to oral maintenance treatments.
Ontario HIV Treatment Network[24]	2020	Canada	Grey literature	Report	To describe the possible benefits of offering safe supply to people who use drugs during public health emergencies like COVID-19.	PWUD in general	Multiple	Providing safe supply is a promising strategy for people resistant to other forms of treatment although more research is needed. It is important to continue and expand harm reduction services during COVID-19. Increased rates of take-home doses and benzodiazepine prescriptions should be given to ensure continuity and expansion of services.
Scottish Drugs Forum[59]	2020	Scotland	Grey literature	Guidelines	Guidelines for people providing or planning treatments for people who use drugs during the COVID-19 pandemic.	PWUD in general	Multiple	
St George's House[88]	2019	United Kingdom	Grey literature	Report	Summarize two days of discussion with experts on drug policy reform.	PWUD in general	Multiple	There was little consensus on how drug law reform should be pursued and on the pros/cons of legal regulation compared to alternative options.
Stimson[50]	2003	United Kingdom	Grey literature	Report	Describe challenges to treating heroin use and prescribing heroin in the UK.	PWUD in general	Opioids	Despite a long history of prescribing heroin in the UK there is no consensus surrounding who should be treated and the expected benefits of treatment. Clear clinical guidance is needed so eligible people who use drugs can access prescription heroin.
Strang[134]	2012	Europe	Grey literature	Report	Provide a history of supervised injectable heroin treatment for those who have failed to respond to other treatments.	People who use heroin	Opioids	Supervised injectable heroin studies consistently show improvements in health of participants receiving heroin compared to those receiving oral methadone treatment.
Strang[39]	2019	United States of America	Grey literature	Report	Describe the experiences of four countries with HAT and	PWUD in general	Opioids	HAT programs attracted community concern that it may

					drug consumption sites with regards to barriers and facilitators to implementation.			enable drug use, however these concerns diminished over time. HAT is typically highly structured which may discourage eligible participants. Jurisdictions considering HAT programs must take these pitfalls and program costs into account.
Toronto Public Health[109]	2018	Canada	Grey literature	Discussion paper	Outline a public health rationale for legalizing drugs	PWUD in general	Opioids	Decriminalization can reduce some but not all harms. Legalizing and regulating all drugs would be complicated and time is needed to determine how drugs would be produced, distributed, and sold.
Transform Drug Policy Foundation[135]	2014	United Kingdom	Grey literature	Guidelines	Provide advocates with evidence-based arguments for safe supply.	PWUD in general	Multiple	When advocating for legal regulation of drugs, identify and connect with the audience while emphasizing common ground when opinions differ.
Transform Drug Policy Foundation[136]	2016	United Kingdom	Grey literature	Briefing	Outline the benefits of providing supervised subscription heroin for long-time illicit opioid users.	Long-time illicit opioid users	Opioids	Research suggests HAT is effective. Making treatment widely available could benefit many people dependent on heroin and impact the illicit drug market.
Transform Drug Policy Foundation[86]	2016	Turkey	Grey literature	Briefing	Describe the history of regulatory changes that led to Turkey's legalization of medical opium production.	People who use opioids	Opioids	Orderly transition to a legal market is possible but does not reduce the overall global illicit production.
Transform Drug Policy Foundation[108]	2016	Switzerland	Grey literature	Briefing	Define HAT while outlining pros and cons of treatment.	Patients with opioid dependence	Opioids	Research shows HAT has many benefits and there is little evidence to support theorized downsides to HAT including increased drug use.
Transform Drug Policy Foundation[72]	2019	United Kingdom	Grey literature	Briefing	Recommendations for alternative funding strategies for HAT.	People who use opioids	Multiple	HAT should receive increased funding from Proceeds of Crime Act (POCA) and be backed by senior police officers.
Vancouver Coastal Health[107]	2020	Canada	Grey literature	Guideline	To describe guidelines put in place to help people who use drugs going through withdrawal symptoms during COVID-19.	PWUD who need assistance managing withdrawal symptoms	Multiple	Pharmacists are instructed to follow updated guidelines to support people going through withdrawal during COVID-19 pandemic

Table 1c. Search of heroin-assisted treatment studies (n=99).

First Author	Year	Location	Search source	Study design	Objective	Population	Type of drug used	Conclusions
Bald[137]	2013	Germany	Academic journal	Observational	Determine whether patients with conventional opioid maintenance treatment would prefer a switch to heroin maintenance treatment.	Opioid maintenance program participants	Opioids	People addicted to opioids who have been previously unresponsive to treatment would switch to HAT but most people prefer continuing conventional maintenance therapy.
Blanken[138]	2005	Netherlands	Academic journal	Experimental	Investigate which baseline patient characteristics of treatment-resistant heroin addicts differentially predicted treatment response to medical heroin prescription compared to standard MMT.	People with heroin dependence	Opioids	HAT is most effective for patients who have previously underwent abstinence-oriented treatment.
Blanken[139]	2010	Netherlands	Academic journal	Observational	Describe the four-year treatment retention and treatment response among chronic, treatment-resistant heroin-dependent patients offered long-term HAT.	People with heroin dependence	Opioids	HAT is an effective long-term treatment for chronic heroin users who have not benefited for MMT. Treatment should be continued until there is a compelling reason to stop treatment.
Blanken[140]	2012	Netherlands	Academic journal	Experimental	Investigate HAT vs MMT, and heroin craving and illicit heroin use, their mutual association, and their association with multi-domain treatment response among patients.	People who use heroin	Opioids	HAT reduced heroin cravings and illicit use more than MMT.
Blanken[141]	2016	Netherlands	Academic journal	Experimental	Explore the efficacy of contingency management, targeting cocaine use, as an add-on treatment for those in a supervised HAT program with frequent cocaine use.	HAT patients who frequently use cocaine	Multiple	Contingency management does effectively reduce cocaine use for those in a supervised HAT program.
Blanken[142]	2020	Netherlands	Academic journal	Experimental	Assesses whether SR-dexamphetamine treatment also improves the health status of cocaine-dependent HAT participants.	Cocaine-dependent HAT participants	Multiple	Sustained-release dexamphetamine reduces cocaine use and may improve relevant health outcomes for heroin maintained patients with co-morbid cocaine dependence.
Blum[143]	2013	Switzerland	Academic journal	Experimental	Examine the acute effects of heroin on emotions in heroin- dependent patients.	People with heroin dependence	Opioids	Heroin administration dampens cravings and negative emotions. Findings

