

Chapter 7

The Need for Structural Interventions for Persons Who Misuse Opioids



Claudia Rafful and Carlos Magis-Rodríguez

Abstract This chapter analyzes structural approaches that emerged as a community and later as evidence-based and policy strategies to improve the health and well-being of persons who use drugs (PWUDs) in general and opioids (PWUOs) in particular.

The first section introduces social determinants of health, structural violence, and structural vulnerability concepts that have served as frameworks for social epidemiologists, medical anthropologists, sociologists, and behavioral researchers to understand and intervene in contexts that harm PWUDs. The second section reviews structural interventions that positively impact PWUDs, including involvement of peers to address substance use and infectious disease risk behaviors, housing and economic assistance programs, medication-assisted treatments, and syringe exchange programs. This chapter also includes unintended consequences, concerns, and considerations when implementing each intervention in different settings.

Keywords Structural violence · Social determinants of health · Persons who use opioids

C. Rafful (✉)

Faculty of Psychology, National Autonomous University of Mexico (UNAM), Mexico City, Mexico

Opioids Working Group, Global Studies Seminar, Faculty of Medicine, UNAM, Mexico City, Mexico

Center for Global Mental Health Research, National Institute of Psychiatry Ramón de la Fuente, Mexico City, Mexico

e-mail: crafful@comunidad.unam.mx

C. Magis-Rodríguez

Opioids Working Group, Global Studies Seminar, Faculty of Medicine, UNAM, Mexico City, Mexico

Faculty of Medicine, UNAM, Mexico City, Mexico

7.1 Overview

Conceptualization of opioid and other substance use disorders (SUD) as chronic brain diseases [1] instead of a moral fault has helped reduce stigma and promote a less judgmental approach to people seeking treatment. While valuable and evidence-based, this biomedical paradigm can be reductionist. Behavioral interventions, mainly cognitive-behavioral therapy approaches, have helped motivate and sustain behavioral changes essential to decrease and cease drug-seeking behaviors.

Priority setting in science – through funding allocation – has allowed significant advances in psychopharmacology and neuroscience, but the importance of the social context can sometimes be left behind. For instance, clinicians and neuroscientists have developed opioid-assisted treatments (OAT) using opiate agonists (methadone or buprenorphine), opioid antagonists (naloxone or naltrexone), and long-delivery opioids that, in theory, would disincentivize persons to use opioids in different quantities or through routes of administration other than those prescribed initially. However, there are social determinants that hinder access to these treatments.

In the past 40 years, two epidemics have shaken the concept of health, health promotion, and interventions. First, the HIV epidemic rapidly evidenced health disparities across countries and socioeconomic status, adding layers of complexity and intersectionality of social risk factors that decrease the odds of health and well-being for those living in poverty, gender minorities, racialized communities, and persons who use drugs (PWUDs). Second, the current epidemic of opioid-related deaths started with the unethical prescription of opioids for chronic pain and later shifted to street opioids, including fentanyl. The inadequate and late response of health systems to the opioid epidemic also exposed health disparities that non-governmental organizations (NGOs) and affected communities have effectively addressed but that need to be supported by structural interventions to have long-lasting effects. The evidence of the structural determinants of the opioid crisis is now so overwhelming that Dr. Nora Volkow, the director of the National Institute on Drug Abuse (NIDA), has recently acknowledged the crucial role of social pain in the opioid crisis [2]. In her commentary, Dr. Volkow expressed the importance of isolation, despair, economic inequities, social exclusion, rejection, and stigma (more severely suffered by racialized populations) as risk factors for opioid use disorders.

Another institutional shift toward a more comprehensive approach to SUD is the recently approved funding for the most significant implementation science in the history of SUD in the United States. This approach includes structural factors such as changes in opioid prescription practices, increased availability of drug treatment programs, naloxone to counteract opioid overdoses, and improved linkage to care [3]. Although these structural components may help reduce opioid-related deaths, they are still insufficient to truly change the structures that account for the despair context in which the opioid overdose has taken place.

There was a significant shift in the public acknowledgment of the crucial role of structural interventions for opioid use in the past decade. In particular, health and public institutions that historically supported abstinence-only treatments changed to a more “real-life” paradigm, mainly harm reduction [4] and medication-assisted programs.

7.2 Conceptual Frameworks

Theoretical and conceptual frameworks help understand the conditions in which people have misused opioids. With such understanding, it is possible to improve the quality of life – and not only promote drug abstinence – of persons who use opioids.

From a structural perspective, health is a product of social structures and processes, which may be affected by political, legal, and cultural contexts. As such, health outcomes depend less on individual behaviors and more on social processes and structural vulnerabilities [5]. The benefit of using structural frameworks in health research is that adequate interventions and policy reforms can modify structural factors that aim to reduce vulnerability and create healthier environments [6].

The intersection of social disadvantage, isolation, and pain cannot be addressed only through primary care [7] or pure biomedical approaches. Poverty and substance use problems act in synergy, reinforcing mental health problems and unstable housing and employment [7]. Structural variables can predict area-level vulnerability to opioid misuse, overdose, and the syndemic (synergistic epidemic) of opioid use and infectious diseases such as human immunodeficiency virus (HIV) and hepatitis C virus (HCV) [6]. In the following paragraphs, we explain key theoretical concepts.

7.2.1 *Social Determinants of Health*

Social determinants of health are structural forces that affect health outcomes from personal to global levels, including socioeconomic status, inequality, institutional policies, global trade agreements, and political forces [2, 8]. Structural determinants of health are architectural, economic, and political frameworks that create barriers to improving health or perpetuating social inequities. The structural determinant framework helps explain the opioid crisis and may also guide the policy and structural changes needed to improve community health [7].

Social and structural determinants of opioid misuse include stigma, racism, discrimination, heterosexualism, family structure, socioeconomic status, community engagement, and social support systems [9]. In addition, some opioid users are aging population with pain and disabled, under economic distress, that lack social cohesion and can have comorbid psychiatric disorders [7]. For these reasons, to improve public health approaches to the opioid epidemic, it is necessary to address

the social determinants of health with person-centered approaches, implementation science, and improving care systems [10]. Additionally, structural changes within the policy agenda must include universal healthcare, education, and social services.

