REPORT

Harm Reduction Strategies to Address the Opioid Epidemic in Suburban Cook County

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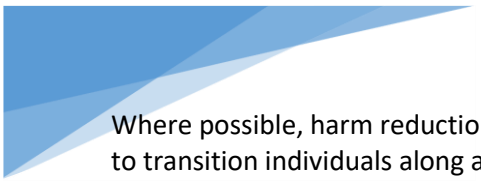
Introduction to Harm Reduction

Psychology research has demonstrated that punishment is a less effective tool for modifying human behavior as compared to positive reinforcement, particularly as an intervention to reduce the prevalence of substance use disorders (Friedman, 2006; Friedman, 2011). Yet punishment is the primary tool used to address substance use and substance use disorders in the United States through stigmatization, strict criminal laws, incarceration and subsequent civil disenfranchisement following a felony conviction. The rationale is that punishment acts as a deterrent against initiation and continuation of drug use (Becker, 1968; Miceli, 2021). The US spends approximately $47 billion USD annually to enforce drug laws (Miron, 2018) and another $12 billion USD annually to incarcerate drug offenders (Friedman, 2011). The federal government consistently invests more in law enforcement strategies than in treatment and prevention activities (GAO, 2016; Miron, 2018), with an exception of the current Biden administration which has increased treatment spending to account for the majority of the federal drug control funding in both 2021 and 2022 (Office of National Drug Control Policy, 2021). Despite the shift in funding under the current



Where possible, harm reduction strategies aim to transition individuals along a continuum from illicit drug use to safer potent opioids, to MATs, to non-opioid treatments and finally sobriety while simultaneously working with individuals to address other personal needs and removal of risk factors that causes harm to the individual, their social network and society.

administration, SAMHSA's annual budget is only around 5.8 billion with a large part of the budget going to funding mental health programs unrelated to SUD treatment.

The brute force approach has failed to solve the endemic problem of substance use disorders. An alternative model needs to be tested that prioritizes a public health approach, particularly on the consumption side of the drug supply chain. Any public health approach must be comprehensive. For substance use, this would mean that the approach includes treating the substance use disorder and adverse health effects of withdrawal and associated health conditions (treatment), while simultaneously addressing the root causes of addiction, other mental health needs of affected individuals (prevention of initiation and relapse), and providing comprehensive structural support to assist with transitioning away from high risk behaviors. Recovery from substance use disorders is a lifetime process. If we begin to treat substance use disorders as a chronic medical condition, we can begin to conceive of destigmatized programs similar to those used for the treatment and maintenance of diabetes or heart disease.

There are several key facts that provide a strong argument in favor of shifting away from punitive strategies and increasing investment in public health strategies to control the opioid public health crisis:

- **All humans are neurologically wired for potential addiction**. We all have pleasure centers in the brain that are triggered by a variety of agents and behaviors. When reinforced, addiction may develop. There is a strong association between duration of opioid use and eventual misuse/opioid use disorder (OUD) (Vowles et al., 2015; Krashin et al., 2016; Volkow, 2016). Approximately a quarter of patients treated with long-term opioids to manage chronic pain report opioid misuse and around 10% develop OUD (Vowles, 2015; Volkow, 2016). In fact, research shows that approximately 2% of persons prescribed opioids in an emergency department will develop an OUD (Barnett et al., 2017).
- **Substance use disorders are a disease**, not a failure of personal character, that are inextricably linked to physiologic reward seeking behavior, trauma, and mental health conditions (NAS, 2017).
- **Substance use disorders are highly prevalent in the United States.** An estimated 10-27% of the population will struggle with some form of substance use disorder during their lifetime. This prevalence rate does not include other addictive behaviors that rely on the same neurologic reinforcement pathways such as food, sex and gambling. In the U.S., the most common substance use disorder involves alcohol, but approximately 10% will misuse opioids during their lifetime (Saha, 2016; SAMHSA, 2019) and 2-3% will develop OUD (Saha, 2016).

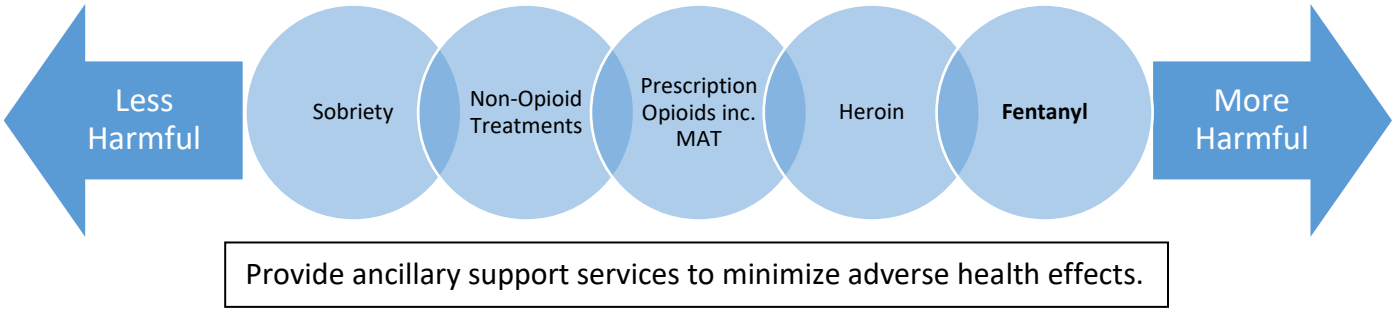
- **Substance use disorders (SUDs) are one of the few clinical diseases that are still criminalized and excluded from many legal protections**. Beyond the expansion of laws to criminalize substance use disorders (NAS, 2017), persons with SUDs, including alcohol, are not protected under Title VII of the Civil Rights Act of 1964. This intentional omission from protection means that persons with substance use disorders are explicitly excluded from discriminatory hiring, firing, compensation and employment protections under Title VII. This allows employers to fire employees that are struggling with addiction, except if the employee is receiving care through a substance use program.
- **The current war on drugs that has been waged for the last 50 years has led to no marked reduction in consumption or prevalence of substance use disorders** relating to controlled substances (Lipari, 2017). In fact, heroin and prescription opioid use has increased slightly since 2002 (Lipari, 2017), despite the exponential increase in deaths. Research also shows that heightened drug related law enforcement activity at the local level is not associated with a reduction in substance use (Cooper, 2005; Friedman, 2006; Friedman 2011).
- **The war on drugs has numerous marked adverse outcomes** including mass incarceration, militarization of law enforcement, disenfranchisement of civil rights following convictions, mass seizure of personal property in absence of convictions, and the massive cost to society to fund the police and a criminal justice system that must cope with enforcing these laws (NAS, 2017; Sawyer, 2021). Additionally, the war on drugs has created a robust illicit market for controlled substances that without regulation allows for the introduction of more harmful and deadlier substances, such as illicitly manufactured fentanyl (IMF).
- **The war on drugs perpetuates systemic racism**. Despite clear evidence that the prevalence of misuse of illicit drugs and substance use disorders impact persons of all racial/ethnic backgrounds similarly, the war on drugs has disproportionately impacted persons of color in the U.S. Despite comprising only 12% of the total U.S. population, Black/African Americans comprise over a third of the incarcerated population for drug offences (Taxy, 2015; Pew Research Center, 2019; Sawyer, 2021). Latinos make up 19% of the incarcerated population which is nearly equivalent to the proportion in the general population (18.5%). In contrast, white non-Hispanics make up a far smaller proportion of the incarcerated population (39%) than they do in the general population (60.1%) (Sawyer, 2021; USCB, 2021).
- **Research demonstrates an association between OUD and structural determinants of health** (NAS, 2017). Underserved communities characterized by inadequate infrastructure, limited

employment opportunities and disenfranchisement due to racism have higher rates of SUDs. (Carpenter et al., 2016; Compton et al., 2014; Nagelhout et al., 2017).