								underscore the important of OST and HAT for heroin-dependent patients.
Bond[144]	2012	Australia	Academic journal	Qualitative	Understand if slow-release oral morphine is an acceptable maintenance medication in heroin users currently being prescribed injectable DAM, who are intolerant to supplementary methadone.	Chronic heroin users	Opioids	SROM is an acceptable alternative for patients intolerant to methadone maintenance therapy.
Boyd[49]	2013	Canada	Academic journal	Qualitative	Highlights the experiences of NAOMI Patients Association members in the NAOMI research trial.	Chronic injection opioid users	Opioids	NAOMI had both positive and negative impacts on the lives of participants. Former participants advocate for the end of drug prohibition.
Boyd[48]	2017	Canada	Academic journal	Qualitative	Explores experiences of the SALOME/ NAOMI Association of Patients (SNAP) regarding HAT and need to regulate currently criminalized drugs.	SNAP members	Opioids	HAT benefits former HAT trial participants and the SNAP advocacy group argues that permanent HAT programs should be established to reduce harms.
Brar[96]	2019	Canada	Academic journal	Observational	Describes case study of patient with opioid-use disorder who was prescribed iOAT in a supportive housing setting.	Patient with opioid-use disorder	Opioids	Supportive housing environments could be used to provide iOAT for PWUD that are disengaged from the medical system.
Broers[145]	2014	Switzerland	Academic journal	Observational	Understand whether daily administration of DAM in a maintenance program will have a negative impact on immunological parameters of the patients.	People who use drugs	Opioids	There is no evidence that DAM maintenance treatment negatively affects the immunity status of PWUD.
Colledge[146]	2017	Switzerland	Academic journal	Experimental	Assess the feasibility, acceptance, and effects of an exercise intervention for individuals receiving outpatient HAT.	People with opioid-dependence	Opioids	An exercise intervention is a feasible and acceptable to people receiving HAT.
Colom Farran[103]	2012	Spain	Academic journal	Experimental	Evaluate the feasibility of conducting double-blind controlled randomized clinical trials using twice-a-day immediate-release oral DAM in heroin-dependent patients.	People with heroin dependence	Opioids	Phase II trials of immediate-release oral DAM are feasible allowing for further phase III trials.
Cruz[147]	2007	Canada	Academic journal	Observational	Document the public opinion towards drug interventions in the Ontario general population, as well as to examine to which extent select socio-demographic, drug use and other attitudinal factor in the population	Ontario general population	Opioids	Understanding the Canadian public's opinion is crucial for the feasibility and sustainability of HAT and safe injection facilities.

					influence opinions towards these issues.			
Dammann[148]	2017	Switzerland	Academic journal	Observational	Compare psychopathological symptoms of opioid-dependent patients receiving HAT, with and without a comorbid personality disorder.	People with opioid-dependence	Opioids	People with OUD and co-occurring personality disorder may represent a more severely ill subgroup which could benefit from treatment for their personality disorder symptoms.
Demaret[35]	2012	Belgium	Academic journal	Qualitative	Report concerns of nursing staff at HAT centres regarding the administration of heroin.	HAT centre staff	Opioids	HAT staff are most concerned about patient overdosing and/or smuggling DAM doses.
Demaret[149]	2014	Belgium	Academic journal	Qualitative	Explore the reasons why heroin users did not want to participate in a research trial.	TADAM trial non-participants	Opioids	The limited length of a HAT trial may have demotivated heroin users from participating despite the possible treatment benefit.
Demaret[84]	2015	Belgium	Academic journal	Experimental	Assess the efficacy of HAT in a controlled and supervised setting compared to a liberal system of MMT.	People who use illicit heroin	Opioids	The study provides support for the short-term efficacy of HAT for methadone-treatment resistant patients.
Demaret[150]	2016	Belgium	Academic journal	Secondary analysis	Evaluate whether the benefits of a HAT trial were sustained three months after the trial.	People who use heroin	Opioids	Forced end of HAT was followed by a significant increase in the use street drugs.
Dursteler-MacFarland[44]	2006	Ireland	Academic journal	Observational	Outline prevalence rates of side effects experienced by DAM patients.	People with opioid-dependence	Opioids	People prescribed DAM report a number of minor and more threatening symptoms that need to be further explored to improve HAT safety.
Dursteler-MacFarland[151]	2010	United States of America	Academic journal	Observational	Compare symptom complaints of MMT patients to those prescribed injectable heroin.	People who use opioids	Opioids	Patient-reported MMT and injectable heroin treatment side-effects did not differ considerably, both treatment appear equally tolerable.
Dursteler-MacFarland[152]	2013	Switzerland	Academic journal	Experimental	Evaluate the feasibility, tolerability, and efficacy of methylphenidate and cognitive-behavioral group therapy for cocaine dependence in patients	Cocaine-dependent heroin-maintained patients	Multiple	Methylphenidate and cognitive-behavioral group therapy did not significantly reduce cocaine use when compare to usual treatment.