7.2.2 Structural Violence

Structural violence is the social arrangement that may harm persons and populations and is embedded in the global socioeconomic organization [11]. Specifically, the current opioid crisis in the United States and Canada was detonated by over-prescription within the context of economic and social distress, especially among persons suffering physical and psychological trauma, inequality, isolation, and hopelessness [7]. Opioid fatal overdoses have also been considered deaths of despair [12, 13]. This concept refers to poverty, income inequality, unemployment related to deteriorating labor markets, reduced social capital, and high social isolation as the root causes for some deaths from opioid overdose [9]. In deprived communities, manufacturing and service jobs dominated the job market. Most of these works entail physical hazards and potential injuries that may lead to chronic pain conditions resulting in disability, poverty, and a perfect set for the quest for prescription and self-medication [7, 14].

7.2.3 Structural Vulnerability

Structural vulnerability refers to suffering-constrained individuals based on their social position within the hierarchical social structures [11]. It encompasses society's multiple overlapping and mutually enforcing power hierarchies, including institutional and policy-level status that may limit a person's ability to access healthcare and engage in healthy lifestyles [8]. As social determinants of health, structural vulnerabilities also highlight how the individuals' agency is constrained within socioeconomic and political processes such as income, housing, discrimination, and experiences of colonization [8, 15]. Quantitative assessment of structural vulnerabilities includes financial security, residence, risk environment, food access, social network, legal status, education, and discrimination [8].

This concept has helped understand the intersectionality of overlapping and inter-related vulnerabilities that put specific PWUDs at a higher risk of police brutality in more comprehensive social and economic hierarchies [16]. Other findings are the interactions between poor housing, neighborhood conditions, and scarce treatment alternatives, which may disrupt behaviors leading to opioid use disorders [17, 18]. Structural vulnerabilities related to barriers to prevent overdosing include lack of overdose prevention sites, potential eviction, and criminalization of drug use [15]. A significant barrier is the fragmentation of care, lack of behavioral health

services within primary care settings, and lack of wraparound services for people who use opioids [18].

7.3 Structural Interventions

Structural interventions involve policy and law reforms, changes in administrative procedures, advocacy, and community organization, among others [19]. Public health interventions should ensure full participation of PWUDs in overdose prevention programs, developing and implementing all the structural changes to respond to the overdose crisis worldwide [15]. Implementing structural interventions at local, municipal, regional, and national levels impacts individual behaviors [19].

7.3.1 *Peer Involvement*

Involving peers and persons with lived experience to address substance use and infectious disease risk behaviors is extensively recommended, especially in under-resourced (including human resources) settings [20]. Efforts that do not include persons with lived experience in the design and implementation usually encounter difficulties that “real-life” experts can prevent. These experts play a fundamental role in overdose prevention, which tends to be overshadowed by public health partners [21], harm reduction activists, and academic partners.

A systematic review of low- and middle-income countries found substance use interventions that included peers in Ukraine, Russia, Vietnam, Thailand, Senegal, China, Malaysia, Georgia, South Africa, Iran, Kenya, India, Puerto Rico, and Zimbabwe [20]. However, most of the data of peers in substance use and, specifically, in opioid use interventions are from high-income countries: mainly Canada, Europe, and the United States.

The Vancouver Area Network of Drug Users (VANDU) and Downtown Eastside SRO Collaborative in British Columbia [22] is an example that deserves proper consideration. VANDU began in the 1990s as a community response to the opioid and HIV syndemic. Since its establishment, VANDU has led interventions and worked with other local and international activists, academia, and public officers. In addition, VANDU has played a fundamental role in all the structural interventions in Vancouver East Side (syringe exchange programs, safe consumption sites – in all the available versions – and civic actions) [21]. VANDU has also been vocal and is one of the main stakeholders and presenters in improving the health and well-being of PWUDs.

While the participation of persons with lived experience is of great benefit, there are some criticisms regarding the burden that implies the task-shifting in healthcare. The balance between community participation and task-shifting is still a challenge. In the current opioid crisis, most of the response has been provided by peers that

have intensely worked in naloxone distribution and overdose prevention training of other PWUDs. Some unintended consequences for PWUDs can be fear of arrest and physical and mental health comorbidity [21]. Persons with lived experience that work in harm reduction services still belong to one of the most marginalized groups in any setting. There is a risk of perpetuating oppression by considering its role as volunteering, low-paid jobs, and no acknowledgment when working with persons with a higher educational level and more overall social capital.

7.3.2 Housing Programs and Income Assistance

Providing access to stable and dignified housing and income assistance are critical structural interventions. Housing interventions reduce overdose deaths [23] and are especially important for PWUDs and those who have comorbid mental health conditions, marginalized youth, women, and people recently released from prison [24–26]. Housing is such a complex problem that it goes beyond ensuring stable housing and considering the needs of the tenants. There must be a balance between basic public regulations and realistic regulations that may benefit persons. That is, regulations usually prohibit drug use on premises. However, in addition to being unrealistic, compliance with these regulations may put persons at greater risk if they use drugs in public venues or other unfamiliar locations. As a basic need, housing should be stable before drug treatment or any other intervention. It is not possible to require persons' drug abstinence when they lack stable housing.

Housing programs often include PWUDs as tenants, who are usually threatened with eviction if found using drugs on the premises. Eviction [27] and even changes in unstable housing arrangements [2] correlate with increased risk of HIV, overdose, spatial patterns of drug use changes, shifts in substance use, financial hardship, and changes in drug supply.

Structural interventions that ensure income security and employment may also reduce overdose deaths [23], especially among people with mental health disorders and recently imprisoned [24]. Cash transfer programs have been implemented among vulnerable populations, including PWUDs. However, a randomized clinical trial has found that payment days are associated with increased substance use and related harms, including overdose [28]. Innovative interventions have tested desynchronized monthly and biweekly payments, and, although they showed decreased odds of increased drug use, they also found an increase in exposure to violence [29].

7.3.3 Access to Essential Services

Many healthcare systems have inadequately responded to the international opioid crisis, with a slow response to excessive opioid prescription and pharmaceutical marketing of opioids, and a lack of timely treatment response. As such, healthcare systems have acted as structural determinants of the opioid crisis [18].

In general, healthcare services have been unwilling to identify appropriate intervention points and care delivery strategies [18]. The response to the prescription opioid crisis was inadequate because of punitive and controlling measures for patients and providers. Patients can be suspected of pretending pain to get opioids, and providers are burdened with institutional and insurance paperwork and constant prescription monitoring. This situation has also affected racialized populations that have restricted access to pain medication and promotes mistrust between patients and providers [7].