Harm reduction as a public health strategy encompasses a broad array of interventions. Conceptually, the goal of harm reduction is to minimize harm caused by risky behaviors or exposures that for various reasons cannot be avoided or eliminated entirely. The philosophy of harm reduction is common practice throughout public health and has been used to blunt the adverse effects of tobacco, alcohol, motor vehicle use, releases of environmental pollutants, and many other hazards to human health.

In the case of opioid use disorders (OUD), the focus is on the prevention of harm associated with opioid use rather than a singular focus on the prevention of using opioids themselves. In other words, cessation of opioid use is not the only measure of successful interventions, but one of many potential objectives. One key component of harm reduction for OUD is to disrupt use of more harmful opioids (e.g. heroin/fentanyl) by providing treatment with less harmful substances. In addition, harm reduction aims at reducing other harmful outcomes associated with substance use (e.g. blood borne diseases, traumatic injury, overdose, crime) by promoting destigmatization, social support, naloxone distribution, clean needle exchanges, safe injection facilities, education materials to improve safe drug use, mental health services, as well as many other interventions (Figure 1). OUD harm reduction programs prioritize maximizing engagement of individuals and communities with a focus on listening to affected persons about their priority needs and addressing realistic outcomes: a combination of "nothing about us without us" and "any positive change".

Figure 1: Scale of Harm Based on Scientific Evidence of Fatality Rates, Addictiveness, & Legal Repercussions



While this approach is not focused on the immediate cessation of OUD, it can lead to substantial reductions in adverse public health outcomes. In the context of OUD, the idea is to replace the current model where we use force to move people from the most extreme end of the continuum ("illicit" drug use) into sobriety principally through punishment (negative outcomes in response to SUD behavior). In fact, research has demonstrated that positive reinforcement - rewarding constructive behavior through contingency management interventions -- is more effective than punishment in the treatment of SUDs (Prendergast, 2006; Lussier, 2006; Peirce, 2006; Dutra, 2008; Friedman, 2011). Harm reduction is about pragmatism and minimizing adverse outcomes instead of focusing on the elimination of the high-risk behavior itself. It is akin to improving road safety by implementing policies such as mandatory seat belts, safer vehicle designs, and speed limits, as opposed to prohibiting the use of vehicles which kills approximately 40,000 persons in the U.S. annually -- but would kill many more without these harm reduction controls.

The pragmatic harm reduction model also takes into account that individuals with SUDs move along the continuum in both directions (allowing for relapse), which is in direct opposition to traditional zero-tolerance models. The role of public health practitioners is to meet individuals "where they are" instead of ineffectively forcing individuals with SUDs and those assisting these individuals to adhere to a singular and unidirectional intervention path.

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Medication Treatment for Opioid Use Disorder

Initiation of opioid misuse occurs principally through two pathways: treatment to manage pain (clinical) and exposure in a social setting (recreational). Surprisingly, research does not demonstrate that long-term use of prescription opioids is the most effective strategy to treat chronic pain (Chou et al., 2015). Long term use of prescription opioids is associated with OUD as well as other adverse health outcomes such as hypogonadism, increased pain perception, increased risk of falls and fractures, sleep apnea, and unintentional overdose (Baldini, 2012; Chou, 2015). A strategy to minimize the long-term risk of developing OUD among those treated with prescription opioids to manage pain is to consider reducing dosage of prescription opioids in populations with chronic use, within appropriate clinical guidelines for pain management. The evidence regarding the efficacy of opioids in improving quality of life when treating chronic pain is limited and indicates marginal improvement across a broad population of patients (Kalso, 2004; Eriksen, 2006; Turner, 2016; Sehgal, 2013). Using intermittent dosing or low doses have been shown to be equally effective to higher dose regimens in the management of chronic pain (Turner, 2016).

The development of OUD is strongly correlated with dose and duration of prescriptions (IOM, 2011; Shah, 2017). Research also demonstrates a strong correlation between rising prescription opioid use and heroin use (Muhuri, 2013; Jones, 2013; Al-Tayyib, 2017) and that a large proportion of current heroin users in the U.S. initially began using prescription opioids (Siegal, 2003; Muhuri, 2013; Cicero, 2014). But the picture is not that simple. One adverse effect of recent policies aimed at restricting access to prescription opioids by monitoring prescription patterns of physicians and limiting dosages is that persons who had exclusively used prescription opioids have transitioned to using heroin (Unick, 2013;

Compton, 2016). In addition, formulations designed to deter crushing and injecting of prescription drugs have been associated with increased transition to use of heroin (Alpert, 2017).

Both the psychological and physical response to opioids is not solely a function of morphine equivalent dose. Because heroin is seven times and fentanyl is over 100-times more potent than morphine (WHO, 2018), it is well recognized that mixing or replacing other opioids with fentanyl makes it difficult to estimate the effective dose and increases the risk of overdose. Furthermore, opioids differ in their subjective positive reinforcement effects, with intravenous opioid users rating heroin, morphine and oxycodone much higher than fentanyl and buprenorphine (Comer, 2008). In terms of lethality and serious adverse side effects, heroin and fentanyl are more lethal (Spencer, 2019; Serinelli, 2019; Scholl, 2019) and lead to greater medical complications (Baldini, 2012) than other commonly used opioids. Fentanyl analogues are associated with induced hyperalgesia (increased sensitivity to pain stimuli; Angst and Clark, 2006; Eisenach et al., 2015; de Hoogd et al., 2016; Fletcher and Martinez, 2014) requiring higher opioid doses to manage pain in equivalent opioid naïve patients (de Hoogd et al., 2016; Fletcher and Martinez, 2014). In addition, research indicates that fentanyl is far more addictive relative to both heroin and morphine (Comer, 2008), with its respiratory depressant effects increasing with dose and time of usage (FDA, 2021), and has a "shorter high" resulting in users feeling the need to "re-up" more frequently during a 24 hour window (Zibbell, 2021). Compared to heroin, fentanyl has a substantially shorter time to maximum concentration and half-life (Inturrisi, 1984; Rook, 2006; Foster, 2008). These characteristics of fentanyl increase the risk for both overdose and injection related infections.

A very concerning potential trend is that government and toxicology data from autopsies shows that fentanyl is increasingly consumed at about the same time or cut into non-opioid street drugs by sellers, particularly cocaine, methamphetamine and benzodiazepines (LaRue, 2019; DEA, 2021; Park, 2021; Elmarasi, 2021; Patel, 2021). However, it is not clear if fentanyl is intentionally cut into non-opioid street drugs prior to distribution or if these are the result of accidental contamination or intentional polydrug use by persons consuming the drugs. To complicate the problem further, each year more studies are showing that the majority of persons who die from an opioid overdose test positive for multiple agents – multiple opioids, ethanol, and benzodiazepines (Spencer, 2019; Serinelli, 2019). The combination of these agents potentiate respiratory depression and arrest which is the primary cause of death in opioid users (Baldini, 2012; Perez-Mana, 2018; Serinelli, 2019).