					receiving DAM maintenance for heroin dependence.			
Eiroa-Orosa[67]	2010	Germany	Academic journal	Experimental	Evaluate prevalence and correlates of BZD, patterns of BZD prescription for patients in a German heroin trial comparing HAT and MMT in opioid dependent patients	People with heroin dependence	Opioids	BZD use correlated with poorer treatment retention and outcomes. Cautious BZD prescribing may be beneficial and reduce overall illicit use.
Eiroa-Orosa[45]	2010	Germany	Academic journal	Experimental	Analyze gender-related outcome differences in the German trial on HAT.	People with opioid-dependence	Opioids	Significant baseline and outcome differences exist for males and females undergoing HAT which should be considered when treatment effects/
Fairbairn[69]	2019	Canada	Academic journal	Guidelines/recommendations	Provide recommendations focused on defining the patient population that should be considered for iOAT and outline considerations for medication selection and length of treatment.	People who use drugs	Opioids	Injectable OAT should be considered for people with severe treatment resistant OUD, These people should be offered open-ended DAM or hydromorphone treatment.
Frick[27]	2006	Switzerland	Academic journal	Observational	Assess the efficacy and safety of orally administered DAM tablets in substitution treatment of severely addicted opioid users.	People with opioid-dependence	Opioids	DAM tablets may be an effective safe form of HAT but RCTs are need to compare it to other treatments.
Frick[153]	2010	Switzerland	Academic journal	Observational	Assess long-term feasibility and safety of DAM tables for people with severe opioid addictions.	Chronic heroin users	Opioids	DAM tablets are a feasible and safe long-term treatment alternative to injected DAM.
Gartry[65]	2009	Canada	Academic journal	Observational	Summarize the challenges of implementing the NAOMI HAT trial in North America.	People with opioid-dependence	Opioids	NAOMI was a challenging study to conduct but was worth doing to explore HAT in a Canadian context and help pave the way towards making HAT approved in Canada.
Groshkova[33]	2013	United Kingdom	Academic journal	Experimental	Examines expectations and satisfaction of treatment-refractory heroin-dependent patients attending UK's first supervised injectable clinics.	Chronic heroin users	Opioids	Patients consistently reported treatment satisfaction and made suggestions for treatment improvement. This highlights the challenge of incorporating patient

								opinion into shaping treatment.
Gschwend[60]	2004	Switzerland	Academic journal	Observational	Analyzes the course of dose levels during the treatment period of opioid addicts in the PROVE trial.	People with opioid-dependence	Opioids	The role of heroin dosages in HAT should be further explored as doses vary between treatment regimes.
Guttinger[154]	2003	Switzerland	Academic journal	Observational	Compare risk behavior and social situations of participants in HAT programs versus clients who have terminated treatment.	People with opioid-dependence	Opioids	HAT effectively lowers the use of illegal drugs, illegal income, and generally improves social conditions in the long-term even after treatment ends.
Haasen[70]	2007	Germany	Academic journal	Experimental	Describe the effect of HAT for people receiving MMT or not receiving treatment.	People with heroin dependence	Opioids	Despite being higher risk, HAT is more effective treatment than MMT for people with opioid dependence using intravenous heroin.
Haasen[155]	2009	Germany	Academic journal	Secondary analysis	Describe effect of HAT and MMT on alcohol use among opioid-dependent patients.	People with heroin dependence	Opioids	HAT significantly reduced alcohol consumption and Addiction Severity Index composite scores in opioid-dependent patients.
Haasen[156]	2010	Germany	Academic journal	Secondary analysis	Assess the effects of DAM on opioid-dependent patients with no previous maintenance treatment experience.	Chronic heroin users	Opioids	DAM could be considered as a treatment option for severely opioid-dependent patients regardless of previous treatment experiences.
Hartwig[157]	2008	Switzerland	Academic journal	Observational	Describe heroin-maintained pregnancy and birth during HAT.	Chronic multi-substance user	Opioids	HAT may be a safe harm reduction measure for pregnant women who use drugs that are not responding to MMT.
Jozaghi[106]	2014	United States of America	Academic journal	Qualitative	Investigates the role of HAT in transforming the lives of injection drug users in Vancouver, Canada.	People with opioid-dependence	Opioids	HAT improved the personal lives of its participants and there is evidence the HAT program should continue and become permanent.
Jun[81]	2018	Canada	Academic journal	Observational	Present a case study of a PWUD who completed a drug treatment court program and iOAT.	Person with history of illicit opioid use	Multiple	Drug treatment courts in conjunction with iOAT may be an effective treatment modality for those with severe opioid use disorder.