7.3.4 Syringe Exchange Programs (SEP)

SEP, also known as needle/syringe exchange programs, provide users with sterile syringes and injection equipment to reduce transmission of blood-borne diseases. These programs were implemented in the 1980s as a community intervention to prevent HIV and HCV transmission [30–32].

To date, SEP is one of the structural interventions most used by people who inject drugs due to its efficacy to prevent PWUDs' morbidity and mortality. Implementation and coverage of this intervention are the results of decades of work. According to the 2020 Harm Reduction Report [30], by 2020, 86 countries had at least 1 SEP. However, the same report also stressed the concern for the lack of funding and political willingness dependence that most organizations that run SEP face.

One of the most common barriers to open a SEP has been the “Not in my backyard” community opposition [33]. Communities usually show resistance toward having a business (for or non-profit) that serves PWUDs for fear of increases in crime rates, adverse consequences for social cohesion, bad prestige for the zone, and the concern for what children may see in public venues. However, evidence shows that there has not been an increase in delinquency or any other negative consequence in the neighborhoods where SEP or any other harm reduction service has opened [34]. Moreover, harm reduction services that include SEP open in areas where PWUDs are already located. Therefore, neighbors' concern is baseless, considering that the stigmatized population is already in that location.

7.3.5 Safe Consumption Services (SCS)

SCS are centers where drug consumption is allowed. SCS aim to reduce the risk of infection transmission and prevent paraphernalia sharing and inadequate injection patterns (e.g., neck injections). They also intend to prevent overdose deaths and refer drug users to health and social services if needed or requested [35, 36].

SCS serve as a linkage to care for marginalized persons that would not be in contact with healthcare providers, including staff members [21, 37]. Contrary to the previous and current community attitude toward SCS, there is no evidence of such

locations increasing drug injection incidence, drug trafficking, or crime in the surrounding neighborhoods [35].

The first SCS, referred to as safe consumption room, was established in 1986 in Bern, Switzerland, as part of the public health response to drug-related deaths and the HIV epidemic among PWUDs. This SCS opened in conjunction with other harm reduction services such as needle exchange programs and OAT [36, 38]. Other European countries have opened more SCS and are currently operating as integrated, specialized, and mobile services [38].

The integrated SCS are usually embedded in other drug services, including HIV testing, needle exchange programs, wound treatment, other medical care services, psychosocial care, and social services, including shelters. Staff usually controls access and allows a limited number of persons, usually adults. Some centers have kitchen services, showers, washing machines, a sitting area, OAT, inpatient services, detoxification, and several consumption rooms for injection, inhaling, and oral consumption. Professional healthcare providers are available in all rooms and are trained for overdose prevention and to provide referrals for other services.

Specialized SCS are usually part of NGOs that provide a range of services close to the location, but not in the same building. Clients are allowed a specific time slot, and health providers are also available in need and referrals.

Mobile SCS are provided in established small drug scenes in large cities across different locations. Clients are registered and learn the weekly schedule of the vans. A common restriction is also for people registered in OAT who may not be allowed to use the SCS.

One of the most studied SCS is Insite, the first safe injection facility opened in the Americas. Dozens of Insite-related research articles have been published since 2003, supporting the overall benefit SCS provides to the communities. For example, there was a 35% decrease in overdose mortality in Vancouver after implementing SCS and an increase in drug treatment uptake among SCS users compared to other PWUDs [39, 40].

With the recent opioid overdose epidemic in North America, Canada implemented overdose prevention sites (OPS) in 2016 [41, 42]. There are some differences between OPS and SCS. While SCS require an exemption to operate under Canadian federal law, OPS operate under provincial regulations, are more peer-driven, and do not necessarily provide clinical services [22].

Compared to SCS, OPS have a lower cost, are easier to implement, and can be located in tents, trailers, containers, NGOs, and housing facilities [42], among other easily accessed spaces located where PWUDs usually are. Both services aim to provide a safe environment; while SCS initially aimed to prevent HIV and other infectious diseases, they also provided overdose prevention. OPS specifically provide immediate overdose response and other harm reduction services as secondary.

Restrictions implemented in existing facilities include access only to adults, toward occasional or first-time clients, persons in OAT, residents, and intoxicated persons. Other restrictions include unique schedules and centers for women, and it is forbidden to undergo open transactions [38]. In addition, some of the concerns of implementing OPS include legal protection from being arrested on site, agreements

with law enforcement for referrals, the confidentiality of users, and anonymity (e.g., not asking for identification or use of security tapes) [43].

As of July 2021, SCS officially operated in 13 countries: Switzerland, Germany, the Netherlands, Spain, Norway, Luxembourg, Denmark, Greece, France [36], Portugal [44], Belgium [45], Australia, and Canada [46]. Ireland has been working with a permission granted in 2017 [36], but in 2021, it was deemed invalid [47]. In the United States, Rhode Island is the first state to allow SCS within harm reduction premises [48]. California, New York, and Philadelphia have also presented law initiatives, and at least one unlicensed center is running in the United States [49]. Some of the anticipated barriers in the United States are fear of police interaction, privacy, data confidentiality, trust, and transportation [43].

Unofficially, according to the International Network of Drug Consumption Rooms, there are more SCS currently operating in Austria, Brazil, Bulgaria, Colombia, Czechia, Finland, Hungary, Iceland, Iran, Italy, Mexico, Poland, Romania, Serbia, Slovakia, Sweden, the United Kingdom, and the United States [50].

7.3.6 *Opioid-Assisted Treatment (OAT)*

OAT, also known as opioid maintenance treatment, medication-assisted treatment, medication for opioid use disorders (MOUD), and substitution therapy, refers to prescribing specific opioid drugs to persons who use opioids. OAT is preferred over MOUD because persons may not necessarily fulfill the psychiatric diagnoses for opioid use disorder.

OAT have mainly been used to reduce harms associated with opioid injection, such as HIV/HCV transmission through injection risk behaviors [19], to improve HIV treatment adherence [51], to reduce the risks related to street opioid use, and to reduce the odds of opioid overdose deaths [52].

OAT include prescription of opioid agonist (e.g., heroin, hydromorphone, morphine, methadone, and buprenorphine), opioid antagonists (naloxone, naltrexone), or combinations (e.g., suboxone). To date, 84 countries have at least 1 OAT service [30], most of them run by privately funded NGOs. The most prescribed agonist is methadone, which has been used for over 50 years, followed by buprenorphine, which has been used for approximately 20 years (Chap. 14).