It is important to note that there is no silver bullet for the treatment of OUD or SUD. Individuals respond differently to different interventions. For this reason, SUD treatment involves a broad toolkit of

approaches, and treatment needs to be tailored to the individual similar to other psychiatric interventions or the treatment of diabetes and heart disease. The review below focuses on widely used medical treatments and emerging treatments, but does not cover medical treatments specifically designed to minimize withdrawal symptoms associated with cessation of opioids (Kosten, 2019; Doughty, 2019). There are a variety of drugs used to minimize symptoms of withdrawal from α-2 adrenergic agonists (e.g. lofexidine, clonidine), anti-diarrhea agents, antidepressants, and sedatives (Kosten, 2019).

Treatment with Methadone, Buprenorphine and Naltrexone

Illicit "street" opioids suffer from numerous quality control issues including wide variation in purity and dosage of active ingredients, wide variation in type and quantity of other active ingredients (e.g. fentanyl, benzodiazepines, antihistamines), use of dangerous inactive ingredients (e.g. talc and corn starch mixed into injectable formulations), inadequate production standards, and inappropriate storage and delivery which can lead to contamination by biologic and other toxic agents. The low to absent quality control standards in the illicit drug trade contributes substantially to risk of overdose and other adverse health effects.

A key harm reduction strategy has been to treat OUD with opioids that have lower abuse potential, longer biologic half-lives, substantially better quality control protections, and subsequently lower risk for adverse health effects. These medication-assisted treatments (MAT) involve methadone (DOLOPHINE®, METHADOSE™), buprenorphine (SUBOXONE®, ZUBSOLV®) and/or naltrexone (REVIA®, VIVITROL®). Both methadone and buprenorphine are u-opioid receptor agonists with long half-lives while naltrexone is a competitive antagonist with a long half-life. Analogously, naltrexone is the longer acting and less effective sister drug to naloxone which makes it a good treatment for long-term maintenance programs or as a tool for drug tapering programs. MAT programs are used for the treatment of acute withdrawal symptoms during detoxification and as a long-term treatment for OUD.

In general, MAT is a useful strategy for the treatment of OUD particularly when compared to all other common forms of SUD treatment. MAT alone is 3-4 times more effective than counseling alone in reducing return to heroin or prescription opioid use and retaining individuals in treatment programs (Kakko, 2003; Mattick, 2009; Gruber 2008; Kinlock 2007; Weiss, 2011; Schwartz 2006; Thomas, 2014;

Fullerton, 2014; Mattick, 2014). Research also shows that long-term maintenance MAT therapy is far more effective at reducing relapse, disease, and mortality than models based on tapering-detoxification (Evans, 2015; Kimber, 2015; NAS, 2017; Sigmon, 2015; Sordo, 2017).

Overall, MAT programs have retention rates above 50% and between 25-45% of individuals in MAT programs do not return to using heroin or prescription opioids at 1-year follow-up (Sells, 1979; Hubbard, 1986; IOM, 1995; Mattick, 2009; Feelemyer, 2014). MAT treatments are also associated with reductions in criminal activity, continued use of non-opioids, non-fatal overdose risk, transmission of blood-borne diseases and mortality (Kakko, 2003; Schwartz, 2006; Gibson, 2008; Clausen, 2008; Wilson, 2010; Lucas, 2010; Schwartz, 2013; Sigmon, 2015; Sordo, 2017). It is important to note that OUD treatment generally takes years to decades for individuals to cease illicit opioid use, and most studies have relatively short periods of follow-up. Long-term MAT treatment cohorts followed for years/decades show 2 to 4 times lower overdose risk and mortality compared to persons discontinuing MAT treatment (Sordo, 2017). Among individuals in MAT programs, overdose risk declines during the first four weeks of treatment and increases during the first four months after cessation of MAT treatment (Evans, 2015; Kimber, 2015; Sordo, 2017).

The efficacy of methadone and buprenorphine are equivalent in terms of prevention of using other opioids (Mattick, 2014; Sordo, 2017) and mortality (Gibson, 2008; Evans, 2015; Kimber, 2015; Sordo, 2017). However, both methadone and buprenorphine have risks and benefits that make it difficult to identify a preferable treatment from a clinical perspective (Connock, 2007; Bonhomme, 2012; Ma, 2019; Shulman, 2019). Methadone is associated with better treatment of withdrawal symptoms and higher retention rates in treatment during the first 1-year following cessation of heroin and polydrug use (Bonhomme, 2012; Sordo, 2017; Ma, 2019), particularly relative to persons treated at low doses or with variable dosing of buprenorphine ($\leq$6mg; Matick, 2014). In fact, buprenorphine at low doses does not appear to be effective in suppressing heroin use relative to no treatment controls ($\leq$6mg; Matick, 2014).

In contrast, buprenorphine requires less supervision, in most states can be administered by a broader group of health providers (general practitioners, physician assistants, nurses) in different treatment settings, has substantially lower risk of dependence, a lower risk of death during the initial month of treatment, a lower risk of overdose with concomitant opioid or polydrug use, and has lower adverse psychiatric side effects (depression, sexual dysfunction) (Connock, 2007; Bonhomme, 2012; Kimber, 2015; Ma, 2019; Shulman, 2019). While methadone is about 10% of the cost of buprenorphine (Jones, 2009), buprenorphine drug costs may decline over time now that generic formulations are available

(NAS, 2017). Buprenorphine also can be more readily administered in private physician offices which in combination with medical reforms to improve patient accessibility, the overall cost of buprenorphine (inc. cost of medication and treatment/delivery costs) can be comparable to or lower than methadone programs (Jones, 2009).

A third MAT option, naltrexone, is primarily administered alone as an injectable extended release formulation or as surgically implanted pellets (Kunoe, 2014). Early studies found that retention rates were very low when individuals were treated with oral doses because of the short duration of activity and the drug's ineffectiveness to treat withdrawal symptoms (Martin, 1973; Resnick, 1974; Minozzi, 2011; NAS, 2017; Kunoe, 2014). However, new extended release formulations are effective in reducing the effects of opioids (Sullivan, 2006; Bigelow, 2012), result in approximately 50% retention rates in treatment programs, and is associated with modest reductions in heroin use compared to oral formulations of naltrexone or placebo in short term studies lasting up to six months (Lobmaier, 2010; Tiihonen, 2012; Krupitsky, 2012).

One Australian study showed lower initial mortality rates during the first 14 days of treatment for those treated with naltrexone alone compared to methadone alone, with mortality rates becoming equivalent over the next three years of follow-up (Tait, 2008; Kelty, 2012). This is an expected outcome since naltrexone partially blocks the effects of illicit opioid use and it is recognized that a fraction of persons in MAT programs continue to use illicit opioids during treatment, particularly the first 4 weeks. This same cohort also reported lower odds of opioid related overdose in the naltrexone group but not in the methadone group (Ngo, 2008). One concern raised in this cohort study was the substantially elevated odds of non-opioid related overdoses in the naltrexone treatment group (Ngo, 2008), particularly the risk of overdose from benzodiazepines which has been shown previously (Hulse, 2005).