Karow[158]	2010	Ireland	Academic journal	Secondary analysis	Longitudinally investigate health-related quality of life in patients with severe opioid dependence.	People who use drugs	Opioids	Heroin maintenance treatment may improve health-related quality of life more than MMT by improving physical health.
Kilmer[159]	2019	Ireland	Academic journal	Observational	Provides the first nationally representative US data concerning public support for prescribing DAM to dependent users.	USA general population	Opioids	Support for prescribing heroin in the US is low although referring to it as diamorphine may reduce stigma and increase support.
Klimas[160]	2018	England	Academic journal	Secondary analysis	Investigate the possible contribution of HAT to HIV treatment-related outcomes	People living with HIV who use illicit drugs	Opioids	HAT access should be scaled up to include eligible people living with HIV.
Lasnier[161]	2010	Netherlands	Academic journal	Secondary analysis	Evaluates whether the NAOMI heroin prescription trial impacted the occurrence of crime and disorder.	People who use drugs	Opioids	There was no evidence of increased or decreased community-based crime or disorder associated with HAT programs in Canada.
Lobmann[63]	2009	United States of America	Academic journal	Experimental	Examines association between HAT and criminal activity.	People who use heroin	Opioids	HAT reduces illegal drug use which in turn decreases drug-related acquisitive crime.
March[162]	2006	Spain	Academic journal	Experimental	Assess the efficacy of the prescription of intravenous DAM versus oral methadone with medical and psychosocial support.	People with opioid-dependence	Opioids	DAM can be safely provided and is more efficacious in improving outcomes compared to methadone alone.
Marchand[34]	2011	Canada	Academic journal	Secondary analysis	Determine participants' satisfaction with iOAT and test if satisfaction scores vary according to patients' characteristics, the treatment modality received, and treatment outcomes.	People with opioid-dependence	Opioids	Satisfaction is high among those receiving iOAT. Treatment satisfaction measurements can help identify patients within increased or additional needs.
Marchand[92]	2020	Canada	Academic journal	Qualitative	Explore participants' iOAT experiences as they broadly relate to the domains of patient-centered care	People with opioid-dependence	Opioids	Strong patient-provider relationships are fundamental to patient-centered care experienced for people receiving iOAT.
McAdam[47]	2020	Canada	Academic journal	Observational	Present case study of patient with opioid use disorder who uses illicitly manufactured fentanyl after being admitted to hospital.	Person with severe, active opioid use disorder	Opioids	Offering iOAT in the inpatient setting may help retain persons with OUD and improve medical outcomes.

Metrebian[51]	2002	United Kingdom	Academic journal	Observational	Describe the heroin prescribing patterns of UK physicians for people with opiate dependence.	Doctors in the UK with a license to prescribe heroin	Opioids	DAM prescription for PWUD is rare in the UK. There is no consensus on who to treatment with DAM nor how to treat them.
Metrebian[163]	2006	United Kingdom	Academic journal	Observational	Describes the characteristics of patients receiving a DAM prescription in the United Kingdom.	People with opioid-dependence	Opioids	Patients have been prescribed DAM to reduce long-term harms. Prospective studies are needed to determine long-term effects.
Metrebian[164]	2014	England	Academic journal	Experimental	Examine secondary outcomes of the RIOTT trial that compared supervised injectable heroin and supervised injectable methadone with optimized oral methadone.	People with opioid-dependence	Multiple	Supervised injectable heroin and supervised injectable methadone treatment had no clear benefit over oral methadone in terms of drug use, crime, or mental health over a 6-month period.
Mitchell[165]	2006	Switzerland	Academic journal	Experimental	Explore the feasibility and acceptability of intranasal DAM maintenance.	People with opioid-dependence	Opioids	Intranasal DAM administration may be an acceptable alternative method of treatment that warrants further investigation.
Mustaq[66]	2011	United Kingdom	Academic journal	Experimental	Assess the public opinion regarding prescribing heroin to people with opioid addictions.	UK general population	Opioids	The majority of the general public opposed prescription DAM even to reduce crime.
Neale[166]	2015	England	Academic journal	Qualitative	Evaluate a novel contingency management (CM)-related intervention for people experiencing complex drug problems.	People with opioid-dependence	Opioids	The evaluation of the contingency management intervention suggests that programs need stakeholder-informed, patient-centered care models that make patients and staff feel safe.
Nikoo[98]	2018	Canada	Academic journal	Experimental	Explore employment outcomes among individuals with opioid dependence in treatment with DAM or hydromorphone.	People with opioid-dependence	Opioids	Rates of employment among HAT patients were lower than other similar studies. Employment and occupational therapy support should be offered to optimize employment outcomes.