Although OAT is effective, access and relapse are major concerns [10, 53]. Types of structural implementations related to OAT include expanding treatment options and services, improving funding and regulation, and intervening in public perception and attitudes toward persons who use opioids [19].

Geographic treatment availability is an essential structural determinant. OAT is mainly provided in high-income countries and urban settings. That leaves most of the persons that need treatment far from them. In countries with affordable or universal healthcare that includes opioid treatment, rural settings should invest more financially and socially to access treatment than their urban counterparts. The United States and Canada have OAT, and they are the countries where the opioid

epidemic has hit the hardest. Unfortunately, there is almost no access to OAT in the rest of the Americas. Even more, the few resources spent on harm reduction and OAT have been provided by international NGOs. This funding is not sustainable and reliable because priorities and interests may shift while population needs remain unaddressed.

Regulatory systems dispensing OAT limit flexibility and responsiveness of the programs; bureaucracy imposes excessive administrative paperwork and costs that do not guarantee the quality of care. Most of the OAT interventions include a coordinated care model, in which at least two healthcare professionals shared care responsibilities [53]. That is, there are minimum staff requirements that restrain treatment availability. In the United States, the COVID-19 epidemic served as a circumstantial background to a more flexible and take-home OAT prescription [54].

OAT have poor retention rates [10], are underutilized, and suffer from prescription limitations [55]. In particular, retention in methadone and buprenorphine treatments is low; recent data suggest that injectable diacetylmorphine and hydromorphone may be more successful for those with low adherence to previous treatment efforts [23]. Injectable OAT has been used mainly in Europe (e.g., the United Kingdom, Switzerland, Germany, Denmark, and the Netherlands) and more recently in Canada [42, 56]. Injectable OAT is effective for persons who inject drugs, especially for persons with treatment-refractory opioid use disorders; successful outcomes include less opioid use, less criminal behavior, and more well-being [42, 57]. Low-threshold programs, such as oral, snorted, or injected hydromorphone provision, nested within existing drop-in services, and dispensing machines, may provide a viable alternative for OAT provision [55].

Researchers and providers cyclically face political resistance to incorporate injectable OAT; until the more recent overdose epidemic in Canada, provinces have been working toward the incorporation, through constitutional challenges, to extend prescription of injectable opioids to study participants [42]. Injectable OAT is effective but unsuitable for some settings and communities since it requires human and financial resources, infrastructure, and specialized staff training [55].

Regardless of intrinsic difficulties, there is a clear need for comprehensive strategies to reduce illicit opioid supply; expand OAT [58]; scale up low-barrier opioid distribution programs, including hydromorphone prescription; disrupt illegal drug supply; and avoid fatal overdose [55].

7.3.7 *Naloxone Availability*

Naloxone is an effective opioid receptor antagonist that can be delivered intranasally, as a spray, *or* as an injection (Chaps. 5, 8, and 14). The FDA approved naloxone in 1971 to prevent constipation among persons with prescription opioid use [59]. Naloxone has been available for almost half a century but mostly in care settings [60, 61]. In the 1990s and early 2000s, take-home naloxone programs were implemented in the European Union due to the heroin epidemic [59].

Several studies have been performed to understand and design the best practices for naloxone delivery to reduce the odds of overdose. However, new challenges have been found, such as the increased potency of opioids mainly due to heroin adulteration with fentanyl and other synthetic opioids. For instance, in 2016, the proportion of fatal opioid overdose was higher for synthetic opioids than for prescription opioids in the United States [62]. In addition, the use of synthetic opioids, either by choice or accidentally, implies that the usual dose of naloxone may not be as effective as with less potent opioids.

Overdose reversal using naloxone as antidote is a structural intervention for several reasons. First, naloxone is still not approved for over-the-counter purchases in most countries. Second, it is not available in most low- and middle-income countries. Finally, even in countries where naloxone is not a controlled substance, it is hardly available when and where it is most needed.

Some of the barriers to using naloxone include low availability and fear of police encounters. Public-sponsored naloxone distribution programs need to be scaled up in countries in which they are already available (e.g., Canada) and implemented in countries where they do not exist (e.g., Mexico).

Overdose prevention education and naloxone kits have been made available at the community level through health centers, first responders (e.g., firefighters, law enforcement, paramedics), persons who use drugs, peers, and relatives of persons who use drugs, among others.

Law enforcement officers face opioid overdoses in their daily activities, making them an ideal group to receive overdose prevention training and naloxone kits. However, officers' attitudes toward users may need to be changed [63]. In 2010, the National Drug Control Strategy in the United States included working with law enforcement officers to reduce overdose deaths [63, 64]. Also, all states and the District of Columbia have access to naloxone [65], including immunity for prescribers, laypeople who may administer it, and dispenser organizations, among others. Moreover, federal entities encourage first responders to carry and use naloxone in case of opioid overdose [66]. In Vancouver, public-funded naloxone programs in private low-income housing buildings hired peer tenants to provide naloxone training and distribute it to other residents [22].

When a fatal overdose occurs, witnesses may respond inadequately and end up harassed or arrested at the scene charged for possession [67]. Fear of legal consequences is a barrier to call for help in case of an overdose [63, 68]. Therefore, there must be an agreement not to charge callers for drug possession or use or even murder in case of an overdose. Good Samaritan laws that legally protect potential bystanders of an overdose and overdose prevention training programs are essential, together with access to emergency departments and SCS, among others [67]. Naloxone distribution also needs training and constant reminders to PWUDs to carry it with them all the time [23].

Naloxone's availability is not synonymous with its administration. Therefore, take-home naloxone adoption within a community needs to be understood and explored more deeply than providing administration training and quantifying the number of naloxone kits distributed and used [60]. Naloxone administration involves

close and trusting relationships among different actors. It also needs a policy context that allows PWUDs to acquire and use naloxone freely and first responders who know what to do in case of an opioid overdose. Take-home naloxone programs also hold responsible other PWUDs for saving the lives of their peers [60, 69].

In sites and countries where opioid overdoses are increasing but have not yet reached the epidemic levels of the United States and Canada, some persons who use opioids may be reluctant to use naloxone because of the unpleasant withdrawal effects [60]. These effects can be minimized by carefully monitoring and titrating the naloxone dose through injection [60].