While research overwhelmingly supports the benefits of MAT programs, access remains an important barrier. Methadone can only be distributed by a SAMHSA-certified opioid treatment program (OTP). Buprenorphine can be prescribed by a broader pool of medical professionals in private offices (as opposed to specialized treatment programs) if they receive a buprenorphine waiver (the so-called "X" waiver). However, a 2020 investigation by the U.S. Office of Inspector General found that 40% of counties across the U.S. do not have any providers with a buprenorphine waiver, and the majority of counties with high rates of OUD do not have any waivered providers or are in desperate need for more waivered providers (Barton, 2020). Studies have also shown that most providers with waivers do not treat any patients for OUD or are at less than 50% capacity of their allowable patient limit (limits are 30,

100 and 275 patients) (Jones, 2015; Thomas, 2017; Jones, 2019; Barton, 2020). Overall, there is a substantial shortage in existing MAT capacity in the U.S. Nationally, all existing methadone, buprenorphine and other MAT opioid treatment programs combined could only treat a little more than half of all persons with OUD in the U.S. (Jones, 2015).

Another policy barrier is that many states require counseling to access MAT programs, despite a lack of evidence demonstrating that MAT in conjunction with counseling is more effective than MAT alone ; while counseling can be highly effective for long term SUD recovery, requiring counseling to access medication treatment programs is a barrier to care and has been shown to increase the risk of death from overdose (McLellan, 1993; Fiellin, 2006; Weiss, 2011; Amato, 2011; Nielsen, 2017). Access to drug treatment counseling can be difficult because of high out-of-pocket costs, insurance limits, shortages in trained SUD counselors, and limited capacity in available programs (NAS, 2017). Studies do show that providing access to MAT without counseling is associated with reduced mortality as compared to persons put on wait-lists (Schwartz 2012; Sigmon, 2015; Sigmon, 2016). In fact, many countries (e.g. United Kingdom) do not require counseling to access MAT programs in order to increase patient access to SUD programs (Connock, 2007).

Research on adding psychosocial interventions with MAT programs show at best marginal improvements in retention, personal well-being, and reductions in use of illicit opioids (Dugosh, 2016). One of the largest reviews of psychosocial interventions noted that when compared to MAT long-term maintenance therapy alone, only contingency management or contingency management combined with counseling and community reinforcement approaches improved retention in MAT programs (Rice, 2020). Contingency management interventions are particularly effective at reducing use of illicit opioids during treatment (Ainscough, 2017). Cognitive behavioral therapy (CBT) appears to only modestly improve retention in MAT programs that aim for abstinence through tapering rather than long term maintenance (Dalton, 2021). In a review, even with CBT added to the interventions, retention rates were very low in the MAT tapering programs compared to those reported in long term maintenance MAT programs (Dalton, 2021). Most studies consistently show marginal or no benefits from adding cognitive behavioral therapy to standard MAT interventions (Ray, 2020), and that cognitive behavioral therapy does not appear to be superior to other psychological interventions (Ray, 2020).

Treatment of Illicit Opioids with Nearly Equipotent Opioids

While only an estimated 8% of persons misusing opioids use heroin and fentanyl analogs (SAMSHA, 2019), studies show that fentanyl is found in 50-83% of fatal opioid overdoses (Spencer, 2019; Serinelli, 2019; Scholl, 2019; Friedman, 2020). To complicate matters further, 41.1% of fatal overdoses testing positive for heroin and/or fentanyl were concurrently exposed to least one additional respiratory depressant or drug that causes excessive drowsiness– ethanol, barbiturates, benzodiazepines, other pharmaceutical sedative-hypnotics or anxiolytics, muscle relaxants or antihistamines (Friedman, 2020). Concomitant exposure to these agents increases the risk of respiratory arrest or aspiration of fluids (Friedman, 2020). However, without widespread drug checking programs, including confirmatory testing, it cannot be conclusively determined whether these substances are being mixed prior to sale, or being ingested simultaneously as part of polydrug use.

Because of the danger of heroin and adulterants in illicitly acquired opioids, some countries have introduced treatments that allow for the prescribing of extended release variations of heroin, morphine and hydromorphone or supervised inhalable/injectable heroin (SIH). These programs are principally in Europe – Switzerland, United Kingdom, Netherlands, and Germany. Studies involving heroin users with poor adherence to traditional MAT programs and other SUD therapies, show marked improvement in programs using supervised inhalable/injectable heroin (Rehm, 2001; Ferri, 2011; Strang, 2015). The main feature of these programs is that every dose is administered or monitored by medical professionals, and they only treat individuals who have not been able to adhere to other treatment programs. This is not the same as safe injection sites which require less personnel and intensive services (discussed below).

Compared to methadone replacement therapy, supervised inhalable/injectable heroin programs are associated with equivalent or better program retention rates, that reach almost 90% (Perneger, 1998; van den Brink, 2003; March, 2006; Haasen, 2007; Strang, 2010; Ferri, 2011; Strang, 2015), substantially lower illicit heroin use (Perneger, 1998; March, 2006; Haasen, 2007; Strang, 2010), lower crime (Perneger, 1998; Dijkgraaf, 2005; Haasen, 2007; Metrebian, 2015), and no difference in mortality relative to traditional MAT programs (Perneger, 1998; March, 2006; Haasen, 2007; Oviedo-Joekes, 2009; Strang, 2010; Ferri, 2011; Strang, 2015). A key drawback of SIH compared to methadone treatment is the substantially higher proportion of those in the program reporting adverse side effects related to the opioid treatment (e.g. GI issues, pain sensitivity), which is expected since they are using more potent and shorter acting opioids (Perneger, 1998; March, 2006; Haasen, 2007; Oviedo-Joekes, 2009; Strang, 2010; Ferri, 2011; Strang, 2015). In one study, the most common side effect was respiratory depression caused by unreported benzodiazepine use in the study subjects (Haasen, 2007). However, supervised

heroin administration is effective for persons that continue to use heroin during methadone treatment or in persons who have unsuccessfully remained in a MAT program after several attempts (Haasen, 2007).

Other studies have evaluated injectable hydromorphone and extended release variations of morphine, heroin, and hydromorphone (Oviedo-Joekes, 2010; Ferri, 2013; Oviedo-Joekes, 2016). A Canadian study found that injectable hydromorphone was comparable to injectable heroin in terms of retention rates (Oviedo-Joekes, 2010). Oral administration of heroin showed high retention rates and reduced withdrawal symptoms compared to methadone (Martins, 2021). The main problem with these alternative medication treatments is the high cost to administer the programs. Each dose must be supervised by a medical professional which requires time and resources to be committed by the person in therapy as well as the medical provider. There is discussion to develop subcutaneous delayed release variations of these drugs to reduce the cost associated with administering these programs.

Evidence of Efficacy of Cannabis for Treatment of OUD

Since California legalized marijuana for medical use in 1996, 36 states have followed suit and legalized marijuana for various medical conditions and 18 states have legalized marijuana for adult recreational use. In the wake of these legal changes, there has been growing interest in evaluating the use of marijuana to treat OUD. However, because marijuana continues to be labeled a schedule 1 drug (the same category as heroin), it has been difficult to conduct research in the U.S. to evaluate the pharmacokinetics of the active compounds in marijuana or possible therapeutic uses. As such, a disproportionate amount of marijuana research occurs outside of the U.S. As research expands globally into the pharmacologic properties of marijuana, more active cannabinoids will be identified beyond the widely recognized δ-9-tetrahydrocannabinol (THC).