Nosyk[167]	2010	Ireland	Academic journal	Secondary analysis	Determine whether baseline motivational status was predictive of early dropout, 12-month retention, 12-month response to treatment, and time to discontinuation of treatment in the NAOMI HAT trial.	Chronic injection opioid users	Opioids	Patients were retained in the study regardless of motivation but motivated patients showed better response to treatment in terms of decreased crime and illicit drug use.
Nuijten[104]	2016	Netherlands	Academic journal	Experimental	Assess the acceptance, efficacy, and safety of a robust dose of 60 mg/day oral sustained-release dexamphetamine in chronic crack-cocaine-dependent patients with comorbid heroin dependence, currently on HAT.	HAT patients with chronic crack-cocaine dependence	Multiple	Sustained-release dexamphetamine is an acceptable, effective, and safe form of treatment for HAT patients with comorbid, refractory cocaine dependence.
Oviedo-Joekes[78]	2008	United States of America	Academic journal	Secondary analysis	Analyze the profile of the NAOMI HAT trial participant cohort in the context of illicit opioid use in Canada and to evaluate its comparability with patient profiles of European HAT studies.	Chronic injection opioid users	Opioids	The study cohort resembles those found in European HAT trials and raises concerns about crack cocaine use and social marginalization among the study population.
Oviedo-Joekes[101]	2009	Canada	Academic journal	Experimental	Compare injectable DAM with oral methadone maintenance therapy in patients with opioid dependence that was refractory to treatment.	Chronic injection opioid users	Opioids	Injectable DAM is more effective than oral methadone but should be provided in a setting with prompt medical intervention because of potential side-effects.
Oviedo-Joekes[79]	2009	England	Academic journal	Research commentary	Detail specific objectives of the NAOMI HAT trial, study design, patient population, and trial management including discussion of some of the key scientific and political issues in the design and conduct of the study	Chronic injection opioid users	Opioids	Moral beliefs and political pressure surrounding HAT influenced study design more than is typical for randomized controlled trials of non-stigmatized disorders and treatments.
Oviedo-Joekes[168]	2010	Canada	Academic journal	Secondary analysis	Evaluate HAT treatment effects for gender differences.	Chronic injection opioid users	Opioids	DAM is more effective than methadone for treatment resistant women. Women receiving DAM showed less improvements than men.
Oviedo-Joekes[100]	2010	Canada	Academic journal	Experimental	Compare the effectiveness of injectable DAM or hydromorphone with optimized MMT in the treatment of long-term opioid-dependent Aboriginal patients.	Aboriginals with long-term opioid-dependence	Opioids	HAT may be an effective way to attract and retain treatment-resistant Aboriginal people and

								reduce risk of HIV infection.
Oviedo-Joekes[64]	2010	Spain	Academic journal	Observational	Evaluate the health and drug use status of participants, 2 years after the completion of a HAT trial.	Chronic-opioid dependent people with severe drug-related health problems	Opioids	HAT patients showed better outcomes compared to those who did not receive HAT. Results strengthen evidence for the long-term effectiveness of HAT.
Oviedo-Joekes[80]	2010	United States of America	Academic journal	Secondary analysis	Test if hydromorphone and DAM differ in their safety and effectiveness for the treatment of opioid-dependence.	Chronic injection opioid users	Opioids	Hydromorphone and DAM may be similarly safe and effective opioid agonist treatments for those with chronic opioid-dependence.
Oviedo-Joekes[36]	2014	England	Academic journal	Secondary analysis	Explore outcomes of individuals that received injectable DAM and voluntarily transitioned to oral methadone.	Chronic injection opioid users	Opioids	Voluntary and patient-centered decision making is important for retention and maybe for treatment outcomes. Diversified treatment options should be available for patients and physicians to flexibly choose the best treatment.
Oviedo-Joekes[40]	2014	Canada	Academic journal	Qualitative	Explore participants' perceptions of treatments delivered during a HAT trial in order to improve our understanding of the effectiveness of treatments and the model of care.	Chronic injection opioid users	Opioids	HAT participants preferred DAM or hydromorphone over MMT and considered it effective treatment for their opioid dependence. Patient engagement will identify treatment needs and barriers.
Oviedo-Joekes[41]	2015	Canada	Academic journal	Secondary analysis	Investigate baseline and concurrent predictors of non-use of illicit heroin among participants in NAOMI HAT trial.	Chronic injection opioid users	Opioids	The benefits of iOAT extends beyond the provision of medication alone to other independent factors that predict non-use of illicit heroin.
Oviedo-Joekes[74]	2015	Canada	Academic journal	Experimental	Describe the recruitment experiences of the SALOME HAT trial and discuss the strategies that were employed	Chronic injection opioid users	Opioids	Recruitment took longer than planned although challenges were overcome due to the high number of applicants.
Oviedo-Joekes[29]	2016	Canada	Academic journal	Experimental	Test whether injectable hydromorphone is non-inferior to injectable DAM for long-term opioid dependence.	Chronic injection opioid users	Opioids	Hydromorphone may be non-inferior to DAM as a treatment for long-term opioid dependence and

								could be considered an alternative treatment if DAM treatment is not possible or unsuccessful. Opioid-related side-effects of injectable hydromorphone and DAM were mitigated when dosed and monitored by health care providers. Injectable opioid treatment should be an option for some people.
Oviedo-Joekes[102]	2017	Canada	Academic journal	Experimental	Review the safety profile of injectable hydromorphone and DAM and explore if adverse events or serious adverse events were associated with dose and patterns of attendance.	Chronic injection opioid users	Opioids	
Oviedo-Joekes[82]	2018	Australia	Academic journal	Secondary analysis	Determine the effectiveness of injectable hydromorphone and DAM for Indigenous participants in SALOME HAT trial, as well as the prevalence and frequency of crack cocaine use among subgroups of participants.	Chronic injection opioid users self-identifying as First Nations, Métis or Inuit	Opioids	DAM and hydromorphone could serve as an accessible medication for indigenous people who do not respond to first-line treatments.
Oviedo-Joekes[169]	2019	United States of America	Academic journal	Secondary analysis	Determine if treatment retention among participants receiving open-label injectable hydromorphone at a clinic differed from the period when they received double-blinded iOAT treatment in the SALOME HAT trial.	Chronic injection opioid users	Opioids	There is evidence that high retention rates observed during HAT clinical trials are maintained when participants start injectable hydromorphone.
Palis[170]	2017	Canada	Academic journal	Experimental	Determine whether gender differences in treatment response and effectiveness in an iOAT trial.	Long-term injection opioid users	Opioids	Treatment outcomes and opinions on treatment did not differ significantly between men and women. The supervised injection model is suitable for men and women.
Palis[171]	2018	Canada	Academic journal	Secondary analysis	Explores the association between nicotine dependence and physical health among participants of the SALOME HAT trial at baseline and six-months.	People with opioid-dependence	Opioids	Nicotine dependence is related to the physical health of people participating in iOAT. Therapies for nicotine dependence should be integrated into iOAT care.
Palis[172]	2020	Canada	Academic journal	Observational	Collect and report on iOAT patient ratings of physician communication, and test associations between ratings of physician communication and patient and treatment characteristics	iOAT patients	Opioids	It is critical that physician-patient interactions address comorbid physical health problems and patient medication preferences for those undergoing iOAT.