Other considerations include that newly abstinent persons are at higher risk of opioid overdose due to their tolerance loss and would benefit from carrying naloxone with them [70, 71].

7.3.8 *Drug Checking*

Europe introduced drug checking in the 1990s, originally thought of as a harm reduction service for nightlife and partying settings [42, 72]. Drugs can be checked with low-cost portable devices or more expensive stationary technologies.

Drug checking immediately informs persons before their drug consumption whether the substance they intend to use is what they thought they purchased and provides information about drug quality, purity, and potential harms. A second effect is information gathering for service users and the general population through public warnings [42].

In the case of the opioid epidemic, drug checking services have been mostly used to prevent overdosing due to drug adulteration with fentanyl and other synthetic opioids. Thanks to drug checking in the community setting, fentanyl has been found not only in heroin but also in combination with stimulants (i.e., cocaine, methamphetamine) [73, 74].

As it happens with other interventions, drug checking has nuances; in particular, this service has a limited effect in decreasing overdose rates. Although it may dissuade persons from using substances containing fentanyl, at this point, it is unclear whether they would have such effect [23]. Some factors related to vulnerabilities of the populations may limit the success of drug testing services. Some examples are having to give up a sample, time constraints, discrepancies, inaccuracy, ambivalence toward overdose risk, and availability of drug checking technologies [75]. Also, users may prefer using more potent substances (i.e., fentanyl).

Legal exemptions and implementation barriers are also structural challenges for drug checking [15]. In addition, safety and potential consequences need to be considered when introducing drug checking or any other intervention to which PWUDs may be unfamiliar.

Finally, it may be that that substance is the only one available in a particular location, and individuals may prefer to accept the risk than suffer withdrawal. It is not only knowledge and preference that relate to the use of contaminated/altered

samples. Drug checking services may, by themselves, alter drug-using behaviors and lead to drug disposal in some settings [75] but not others, based on the vulnerability and poverty levels of the persons who use drugs [75]. For this, engagement of drug dealers in drug checking may be an option in settings in which users may not be willing to through contaminated drugs and where criminalization and struggle to obtain the substance result in a significant sacrifice for users [75].

7.3.9 Safe Drug Supply

As previously stated, some persons who use opioids have expressed a preference for fentanyl use [43]. This information should not be disregarded in overdose prevention and other opioid-related interventions. If research, policy, and the overall community efforts genuinely intend to improve public health and well-being, it must be taken into account that drug criminalization impedes and constrains the public health response to drug use [15]. Safe supply and drug reform to reduce opioid overdose is supported by activists and researchers [42]. However, it is still a bold step that will be deemed controversial for a long time but is already being discussed across the world. In the next years, implementation of drug law reforms will need to be tailored to the special needs and contextual characteristics of specific regions, including access to healthcare systems, infrastructure and human resources, current epidemic status, socioeconomic factors, and others (Chap. 4).

7.3.10 Opioid Prescription Regulations

Opioid prescription regulations can be a double-edged sword. For example, in the United States, they removed long-acting formulations of high-strength opioids to contain the epidemic of prescription opioid use unleashed by long-acting and highly concentrated oxycodone presentation. These regulations have also established monitoring systems and a shared database to oversee opioid prescription [76]. These measures immediately reduced opioid prescription but were followed by an unintended and inadequate increase in opioid discontinuation and tapering [77]. In addition, regulations had unintended spillover effects, including an increase in non-prescription opioid use [78], exposure to street heroin and fentanyl [76], and injection risk behaviors that led to HIV outbreaks among populations in which pain medication was misused. A clear example was the HIV outbreak in Scott County, Indiana [79]. Other effects of opioid prescription regulations paradoxically included increased overdose rates [76, 80] and more admissions to emergency care services [81]. Finally, policies intended to prevent opioid overdose by improving opioid prescription have been seen by PWUDs as propagating stigma, loss of autonomy, and reproducing and producing structural vulnerabilities [76].

Tamper (i.e., crushing or dissolving pills to snort or inject)-resistant formulations can reduce diversion of prescription opioids and fatal overdoses. However, modeling simulations [82] and retrospective studies [83] have found a modest effect on overdose prevention due to unintended consequences such as the increased use of heroin and increased stigma, marginalization, and feelings of “orphaned by the system.” Stringent opioid prescription policies reduce the identity of persons that use opioid to “addict” and become powerless in pain management and opioid use [76]. Therefore, researchers and the pharmaceutical industry need to find a balance between marketing opioid formulations that become attractive for misuse and a human rights approach to pain management.

7.4 Conclusions

Person-centered approaches to drug use should take into account the persons’ needs, values, and preferences [10]. As such, it is necessary to acknowledge that PWUDs are not necessarily interested in engaging in treatment [55] and require non-treatment options to ensure safer opioid use.

All the interventions described in this chapter can and should be expanded wherever they are needed. However, their implementation must be context-grounded, considering sociocultural context, safety, and legal challenges. A chain of associations must be developed in each set to identify where and which interventions may be more effective, when and how advocacy should focus, and the potential implementation and participation barriers [19]. Community engagement is essential to ensure the sustainable adoption of evidence-based programs to address opioid overdose and the root health inequities [84].

There is sound evidence that reducing drug availability [85] and adequate prescription guidelines are necessary but insufficient to prevent overdose. Additionally, much effort has been invested in overdose response programs, naloxone training and distribution, SCS, and other harm reduction services to address the public health crisis entailed by the opioid epidemic, but with modest progress [21, 23, 75]. Consequently, efforts are needed to address determinants of the opioid crisis. Community-driven interventions are key in implementing and sustaining culturally relevant treatment programs that may be more suitable in cases in which the context has an added importance [84].

To effectively address the opioid overdose crisis, stakeholders need responsive political environments incorporating harm reduction and drug policy experimentation (Strike & Watson, 2019). It is necessary to identify which structural elements may have a more significant impact on the health outcome, including the proximal behavioral risks and distal structural sources of these risks [19]. No single response or approach can have a long-lasting effect, for which a broad approach that targets social dynamics is needed. Where and how OAT is provided matter [53]. The diversity of the communities, resources available, values, and competing priorities may influence how engaged a community is in addressing a health problem [84].

Addressing the opioid epidemic requires addressing the social and structural determinants of mental health, HIV, HCV, and other comorbidities [9]. This includes a combination of several – if not all – interventions: overdose prevention sites, safe supply initiatives, drug decriminalization, housing first (i.e., stable housing without abstinence prerequisites) to prevent overdoses, and reducing stigma and shame associated with drug use and relapse [71].