The rationale of using cannabinoids as a treatment for opioids is two-fold: (1) cannabinoids can be used as an alternative to opioids for the treatment of chronic pain and (2) as a new MAT alternative to treat OUD. Cannabinoids have been shown to reduce perception of pain (antinociception; Cichewicz, 1999; Whiting, 2015; National Academies of Sciences, Engineering, and Medicine, 2017; Starowicz, 2017; Donvito, 2018; Soliman, 2021), reduce nausea and anorexia associated with chemotherapy and other conditions (Whiting, 2015), and modifies cravings for opioids (Frederickson, 1976; Vela, 1995; Lichtman, 2001; Yamaguchi, 2001). All of these positive therapeutic attributes, address the sentinel features of

opioid withdrawal and/or chronic pain associated with certain medical conditions (e.g. cancer). Marijuana, unlike most opioids, has a lethal dose (~4g) that is nearly impossible to reach in humans because of a variety of pharmacokinetic limiting factors. As such, marijuana may be less harmful compared to most opioids.

However, cannabinoids do have adverse health outcomes, in particular an increased risk for incidence and exacerbation of psychiatric conditions. Research indicates that heavy marijuana users and those that meet the DSM-V criteria for marijuana use disorder have approximately a 2-fold higher odds of developing any type of psychosis associated with major depression, schizophrenia, bipolar disorder and other mental health conditions (Myles, 2012; Whiting, 2015; Hasan, 2020). In addition, marijuana related psychosis is associated with an earlier age of onset by up to 32 months (Myles, 2012) and higher symptom severity during use (Myles, 2012; Hasan, 2020), both of which are associated with poorer response to future psychiatric care. Clinicians need to take into account the psychiatric risks when considering cannabinoids for the treatment of chronic pain or OUD, particularly since the prevalence of these mental health conditions is approximately 10% in the U.S. population and persons with OUD have a higher prevalence of mental health issues (SAMHSA, 2018).

Cannabinoids as a treatment of chronic pain instead of opioids

Research has shown that many persons with OUD report chronic pain (Rosic, 2021) and a large proportion of individuals treated with opioids for chronic pain develop OUD (Baldini, 2012; Chou, 2015). Cannabinoids act on the perception of pain caused by inflammation and neuropathy (Cichewicz, 1999; Soliman, 2021). Cannabinoid receptors are prevalent throughout pain pathways in the body and appear to inhibit neural activity of these pathways (Starowicz, 2017; Donvito, 2018; Soliman, 2021). Marijuana may indirectly potentiate the pain relieving properties of opioids, allowing for lower opioid doses (Roberts, 2006), and patients treated for chronic pain generally prefer marijuana over opioids and reduce their opioid consumption when offered medical cannabis during course of pain management (Boehnke, 2016; Haroutounian, 2016; Kral, 2015). However, the findings are not entirely conclusive in regards to cannabinoids impact on opioid consumption. A large cohort study found that concurrent use of marijuana to treat chronic pain was not associated with a reduction in opioid use (Campbell, 2018). For the treatment of chronic pain, replacing or augmenting opioids with cannabinoids could address one of the key pathways leading to OUD, but further research is needed to better understand the efficacy of cannabinoids. Also, it is important to note that marijuana is addictive and in some studies has been shown to increase risk of developing OUD (Olfson, 2018). From a harm reduction perspective, marijuana

is a potential treatment for opioids because of its low lethality and low prevalence of adverse side effects (with the exclusion of people at risk for or already diagnosed with schizophrenia and/or major depression, in which case a clinician should work with the patient to discuss risk for adverse psychiatric outcomes before prescribing marijuana as a treatment for OUD). Clinicians should conduct a comprehensive psychiatric evaluation of their patient before considering cannabinoids for the treatment of chronic pain, as well as monitor psychiatric symptoms during treatment.

Cannabinoids as a new MAT alternative

Marijuana also reduces cravings for opioids by increasing release of dopamine in the reward centers of the brain (Hurd, 2019; Calpe-López, 2019; Spanagel, 2020) and modulating craving induced by environmental cues (Frederickson, 1976; Vela, 1995; Lichtman, 2001; Yamaguchi, 2001; Hurd, 2019; Spanagel, 2020). In animal studies, marijuana has been shown to be a naloxone antagonist in opioid dependent animals and reduces withdrawal signs caused by naloxone (Frederickson, 1976; Vela, 1995; Yamaguchi, 2001). Additionally, naloxone induces withdrawal symptoms in THC dependent animals and morphine reverses the withdrawal symptoms (Lichtman, 2001). Research has demonstrated that cannabinoid receptors are involved in opioid dependence and withdrawal (Vela, 1995), but marijuana has been repeatedly shown to not be associated with continued opioid misuse (McBrien, 2019). However, while cannabinoids share similar neurologic pathways as opioids, cannabinoid receptors do not result in the same actions as opioid receptors. Substances that act on cannabinoid receptors results in aversion to morphine and agents that block cannabinoid receptors potentiates the effects of morphine in animal models (Ahmad, 2013; Sagheddu, 2015)

Because of the effects of marijuana, early researchers hypothesized that marijuana could assist with OUD withdrawal symptoms and reduce opioid use in persons participating in MAT programs. Most of the current research has evaluated concomitant marijuana use in persons participating in methadone and buprenorphine MAT programs, or marijuana's effect on reducing withdrawal symptoms during opioid detoxification and during the early phase of MAT programs. Marijuana does reduce withdrawal symptoms during the first week of detoxification (Handelsman, 1987; Raby, 2009; Bisaga, 2015), primarily by improving mood, reducing pain sensitivity, minimizing insomnia, increasing appetite and reducing GI distress (Best, 1999; Wesson, 2003; Scavone, 2013; Bisaga, 2015). In naltrexone only MAT treatment programs, intermittent use of marijuana is associated with higher program retention rates,

lower positive urine samples for opioid use, and higher compliance with naltrexone (Church, 2001; Raby, 2009).

Studies evaluating concomitant use of marijuana with methadone or buprenorphine have shown varied results, with the majority showing no association between marijuana use and non-MAT opioid use during treatment (McBrien, 2019; Rosic, 2021). However, both non-fatal and fatal overdose incidents is lower among those using marijuana during methadone treatment (Bryson, 2021). Concurrent use of marijuana does not appear to impact retention in MAT programs using opioid agonists (Scavone, 2013; Rosic, 2021), but the findings do vary by country and study population (McBrien, 2019). While most of the past studies use urine or blood testing to confirm both marijuana and non-MAT opioid use during treatment, studies have shown that a large proportion of individuals in MAT programs, in many studies over 50%, report concurrent use of marijuana (Rosic, 2021), which complicates study designs attempting to evaluate the impact of medically prescribed marijuana use on retention in MAT programs and use of non-MAT opioids during treatment.