Perea-Milla[173]	2009	England	Academic journal	Secondary analysis	Analyze data from the Andalusian HAT trial by formally applying prior empirical evidence reported on the evidence of this treatment.	Long-term, socially excluded heroin injectors	Opioids	Results suggest that injectable DAM treatment is superior to oral methadone for treatment-resistant people who inject heroin.
Perneger[174]	2000	Switzerland	Academic journal	Secondary analysis	Describe opiate use over time among heroin addicts who had access to legally prescribed intravenous heroin and oral opiates.	People with heroin dependence	Opioids	The daily amount of heroin consumed tends to either remains stable or decreased over time. Few patients transition to other treatments after heroin maintenance.
Rehm[75]	2001	England	Academic journal	Observational	Ascertain the feasibility, safety, and efficacy of HAT.	People with opioid-dependence	Opioids	HAT may effective for people with chronic opioid-dependency who have not responded to other treatments.
Rehm[175]	2005	Switzerland	Academic journal	Secondary analysis	Assess mortality of participants in HAT in Switzerland from 1994-2000, and to compare this mortality to the general population and to other populations of opioid users.	People with opioid-dependence	Opioids	Mortality rates among people undergoing HAT were low compared to other opioid users and opioid users in other maintenance treatments in other countries despite participants being treatment resistant in the past.
Reimer[176]	2011	Germany	Academic journal	Experimental	Evaluate physical and mental health and compare treatment outcomes in opiate-dependent patients substituted either with heroin or methadone.	People with opioid-dependence	Opioids	HAT and MMT both have positive effects on the mental and physical health of people who inject drugs with HAT showing greater positive effects.
Ribeaud[177]	2004	Switzerland	Academic journal	Observational	Analyze the long-term development of criminal involvement of the population treated with heroin in the context of the heroin prescription trials.	People with opioid-dependence	Opioids	Overall, results indicate that heroin prescription reduces drug-related crimes and stabilizes the daily lives of PWUD.
Romo[62]	2009	Spain	Academic journal	Qualitative	Evaluate the effectiveness of intravenous heroin and orally-administered methadone prescription for long-term socially-excluded opiate addicts for whom other treatments have failed.	Long-term opioid users	Opioids	Administering heroin in a therapeutic context helped to break the habit of consuming street heroin and improved patient personal life and overall health.

Schafer[58]	2010	Switzerland	Academic journal	Secondary analysis	Assess the effects of psychiatric comorbidity on the outcome of HAT using data of the German heroin trial.	People who use heroin	Opioids	HAT outcomes were greater than MMT in both groups with and without psychiatric comorbidities.
Sell[46]	2004	United Kingdom	Academic journal	Observational	Describe the opinions and treatment experiences of patients' prescribed injectable opiate treatment.	People with opioid-dependence	Opioids	Injectable opioid treatment is the preferred treatment among people receiving treatment for heroin use in the UK. Patients consistently reported the treatment added stability to their lives.
Soyka[178]	2011	England	Academic journal	Experimental	Compare cognitive functioning in healthy controls and in opioid-dependent patients treated with buprenorphine, heroin, or methadone maintenance.	People with opioid-dependence	Opioids	There is some evidence that patients undergoing heroin maintenance therapy may be more cognitively impaired than those treated with buprenorphine or methadone, and healthy controls.
Steffen[179]	2001	Switzerland	Academic journal	Experimental	Present descriptive evaluation on health aspects of severely dependent drug users who received medically prescribed heroin in PROVE trial, including its effectiveness in preventing HIV and hepatitis infections.	People with opioid-dependence	Opioids	Street heroin and cocaine use were reduced during treatment as was risk-taking behavior.
Steffen[180]	2001	Switzerland	Academic journal	Secondary analysis	Present the prevalence and incidence of HIV and hepatitis B/C infections in the socio-medical context of HAT trial participants.	People with opioid-dependence	Opioids	Descriptive analyses showed a reduction in viral hepatitis infection risk among HAT patients due to lower risk behaviors.
Stoermer[28]	2003	United States of America	Academic journal	Experimental	Report the findings about the effects of injectable opioids in dependent patients in stable iOAT under controlled laboratory conditions.	People with opioid-dependence	Opioids	More studies are needed to optimize the IV opioid treatment to prevent serious health complicates and to evaluate the appropriateness of treatment in its current form.
Strang[181]	2006	England	Academic journal	Observational	Describe the pattern of changes in prescribing practice during the first 15 years of national drug clinic operations.	People with opioid-dependence	Opioids	Prescribing practices have changed over time with a steady decrease in prescription injectable heroin and method in favor of oral methadone.