Instead of temporary exemptions for organizations that provide services to PWUDs, and the constant threat of closing, sustained community and public efforts should be accompanied by law reforms that guarantee access to services and ensure providers will not face legal problems while saving lives.

Overdose prevention training and naloxone distribution aim to empower PWUDs, provide agency, and reduce health inequalities; however, unintended consequences include a deeper healthcare marginalization by segregating PWUDs [21].

Low-threshold care services have proven to successfully prevent and reduce HIV incidence among PWUDs [86]. Low-threshold treatments, including underage populations [87], need to be expanded to act as alternatives that replace illicit drug supply. Even these treatment programs have low retention rates and high relapse rates: for this, safe supply and harm reduction are essential interventions [23]. According to the healthcare system and accessibility, persons in need of OAT may not have the opportunity to access it. Under these circumstances, harm reduction, cultural competency, and low-threshold OAT at emergency settings are successful for economically disadvantaged populations, unstably housed, and with polysubstance use [88].

Changing the addiction paradigm from a will-failure disorder to a brain disease helped reduce stigma and develop effective medical treatments. However, it is time to recognize that many sociological determinants influence the initiation and progression of this disease. Only then, a multifactorial problem will be addressed with holistic approaches, including structural interventions other than OAT.

References

1. Leshner AI. Addiction is a brain disease, and it matters. *Science*. 1997;278:45–7.
2. Volkow ND. To end the opioid crisis, we must address painful social disparities. *Drug Alcohol Depend*. 2021;222:108678.
3. Chandler RK, Villani J, Clarke T, McCance-Katz EF, Volkow ND. Addressing opioid overdose deaths: the vision for the HEALing communities study. *Drug Alcohol Depend*. 2020;217:108329.
4. Strang J, Volkow ND, Degenhardt L, Hickman M, Johnson K, Koob GF, et al. Opioid use disorder. *Nat Rev Dis Primers*. 2020;6:1–28.
5. Heimer R, Clair S, Teng W, Grau LE, Khoshnood K, Singer M. Effects of increasing syringe availability on syringe-exchange use and HIV risk: Connecticut, 1990–2001. *J Urban Health: Bull N Y Acad Med*. 2002;79(4):556–70.
6. Perlman DC, Jordan AE. The syndemic of opioid misuse, overdose, HCV, and HIV: structural-level causes and interventions. *Curr HIV/AIDS Rep*. 2018;15:96–112.
7. Dasgupta N, Beletsky L, Ciccarone D. Opioid crisis: no easy fix to its social and economic determinants. *Am J Public Health*. 2018;108(2):182–6.

8. Bourgois P, Holmes SM, Sue K, Quesada J. Structural vulnerability: operationalizing the concept to address health disparities in clinical care. *Acad Med: J Assoc Am Med Coll.* 2017;92:299–307.
9. El-Bassel N, Shoptaw S, Goodman-Meza D, Ono H. Addressing long overdue social and structural determinants of the opioid epidemic. *Drug Alcohol Depend.* 2021;222:108679.
10. Blanco C, Wiley TRA, Lloyd JJ, Lopez MF, Volkow ND. America's opioid crisis: the need for an integrated public health approach. *Transl Psychiatry.* 2020;10:1–13.
11. Quesada J, Hart LK, Bourgois P. Structural vulnerability and health: Latino migrant laborers in the United States. *Med Anthropol: Cross Cult Stud Health Illn.* 2011;30:339–62.
12. Case A, Deaton A. Opioids. In: *Deaths of despair and the future of capitalism.* Princeton: Princeton University Press; 2020. p. 109–30.
13. Case A, Deaton A. Rising morbidity and mortality in midlife among white non-Hispanic Americans in the 21st century. *Proc Natl Acad Sci U S A.* 2015;112:15078–83.
14. Rigg KK, Monnat SM. Urban vs rural differences in prescription opioid misuse among adults in the United States: informing region specific drug policies and interventions. *Int J Drug Policy.* 2015;26:484–91.
15. Kolla G, Strike C. 'It's too much, I'm getting really tired of it': overdose response and structural vulnerabilities among harm reduction workers in community settings. *Int J Drug Policy.* 2019;74:127–35.
16. Friedman J, Syvertsen JL, Bourgois P, Bui A, Beletsky L, Pollini R. Intersectional structural vulnerability to abusive policing among people who inject drugs: a mixed methods assessment in California's central valley. *Int J Drug Policy.* 2021;87:102981.
17. Matthew DB, editor. *Un-burying the lead: public health tools are key to beating opioid epidemic.* 2018.
18. Terry NR. Structural determinism amplifying the opioid crisis : it's the healthcare, stupid !*. *Northeast Univ Law Rev.* 2018;11:315–71.
19. Heimer R, Bray S, Burris S, Khoshnood K, Blankenship KM. Structural interventions to improve opiate maintenance. *Int J Drug Policy.* 2002;13:103–11.
20. Satinsky EN, Kleinman MB, Tralka HM, Jack HE, Myers B, Magidson JF. Peer-delivered services for substance use in low- and middle-income countries: a systematic review. *Int J Drug Policy.* 2021;95:103252.
21. Jozaghi E. The opioid epidemic: task-shifting in health care and the case for access to harm reduction for people who use drugs. *Int J Health Serv.* 2020:1–8.
22. Bardwell G, Collins AB, McNeil R, Boyd J. Housing and overdose: an opportunity for the scale-up of overdose prevention interventions? *Harm Reduct J.* 2017;14:77.
23. Kerr T. Public health responses to the opioid crisis in North America. *J Epidemiol Community Health.* 2019;73:377–8.
24. Luchenski S, Maguire N, Aldridge RW, Hayward A, Story A, Perri P, et al. What works in inclusion health: overview of effective interventions for marginalised and excluded populations. *Lancet.* 2018;391:266–80.
25. Somers JM, Patterson ML, Moniruzzaman A, Currie L, Rezansoff SN, Palepu A, et al. Vancouver at home: pragmatic randomized trials investigating housing first for homeless and mentally ill adults. *Trials.* 2013;14:365.
26. Zabkiewicz DM, Patterson M, Frankish J, Somers JM. The Vancouver at home study: overview and methods of a housing first trial among individuals who are homeless and living with mental illness. *J Clin Trials.* 2012;2:1–7.
27. McNeil R, Fleming T, Collins AB, Czechaczek S, Mayer S, Boyd J. Navigating post-eviction drug use amidst a changing drug supply: a spatially-oriented qualitative study of overlapping housing and overdose crises in Vancouver, Canada. *Drug Alcohol Depend.* 2021;222:108666.
28. Richardson L, Dong H, Kerr T, Milloy MJ, Hayashi K. Drug-related harm coinciding with income assistance payments: results from a community-based cohort of people who use drugs. *Addiction.* 2021;116:536–45.