However, the current research is encouraging that marijuana could improve success of traditional MAT programs. As with MAT programs themselves, not every person responds the same way to marijuana co-treatment. Persons with earlier age of onset of marijuana use and individuals that report craving marijuana do not show a noticeable reduction in opioid use and retention while in MAT programs (Rosic, 2021), while other studies have shown that concurrent use of marijuana did not result in different outcomes from those exclusively receiving Methadone or buprenorphine (Budney, 1998; Hill, 2013; Bagra, 2018). Given legal limitations and poor investment, it is premature to make an adequate assessment of the efficacy of marijuana for the treatment of OUD at this point.

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Evidence for Providing Individuals with Naloxone, Paraphernalia and Information to Minimize Harm from Opioids

Increase availability of naloxone outside of pharmacies/physicians

Naloxone is an opioid antagonist that is the most effective treatment for reversing respiratory depression caused by opioids. It is on the World Health Organization Model List of Essential Medicines (WHO, 2021) because of its critical role in reversing opioid activity. Naloxone is nearly 100% effective in reversing opioid activity for up to 60 minutes. Re-administration every 2 to 60 minutes is often necessary to prevent a rebound overdose when an individual is exposed to high doses of opioids, opioids with higher binding affinities (e.g. fentanyl analogues), or opioids with long half-lives (e.g. methadone). Frequency and intervals for re-administration varies widely between persons experiencing overdoses and is dependent on the type of opioid initially administered, degree of physical tolerance to opioids, initial dose and route of administration of both the opioid and naloxone, and concomitant exposure to other agents that potentiate the effects of opioids (Chou, 2017). Individuals treated with naloxone in a pre-hospital setting can in most cases be released without subsequent transport to a hospital, when after a 1-hour observation period the individual shows no signs of mental impairment, vitals have returned to normal, the person has no severe withdrawal symptoms, and has not been exposed to other agents (Willman, 2017; Stam, 2018). Various studies show that survival following naloxone administration ranges between 80-100%, but it appears that most fatal outcomes

are the result of delays in administering naloxone rather than a failure of the drug's activity (Clark, 2014; EMCDDA, 2015).

The most common expected side effect of naloxone administration is that up to 50% of opioid dependent individuals typically experience withdrawal symptoms shortly after administration of the drug (Clarke, 2005). As for other side effects, naloxone is considered a safe drug with side effects occurring in less than 2% of those administered the drug. However, it is unclear if these other adverse side effects are the result of naloxone administration or the precipitating opioid exposure and subsequent hypoxia associated with respiratory depression (Buajordet, 2004; Osterwalder, 1996; Yealy, 1990). Adverse side effects include convulsions, pulmonary edema, and cardiac arrest (Buajordet, 2004; Osterwalder, 1996), but the risk of these adverse effects can be reduced with proper post-administration management and slower administration of the drug (Buajordet, 2004; Osterwalder, 1996). With newer formulations that use auto-injectors or nasal administration, slow administration is not possible. It also appears that the adverse side effects unrelated to withdrawal resolve on their own within 10 minutes following administration of naloxone. In addition, individuals administered naloxone need to be monitored for adequate oxygen supply and risk of aspiration of vomit.

A major limiting factor of wide distribution of naloxone has been its mode of delivery. The original form was as an injectable intramuscular administered drug which limits its use for non-medically trained individuals and in persons who would administer as a bystander but are afraid of needles. New formulations that can be administered intranasal or as an auto-injector (intramuscularly), which even have audio administration instructions built into the devices, have been introduced to the market to eliminate this limiting factor. Research has demonstrated that intramuscular administration is superior to intranasal administration, because it has a faster action, is not diluted by improper administration, and more of the drug is available to block the actions of opioids before being metabolized (Chou, 2017; Tylleskar, 2017; Skulberg, 2018). On the other hand, intranasal formulations allow for broader use/access by non-medical professionals. In addition, intranasal formulations typically have higher doses to correct for the lower bioavailability. The FDA has approved all three formulations – traditional syringe, auto-injector and intranasal- for community distribution and where standing order policies exist for distribution by pharmacists (Sharpless, 2019).

A second limiting factor has been the requirement for a prescription to access the drug. However, local policies have allowed for pharmacy distribution and access to the drug through community organizations and local health departments. Local communities and states have passed laws that allow

for standing orders which provides a mechanism for pharmacists to distribute naloxone to individuals who do not have a prescription for the drug. In addition, the FDA has laid the legal groundwork to allow for over-the-counter distribution of naloxone (Evoy, 2021). The next step is for a pharmaceutical manufacturing company to develop and apply for over-the-counter version of the drug. While accessibility remains an issue across the U.S., these policy solutions have paved the road to improving access to naloxone.

The final limiting factor has been the cost per dose. Naloxone is an expensive drug and sufficient supply has been problematic. The average out-of-pocket cost of traditional generic naloxone syringe is $25 compared to $140 for the patented naloxone nasal spray and $4000 for the auto-injector. There are advocates developing policies to implement price controls and improve supply in the U.S. Contracted group purchases of naloxone (e.g. buyers clubs) results in substantial decreases in the cost per unit to as low as $6 for standard injectable dose, $15 for naloxone kits and $30 for intranasal kits (Leavitt, 2010; Yokell, 2011). However in the U.S. only one company produces each variant of naloxone – traditional injectable naloxone by Pfizer, the nasal spray Narcan by Emergent, and the auto-injector by Kaleo. Without adequate market competition, prices remain inflated for a drug that can be produced as a generic variant. Recently there have been advocates calling for a publicly funded supply of naloxone to address these price and supply issues (Kim, 2021).

Is community level naloxone distribution effective?

The rationale for providing community access to naloxone without a prescription is that it is highly effective at reversing an opioid overdose, and the risk of overdose if very high, particularly among those who use heroin. Among persons reporting injectable heroin use, in the past year between 9 to 16% report a non-fatal overdose (Milloy, 2008; Jenkins, 2011) and 23-68% report a non-fatal overdose at any point during their lifetime of using opioids (Darke, 1996; Gossop, 1996; Milloy, 2008; Hakansson, 2008), with the risk of overdose increasing after the first overdose (Stoove, 2009; Darke, 2011). Another rationale for community distribution is that a large proportion of physicians and pharmacists report an unwillingness to ever prescribe naloxone to persons with SUDs and have high rates of stigmatized views of individuals with SUD (Mueller, 2015; Binswanger, 2015). Community organizations provide an additional avenue for wider naloxone distribution.

There is limited research about the impact of community access to naloxone without prescriptions on overdose mortality in the community setting (Chou, 2017). There is a need for investment in this research, but initial findings are promising but not entirely consistent. A large national study in Scotland

found that the national program involving the distribution of naloxone take home kits was not associated with a decline in ambulance calls for the treatment of overdoses over a four year period (McAuley, 2017), but the program was unable to determine overall use of take home kits or whether the distribution of kits was making it to those using opioids. However, other studies have observed a reduction in mortality following community distribution of naloxone, particularly when it was accompanied by training on (1) how to recognize the signs of an opioid overdose, (2) administration of naloxone, and (3) post-naloxone administration protocols (Enteen, 2010; Bennet, 2012; Clark, 2014; Chimbar, 2018). Community training programs are shown to improve knowledge about all three aspects of the training noted above immediately after completion of training (Bennet, 2012; Tobin, 2009) and up to six months following training (McAuley, 2010; Strang, 2008; Gaston, 2009). However, because of well recognized inhibitions to using syringes in the general population, training programs involving intranasal administration appear to be more effective long term than those involving intramuscular administration (Ashrafioun, 2016).