Strang[182]	2010	England	Academic journal	Experimental	Compare effectiveness of supervised injectable treatment with medicinal heroin or supervised injectable methadone versus optimized oral methadone for chronic heroin addiction.	Chronic heroin users	Opioids	Supervised injectable heroin treatment reduces street heroin use more than supervised injectable methadone or oral methadone.
Tweed[71]	2018	England	Academic journal	Observational	Investigated the characteristics and health needs of people who inject drugs in public in Glasgow, Scotland.	People who inject drugs in public	Opioids	Injection environment and context is a key determinant of harm. Stakeholders are in favor of opening a safer injecting facility, and there are plans to establish a HAT service.
Uchtenhagen[85]	2009	Switzerland	Academic journal	Observational	Describe the intentions, process and the results of prescribing heroin to treatment resistant heroin addicts, as an example of drug policy change.	People who use drugs	Opioids	Major drug policy change occurred in Switzerland and was facilitated by the severity and magnitude of the country's heroin problem and the pragmatic attitudes toward private initiatives.
Uhlmann[83]	2015	Canada	Academic journal	Observational	Assess the willingness to participate in a randomized control trial for addiction treatment.	People who use drugs	Opioids	PWUD are willing to participate in pharmacological addiction treatment trials. It is viable for studies to recruit representative samples of this community.
Van den Brink[183]	2003	Netherlands	Academic journal	Experimental	Examined the effectiveness of medically co-prescribed heroine.	People with heroin dependence	Opioids	HAT is feasible, more effective than, and as safe as methadone alone for the treatment of physical, mental, and social problems of treatment resistant heroin users.
Verthein[184]	2008	England	Academic journal	Secondary analysis	Describe the association between two years of heroin treatment and improvements in health and social stabilization, as well as illicit drug use.	People with opioid-dependence	Multiple	HAT is associated with improved mental and physical health, and reductions in street heroin and cocaine use.
Verthein[185]	2011	England	Academic journal	Secondary analysis	Analyze patient health and drug use after switching from 12-month methadone to 12-month DAM treatment in a HAT trial.	People with heroin dependence	Opioids	Changing from optimized methadone treatment to DAM is associated with improvements in treatment-

								resistant opioid-dependent patients.
Vogel[186]	2013	England	Academic journal	Observational	Investigate prevalence, motives and patterns of BZD use and potential differences in patients maintained on oral opioid agonists or DAM.	People with opioid-dependence	Multiple	Patients maintained on different opioid agonists may have different motives for using BZDs. Treating psychiatric comorbidities may help reduce BZD use.
Vogel[187]	2019	United States of America	Academic journal	Observational	Present case report of a 35-year-old opioid-dependent woman treated with injectable pharmaceutical heroin, who was induced on buprenorphine with the "Bernese method" with the goal of blocking DAM-induced euphoria.	Person with opioid-dependence	Opioids	A combination of low doses of buprenorphine with intravenous DAM may be acceptable treatment that reduces withdrawal symptoms.
White[73]	2008	England	Academic journal	Observational	Compare injectable opiate prescribing practices with national guidelines, examine the areas of divergence, and establish complication rates for methadone and DAM.	People with opioid-dependence	Opioids	Injectable DAM had fewer complications than methadone although intramuscular injection tended to be more problematic.
Wilson[68]	2020	Canada	Academic journal	Observational	Describe case report of a 48-year-old man with severe opioid use disorder receiving iOAT.	Person with opioid-user disorder	Opioids	A primary care and pharmacy-based model for iOAT may be feasible means of expanding treatment options for people with severe OUD.

Table 2. Descriptive summary of included articles from combined searches (N= 169)

Published year	**Frequency (n, %)**
2020	35 (21)
2019	13 (8)
2018	14 (8)
2017	12 (5)
2016	9 (5)
2015	6 (4)
2014	9 (5)
2013	6 (4)
2012	6 (4)
2011	4 (2)
2010	16 (9)
2009	9 (5)
2008	6 (4)
2007	2 (1)
2006	7 (4)
2005	3 (2)
2004	3 (2)
2003	5 (3)
2002	1 (1)
2001	3 (2)
2000	1 (1)
Geographic location	
Australia	5 (3)
Belgium	4 (2)
Canada	43 (25)
China	2 (1)
Copenhagen	1 (0.6)
Czech Republic	1 (0.6)
Germany	7 (4)
India	2 (1)
Ireland	4 (2)
Italy	1 (0.6)
Mexico	1 (0.6)
Netherlands	8 (5)
New Zealand	2 (1)
Scotland	1 (0.6)
Spain	4 (2)
Switzerland	21 (12)
Turkey	1 (0.6)
United Kingdom	28 (17)
United States of America	27 (16)
Other*	5 (3)

Literature source	
Academic	135 (79)
Grey	36 (21)
Study design	
Case study	9 (5)
Case crossover	1 (0.6)
Cohort study	16 (10)
Commentary, Letters to Editors, Field Notes, Editorials	21 (12)
Cross-sectional	9 (5)
Postal survey	1 (0.6)
Guidelines	10 (6)
Health needs assessment	1 (0.6)
Mixed methods	1 (0.6)
Policy brief	8 (5)
Qualitative	24 (14)
Randomized control trial	28 (17)
Reports**	15 (9)
Secondary analysis	24 (14)
Drugs addressed	
Buprenorphine and/or methadone	10 (6)
Opioids in general***	109 (65)
Multiple****	8 (5)
Not specified or unclear	41 (2)

*Includes studies focused on Italy, North America in general, and one unspecified location.
**Non peer-reviewed reports from the grey literature created by groups advocating for PWUD like the Drug Policy Alliance and CAPUD.
***Opioids were addressed in general without reference to any particular drug.
****Discussion was focused on drugs as a whole on multiple drugs not limited only to opioids

Table 3. Barriers and facilitators to safe supply in pandemics or other public health emergencies.