29. Richardson L, Laing A, Choi JC, Nosova E, Milloy MJ, Marshall BD, et al. Effect of alternative income assistance schedules on drug use and drug-related harm: a randomised controlled trial. *Lancet Public Health*. 2021;6:e324–e34.
30. Harm Reduction International. *The global state of harm reduction*. 7th ed. London: Harm Reduction International; 2020.
31. Des Jarlais DC, McKnight C, Goldblatt C, Purchase D. Doing harm reduction better: syringe exchange in the United States. *Addiction*. 2009;104(9):1441–6.
32. Gibson DR, Flynn NM, Perales D. Effectiveness of syringe exchange programs in reducing HIV risk behavior and HIV seroconversion among injecting drug users. *AIDS*. 2001;15(11):1329–41.
33. Davidson PJ, Howe M. Beyond NIMBYism: understanding community antipathy toward needle distribution services. *Int J Drug Policy*. 2014;25:624–32.
34. Chami G, Werb D, Feng C, DeBeck K, Kerr T, Wood E. Neighborhood of residence and risk of initiation into injection drug use among street-involved youth in a Canadian setting. *Drug Alcohol Depend*. 2013;132(3):486–90.
35. Potier C, Lapr vete V, Dubois-Arber F, Cottencin O, Rolland B. Supervised injection services: what has been demonstrated? a systematic literature review. *Drug Alcohol Depend*. 2014;145:48–68.
36. European Monitoring Centre for Drugs and Drug Addiction, editor. *Perspectives on drugs. Drug consumption rooms: an overview of provision and evidence*. 2018.
37. Marshall BDL, Milloy MJ, Montaner JSG, Kerr T. Reduction in overdose mortality after the opening of North America’s first medically supervised safer injecting facility: a retrospective population-based study. *Lancet*. 2011;377:1429–37.
38. Sch ffler D, St ver H, Weichert L, editors. *Drug consumption rooms in Europe: models, best practice and challenges*. 2014.
39. DeBeck K, Kerr T, Bird L, Zhang R, Marsh D, Tyndall M, et al. Injection drug use cessation and use of North America’s first medically supervised safer injecting facility. *Drug Alcohol Depend*. 2011;113:172–6.
40. Marshall BDL, Milloy MJ, Wood E, Montaner JSG, Kerr T. Reduction in overdose mortality after the opening of North America’s first medically supervised safer injecting facility: a retrospective population-based study. *Lancet*. 2011;377:1429–37.
41. Arke ll C. Harm reduction in action: supervised consumption services and overdose prevention sites. *CATIE-Canada’s source for HIV and hepatitis C information*. 2018:6.
42. Strike C, Watson TM. Losing the uphill battle? Emergent harm reduction interventions and barriers during the opioid overdose crisis in Canada. *Int J Drug Policy*. 2019;71:178–82.
43. Park JN, Sherman SG, Rouhani S, Morales KB, McKenzie M, Allen ST, et al. Willingness to use safe consumption spaces among opioid users at high risk of fentanyl overdose in Baltimore, Providence, and Boston. *J Urban Health*. 2019;96:353–66.
44. Pinto de Oliveiraa A, Gautier D, Nunes P, Correia V, Leite A, Taylor H, et al. First year of implementation of a drug consumption room in Lisbon: the client’s profile. *Eur J Public Health*. 2020;30. <https://doi.org/10.1093/eurpub/ckaa166.403>.
45. Castillo T. A safe place to use drugs: lessons from Europe’s supervised consumption sites the fix. 2019.
46. Drug Policy Alliance. *Supervised consumption services*. 2021.
47. MacNamee G. ‘Devastating news’: planning permission given to supervised injection centre is deemed invalid. *TheJournal.ie*. 2021.
48. Sutton M. Drug policy Alliance statement on Rhode Island becoming first in the nation to authorize harm reduction centers to prevent overdose deaths. New York: Drug Policy Alliance; 2021.
49. Kral AH, Davidson PJ. Addressing the nation’s opioid epidemic: lessons from an unsanctioned supervised injection site in the U.S. *Am J Prev Med*. 2017;53:919–22.
50. International Network of Drug Consumption Rooms. *Drug Consumption Rooms (DCRs) in the world*. 2021.