A common problem reported in the literature was that 50% or more of trainees reported either omitting important treatment protocols or used interventions that were not clinically appropriate for overdose interventions (Bennet, 2012; Tobin, 2009; Gaston, 2009; Enteen, 2010; Bennett, 2011; Lankenau, 2013). Another problem highlighted in the literature was that the majority of trainees did not administer naloxone during an overdose (Strang, 2008; Doe-Simkins, 2009; Gaston, 2009; McAuley, 2010; Leece, 2013).

Despite not following protocols for overdose intervention, when naloxone was administered survival rates remained very high (Strang, 2008; Bennet, 2012; Tobin, 2009; Gaston, 2009; Doe-Simkins, 2009; Enteen, 2010; McAuley, 2010; Bennett, 2011; Lankenau, 2013; Walley, 2013; EMCDDA, 2015; McDonald, 2016). However, there is limited research on the impact of distribution of naloxone to non-medical personnel and overall community mortality from opioid overdoses. Two studies, including one involving the Chicago Recovery Alliance, showed a reduction in overdoses or flattening of the increasing trend in overdose deaths in communities that had intensive naloxone outreach and training (Maxwell, 2006; Walley, 2013). An unexpected adverse effect of bystander interventions with naloxone has been harassment by ambulance service personnel and police called to the scene following naloxone administration or having their naloxone confiscated by police (Sherman, 2008; Doe-Simkins, 2009; Enteen, 2010; Lankenau, 2013).

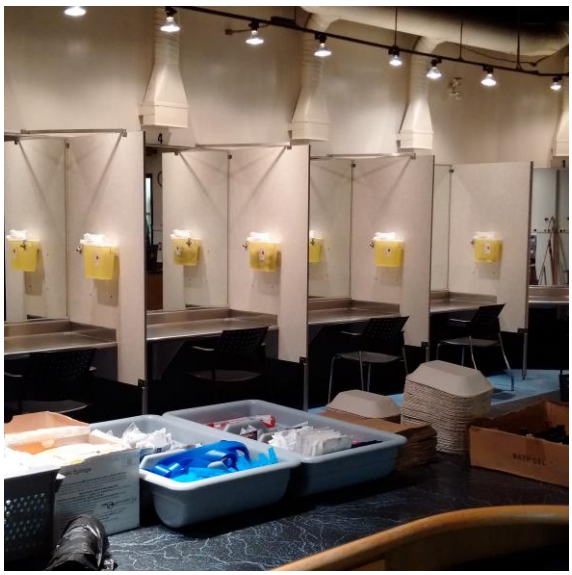
Overall, a review of multiple studies indicates that only approximately 9% of naloxone kits will be used during the first 3 months after distribution in general community outreach programs (McAuley, 2015). Two risk assessment studies estimate that a 6% reduction in opioid overdose mortality can be achieved for every 20-30% of heroin users that are provided naloxone kits (Coffin, 2013; Langham, 2018). Data regarding the distribution of naloxone to populations using prescription opioids only is sparse. One large study of patients who were prescribed opioids for chronic pain (predominately oxycodone) found that opioid related emergency visits to a hospital declined by 63% over one year in the patient group that was prescribed intranasal naloxone (Coffin, 2016). This decline occurred even though the naloxone treatment group was initially a higher risk group that had presented during the prior 12 months to an ED for an opioid related condition (Coffin, 2016). The same researchers reported that opioid dosage did not significantly increase in the naloxone treatment group compared to the control group over the 18 months of follow-up, and in one subgroup, naloxone administration was significantly associated with a decrease or cessation of opioid usage (Coffin, 2016).

Because research has shown that ex-prisoners with a history of drug use are at an increased risk of overdose during the first two weeks after release from prison, there has been a focus on providing naloxone kits to prisoners with a history of opioid use at the time of release (Merrall, 2010). A study involving distribution of naloxone at time of discharge from prison found that a larger proportion of individuals used their kits on someone else than on themselves (14% vs 5%; Parmar, 2017). This study was conducted in a high risk group that 67% reported injecting heroin during the first two weeks after release from prison (Parmar, 2017). However, among the 61 overdose incidents reported by the study group during the entire period of follow-up, the group that was provided naloxone kits were almost 4x more likely to administer naloxone to reverse an overdose compared to controls (47.2% vs. 12.0%).

Supervised injection facilities (SIFs)

Another harm reduction strategy that has evolved across the globe is the formation of supervised injection sites/facilities (SIFs). These state sanctioned sites currently exist in Canada, Australia, Spain, Luxembourg, Norway, Netherlands, Switzerland and Germany. While SIFs are not permitted in the U.S., due to federal statute, there have been reports of unsanctioned SIFs with the most notable one in San Diego (Kral, 2017). The primary goal of SIFs are to prevent deaths associated with overdoses by staffing the facilities with trained medical professionals and equipment to treat an overdose including Naloxone and oxygen support. These facilities also provide access to clean needles, syringes, alcohol swabs,

fentanyl test strips, and other equipment necessary for safe administration of injectable drugs (Potier, 2014). These facilities do not provide opioids, do not allow sharing of drugs, do not allow individuals to assist one another, and prohibit the sale of drugs on or near the premises. In the U.S., the unsanctioned SIFs appear to be by invitation only (Kral, 2017).



Safe Injection Site
Insite Vancouver, Canada

However, as they have evolved, it became quickly apparent that SIFs also can serve as an important point of contact with persons with OUD to provide referrals to housing, food assistance, legal services, general medical care, treatment for sexually and blood transmitted diseases, referrals to SUD treatment including MAT programs, safe disposal of used needles and other equipment, and a key venue to provide important health education (Beletsky, 2008; Potier, 2014). Where SIFs have been established, they have become critical points of contact to the most vulnerable persons with SUD who may never or rarely interface with other healthcare facilities or staff that don't stigmatize those with SUDs.

The typical population served by SIFs are individuals reporting daily use of injectable drugs (Wood, 2005) often in public (Hadland, 2014), who live near the SIF (Wood, 2005; Hadland, 2014), with a high prevalence of blood borne diseases (Wood, 2005; Potier, 2014), and precarious housing (Wood, 2005; Stoltz, 2007; Hadland, 2014; Kennedy, 2019). One site in Australia estimated that up to 70.7% of persons injecting drugs in a two square kilometer area used their SIF (Kimber, 2008). The key reason for using SIFs by persons with SUDs is the desire for a safe location to inject with sterile equipment (Small, 2012). To be effective, SIF facilities, their staff and those that use SIFs must be safeguarded from law enforcement activities within the facilities and in transit to and from the facilities (Beletsky, 2008). Law enforcement have been known to target persons with SUDs entering and exiting the facilities. In addition, communication strategies are necessary to allay concerns of residents living next to SIFs, but research shows that the majority of residents are supportive of SIFs when benefits are clearly demonstrated and communicated (Cruz, 2007; Salmon, 2007; Philbin, 2009).

Do SIFs reduce overdoses?