Barrier theme	**Barrier sub-theme**	**All studies (N= 119) n (%)**	**Academic literature n**	**Grey literature n**
User-level	Personal-health barriers among PWUD	5 (5)	4	1
	Distrust towards institutions	1 (1)	1	0
	Practical barriers	15 (13)	14	1
	Lack of drug trials or programs reflective of prospective uses and preferences of PWUD	10 (8)	8	2
Prescriber-level	Lack of clinical guidance for/consensus among prescribers	6 (5)	3	3
	Limited prescribing power or prescribers	10 (8)	5	5
Program-level	Programmatic, administrative or logistical difficulties	12 (10)	12	0
	Prohibitive system-level costs	17 (14)	13	4
	Limited safe supply program capacity	3 (3)	2	1
	Lack of effective pharmacological approaches in the treatment of concurrent cocaine addiction	1 (1)	1	0
	Ignoring social and cultural aspects of drug use	2 (2)	2	0
	Small population	1 (1)	0	1
	Lack of evidence	3 (3)	0	3
Society-level	Profit-driven and/or monopolistic industry practices	1 (1)	0	1
	Discrimination because of stigma of using drugs	8 (7)	7	1
Policy-level	Combined political opposition and/or political will, or lack of governance and/or enforcement	5 (5)	2	3
	Restrictive laws or policies	33 (28)	20	13
Facilitator theme	**Facilitator sub-theme**			
User-level	Health insurance	1 (1)	0	1
	Transportation	3 (3)	3	0
Prescriber-level	Availability of medical prescribers	1 (1)	0	1

Program-level	Improving access	5 (5)	2	3
	Supervised dispensing models	7 (6)	6	1
	Less controlled dispensing model	4 (3)	1	3
	Take-home dosing	9 (8)	5	4
	Understanding needs and desires of PWUD	9 (8)	4	5
	Reducing stigma or supportive facility environment	6 (5)	5	1
	Concurrent provision of other therapeutic services	1 (1)	1	0
	Infrastructure or human resources to support safe supply/HAT	2 (2)	2	0
Society-level	Stakeholder engagement or community support	10 (8)	6	4
	Clear communication	13 (11)	8	5
	Advocacy	2 (2)	2	0
Policy-level	Policy reform	10 (8)	2	8
	Strong governance	3 (3)	1	2
	Temporary legal/regulatory exemptions	16 (13)	9	7
	Continued accumulation and dissemination of evidence	1 (1)	1	0

B= barriers; F= facilitators; PWUD= People who use drugs

Table 4. Type and frequency of practical barriers

Studies	Practical barriers
11,15,30	Transportation: Disruptions to public transportation services, lack of affordable options, or difficulty accessing due to physical disabilities
10,16,31-33,35-38	Healthcare: Lack of privacy during telemedicine meetings, lack of funding to afford telemedicine services, extensive wait times, uncomfortable facility conditions, clinic closures due to structural damage, demanding frequency of centre visits, incompatible centre hours with conflicting work priorities, lack of available choices to meet preferred drug consumption method, time constraints to use services, public health restrictions regarding in-person visits
15,40	Law enforcement: Harassment from authorities when travelling to treatment centers
41	Social and economic: Unstable housing and/or lack of secure income to access services such as telemedicine

Table 5. Barriers to barriers to safe supply from PWUD-Adcomm consultations

Barrier theme	**Sample quotations from qualitative studies** (where present)
Stigma, discrimination and racism from healthcare providers	"[…] as soon as [providers] hear I'm on methadone it's like this brick wall goes up. And it becomes a barrier to maybe getting treatment as quickly, or even being treated as a normal person, like you're just put in this whole other category."[27] "When you go to the ED (Emergency Department), they tend to be really sceptical … of methadone patients. Like … you're faking your gallbladder playing up to get some more drugs or something like that when you know there's clearly legitimate issues going on which can be verified with scans or tests."[110]
Over-medicalized safe supply models	"For a long time, I thought that changing the focus away from criminal sanctions to having things managed by health professionals was an answer, but I am strongly disagreeing with that these days, too, because having your life managed by a judiciary, or having your life managed by health professionals, can be just as bad. They can be just as fucking evil with people and play these power trips."[77] "[...]you're getting people making decisions about you, and in making these, sort of, in loco parentis attitude that – as medical people do. You know, all health professionals do: '[Providers] will look after them. Those poor druggies, they can't make these decisions themselves.' So, that's why I say, yes, we want to get paid and be involved, because it's us that the decisions are being made about."[77]
Lack of access to desired substances	"We have a huge part of the drug using population who only smoke crack, meth, or other amphetamines . . . If you want to provide comprehensive services to drug users in Ottawa, you need to provide service to crack smokers."[54] "A lot of people— technically—we need to be turning away if they want to come in and snort fentanyl or cocaine. And that is frustrating."[54]
Child apprehension	Not discussed in peer-reviewed literature.
Lack of cultural competency	Not discussed in peer-reviewed literature.