51. Williams AR, Nunes EV, Bisaga A, Levin FR, Olfson M. Development of a cascade of care for responding to the opioid epidemic. *Am J Drug Alcohol Abuse*. 2019;45:1–10.
52. Fatseas M, Auriacombe M. Why buprenorphine is so successful in treating opiate addiction in France. *Curr Psychiatry Rep*. 2007;9:358–64.
53. Lagisetty P, Klasa K, Bush C, Heisler M, Chopra V, Bohnert A. Primary care models for treating opioid use disorders: what actually works? A systematic review. *PLoS One*. 2017;12:1–40.
54. Joudrey PJ, Adams ZM, Bach P, Van Buren S, Chaiton JA, Ehrenfeld L, et al. Methadone access for opioid use disorder during the COVID-19 pandemic within the United States and Canada. *JAMA Netw Open*. 2021;4(7):e2118223-e.
55. Ivsins A, Boyd J, Beletsky L, McNeil R. Tackling the overdose crisis: the role of safe supply. *Int J Drug Policy*. 2020;80:102769.
56. Fischer B, Rehm J, Kirst M, Casas M, Hall W, Krausz M, et al. Heroin-assisted treatment as a response to the public health problem of opiate dependence. *Eur J Public Health*. 2002;12:228–34.
57. Ferri M, Davoli M, Perucci CA. Heroin maintenance for chronic heroin-dependent individuals. *Cochrane Database Syst Rev*. 2011;12:1–55.
58. Jones MR, Viswanath O, Peck J, Kaye AD, Gill JS, Simopoulos TT. A brief history of the opioid epidemic and strategies for pain medicine. *Pain Ther*. 2018;7(1):13–21.
59. Campbell ND. Naloxone as a technology of solidarity: history of opioid overdose prevention. *CMAJ*. 2019;191:E945–E6.
60. Farrugia A, Fraser S, Dwyer R, Fomiatti R, Neale J, Dietze P, et al. Take-home naloxone and the politics of care. *Sociol Health Illn*. 2019;41:427–43.
61. McDonald R, Campbell ND, Strang J. Twenty years of take-home naloxone for the prevention of overdose deaths from heroin and other opioids—conception and maturation. *Drug Alcohol Depend*. 2017;178:176–87.
62. Jones CM, Einstein EB, Compton WM. Changes in synthetic opioid involvement in drug overdose deaths in the United States, 2010–2016. *JAMA – J Am Med Assoc*. 2018;319:1819–21.
63. Wagner KD, Bovet LJ, Haynes B, Joshua A, Davidson P. Training law enforcement to respond to opioid overdose with naloxone: impact on knowledge, attitudes, and interactions with community members. *Drug Alcohol Depend*. 2016;165:22–8.
64. Office of National Drug Control Policy. National Drug Control Strategy. The White House. 2010.
65. Lieberman A, Davis C, editors. Legal interventions to reduce overdose mortality: naloxone access laws. The Network for Public Health Law. 2021.
66. Guidance for law enforcement and first responders administering naloxone. 2020.
67. Davidson PJ, McLean RL, Kral AH, Gleghorn AA, Edlin BR, Moss AR. Fatal heroin-related overdose in San Francisco, 1997–2000: a case for targeted intervention. *J Urban Health*. 2003;80:261–73.
68. Wagner KD, Liu L, Davidson PJ, Cuevas-Mota J, Armenta RF, Garfein RS. Association between non-fatal opioid overdose and encounters with healthcare and criminal justice systems: identifying opportunities for intervention. *Drug Alcohol Depend*. 2015;153:215–20.
69. Buchman DZ, Orkin AM, Strike C, Upshur REG. Overdose education and naloxone distribution programmes and the ethics of task shifting. *Public Health Ethics*. 2018;11:151–64.
70. Bowles JM, Lankenau SE. “I gotta go with modern technology, so I’m gonna give ‘em the Narcan”: the diffusion of innovations and an opioid overdose prevention program. *Qual Health Res*. 2019;29:345–56.
71. Bowles JM, Smith LR, Mittal ML, Harding RW, Copulsky E, Hennessy G, et al. “I wanted to close the chapter completely ... and I feel like that [carrying naloxone] would keep it open a little bit”: refusal to carry naloxone among newly-abstinent opioid users and 12-step identity. *Int J Drug Policy*. 2021;94:103200.
72. Benschop A, Rabes M, Dirk JK. Pill testing, ecstasy and prevention: a scientific evaluation in three European cities. Amsterdam: Rozenberg Publishers; 2002. p. 138.

73. Fleiz C, Arredondo J, Chavez A, Pacheco L, Segovia LA, Villatoro JA, et al. Fentanyl is used in Mexico's northern border: current challenges for drug health policies. *Addiction*. 2020;115:778–81.
74. Centre on Drug Policy Evaluation. What's in Toronto's drug supply? Toronto's Drug Checking Service. 2021.
75. Bardwell G, Boyd J, Tupper KW, Kerr T. "We don't got that kind of time, man. We're trying to get high!": exploring potential use of drug checking technologies among structurally vulnerable people who use drugs. *Int J Drug Policy*. 2019;71:125–32.
76. Antoniou T, Ala-Leppilampi K, Shearer D, Parsons JA, Tadrous M, Gomes T. "Like being put on an ice floe and shoved away": a qualitative study of the impacts of opioid-related policy changes on people who take opioids. *Int J Drug Policy*. 2019;66:15–22.
77. Ranapurwala SI, Ringwalt CL, Pence BW, Schiro S, Fulcher N, McCort A, et al. State medical board policy and opioid prescribing: a controlled interrupted time series. *Am J Prev Med*. 2021;60:343–51.
78. Coffin PO, Rowe C, Oman N, Sinchek K, Santos GM, Faul M, et al. Illicit opioid use following changes in opioids prescribed for chronic non-cancer pain. *PLoS One*. 2020;15:1–14.
79. Strathdee SA, Beyrer C. Threading the needle. *NEJM*. 2015;373:397–9.
80. Oliva EM, Bowe T, Manhapra A, Kertesz S, Hah JM, Henderson P, et al. Associations between stopping prescriptions for opioids, length of opioid treatment, and overdose or suicide deaths in US veterans: observational evaluation. *BMJ*. 2020;368:1–10.
81. Mark TL, Parish W. Opioid medication discontinuation and risk of adverse opioid-related health care events. *J Subst Abus Treat*. 2019;103:58–63.
82. Wakeland W, Nielsen A, Geissert P. Dynamic model of nonmedical opioid use trajectories and potential policy interventions. *Am J Drug Alcohol Abuse*. 2015;41:508–18.
83. Benintendi A, Kosakowski S, Lagisetty P, Laroche M, Bohnert ASB, Bazzi AR. "I felt like I had a scarlet letter": recurring experiences of structural stigma surrounding opioid tapers among patients with chronic, non-cancer pain. *Drug Alcohol Depend*. 2021;222:108664.
84. El-Bassel N, Gilbert L, Hunt T, Wu E, Oga EA, Mukherjee TI, et al. Using community engagement to implement evidence-based practices for opioid use disorder: a data-driven paradigm & systems science approach. *Drug Alcohol Depend*. 2021;222:108675.
85. Martins SS, Sampson L, Cerdá M, Galea S. Worldwide prevalence and trends in unintentional drug overdose: a systematic review of the literature. *Am J Public Health*. 2015;105:e29–49.
86. Wodak A, McLeod L. The role of harm reduction in controlling HIV among injecting drug users. *AIDS*. 2008;22:S81–92.
87. Marshall BDL, Green TC, Yedinak JL, Hadland SE. Harm reduction for young people who use prescription opioids extra-medically: obstacles and opportunities. *Int J Drug Policy*. 2016;31:25–31.
88. Kalmin MM, Goodman-Meza D, Anderson E, Abid A, Speener M, Snyder H, et al. Voting with their feet: social factors linked with treatment for opioid use disorder using same-day buprenorphine delivered in California hospitals. *Drug Alcohol Depend*. 2021;222:108673.