Multiple studies have reported a total absence of deaths occurring within SIFs (Kerr, 2006; Potier, 2014; Milloy, 2008; Van Beek, 2004). In the most highly researched SIF, Insite in Vancouver, since opening there have been over 3.6 million supervised injections with not a single overdose death despite 6,440 non-fatal overdoses treated on site (VCH, 2021). In the one unsanctioned SIF in the U.S. with available data, there were two overdoses out of 2,574 injections, both of which were reversed (Kral, 2017). Research has also shown a reduction of 35% in deaths in the area surrounding a prominent SIF in Vancouver (Marshall, 2011) and a decline of 68% in ambulance calls for opioid overdoses during the hours that an Australian SIF was open (Salmon,2010).

Relative to the city overall, the area surrounding a SIF had nearly a 4-fold greater reduction in overdose deaths (Marshall, 2011). Numerous other studies using experimental designs and longitudinal cohorts show substantial reduction in non-fatal and fatal overdoses among those who use SIFs (Milloy, 2008; Kerr, 2006; Van Beek, 2004). A recent study following a cohort for 10.5 years found that weekly or greater SIF use was associated with a reduction of overall mortality by half relative to persons reporting never or infrequent SIF use (Kennedy, 2019). However, with the increased prevalence of fentanyl, SIFs have reported nearly a 5-fold increase in overdoses occurring within SIFs, which further justifies the need for SIFs but also highlights the growing burden on the staff within SIFs (Notta, 2019) and the need for drug checking or other market quality controls to address the higher potency of fentanyl.

Is there evidence that SIFs are associated with other public health benefits?

SIFs are also strongly associated with a greater than 2-fold reduction in reusing needles and sharing needles with others (Kerr, 2005; Stoltz, 2007; Milloy, 2009). SIFs also contribute to a reduction in complications related to inappropriate injection (Salmon, 2009; Wood, 2008; Davidson, 2018), a reduction in HIV and Hepatitis C infections (Pinkerton, 2010; Pinkerton, 2011; Kennedy, 2019), 8 days shorter hospitalization stays following complications associated with inappropriate injection (Lloyd-Smith, 2010), increased condom use (Marshall, 2009), increased enrollment in SUD treatment programs (Wood, 2006; Wood, 2007; Kimber, 2008; DeBeck, 2011; Kennedy, 2019), increased participation in safer injection education (Wood, 2008), and a decrease in openly discarded used syringes and other potentially contaminated materials (Wood, 2004; Jozaghi, 2013; Davidson, 2018). Several cost-benefit economic analyses have shown a substantial cost effectiveness of SIFs primarily from a reduction in blood borne diseases and overdoses (Bayoumi, 2008; Pinkerton, 2010; Pinkerton, 2011; Jozaghi, 2013).

Do SIFs increase opioid consumption?

While there is limited research addressing SIFs impact on opioid consumption, studies do not show an increase in opioid consumption as measured by relapse rates, discontinuation of MAT treatment or the initiation of injecting drugs (Kerr, 2006; Kerr, 2007). In one study, over a 16 month period of observation only one person indicated that they injected drugs for the first time at a SIF (Kerr, 2007). Additionally, individuals utilizing SIFs are more likely to enter a SUD treatment program (Kerr, 2005; Wood, 2006; Wood, 2007; Kimber, 2008; DeBeck, 2011). This finding is not surprising in light that SIFs provide comprehensive services including medical and SUD treatment referrals.

Do SIFs increase the number of persons with opioid SUDs and related crime in the area around SIFs?

After the opening of the Insite SIF facility in Vancouver, public injecting declined by almost half (Wood, 2004). In an experimental study from Australia, there was no observed increase in the population of persons with OUD or dealers in the area around the SIF (Freeman, 2005). In addition, in Australia, drug related crimes did not increase after opening of the SIF over a ten year period of observation, despite increases in most other areas in Australia during the same time period (Fitzgerald, 2010). Other studies have also found that SIFs were not associated with increased incarceration rates (Milloy, 2009), drug crimes (Wood, 2006) or theft (Wood, 2006; Freeman, 2005). One negative attribute identified was that SIFs are associated with an increase in loitering in the front and rear of the facilities (Freeman, 2005). However, this is common around MAT facilities too.

Access to Clean Needles, Drug Paraphernalia and Safe Administration Information

Source: Chicago Recovery Alliance

Distribution of clean needles, other paraphernalia and safety information is primarily aimed at reducing the transmission of blood borne diseases, adverse health effects associated with improper administration of opioids, and overdose risk. As with safe injection facilities, programs that distribute paraphernalia and education materials act as a critical point of contact with

persons with OUD to provide referrals to housing, food assistance, legal services, general medical care, testing and treatment for sexually and blood transmitted diseases, safe disposal of used needles and other equipment, information about locally accessible drug treatment services, safe injection sites, and other harm reduction strategies.

The most studied programs have been needle exchange programs which often provide clean syringes and needles, swabs, filters, cookers and other equipment for injecting drugs. One of the primary facilitators to the implementation of needle exchanges in the U.S. has been the AIDS epidemic. Studies indicate that approximately 10% of new HIV incident cases are caused by needle sharing (CDC, 2015) and up to 75% of Hepatitis C (HCV) is prevalent among persons that inject drugs (Cotter, 2018). Both blood borne diseases are very costly to both the affected individual and society at large. Lifetime cost to treat HIV and HCV ranges from $50,000 to $400,000 (Nguyen, 2014; NAS, 2017). While most research has focused on HIV and HCV, needle sharing is associated with the transmission of other blood borne diseases as well (NAS, 2017).

As with most drug related research in the U.S., legal restrictions have made it difficult to conduct studies. This has resulted in limited research on U.S. needle exchange programs which can differ substantially from programs in other countries, particularly in terms of the scope of services provided by needle exchanges. In the U.S., needle exchange programs have been established through pharmacies and public health community outreach programs (NAS, 2017). Many states and local jurisdictions have implemented policies that allow pharmacists and community organizations to distribute needles to persons without a physician prescription (typically reserved for diabetics; NAS, 2017).

Policy reforms allowing for the sale of needles/syringes without a prescription have been followed by increased sales and distribution of free equipment. During the following year after Connecticut allowed for the sale of needles and syringes without a prescription in pharmacies, 83% of pharmacies reported selling syringes without prescriptions and in areas with high injection drug use monthly syringe sales increased by 5-fold (Valleroy, 1995). New York City's program, which included comprehensive community public health distribution programs, saw an increase of 12-fold in the number of syringes distributed during the first 10 years of their program (Des Jarlais, 2005). A recent important policy change has been the lifting of restrictions on the sale of syringes from online pharmacies in most States. Online access to syringes and needles provides semi-confidential access clean syringes, but does not assist those without access to a mailing address, many of whom include some of the most vulnerable subgroups (youth and homeless). However, even when needle exchanges are available in an area, only a

fraction of persons who inject drugs get their needles from needle exchanges and many fear harassment or arrest by police for carrying drug paraphernalia (Gleghorn, 1995; Pouget, 2005).

Needle sharing is associated with a large proportion of HIV and hepatitis C transmission in the U.S. (CDC data). This is important because less than a quarter of persons who inject drugs always use sterile needles and syringes (Abbasi, 2017) and almost 10% of persons reporting injecting drugs in the past 30 days report sharing needles with others (McCoy, 1998). A contact tracing study in Indiana that investigated an HIV outbreak between 2014-2015 noted the risk that an undiagnosed contact tested positive for HIV increased by almost 2-fold if the contact was a syringe sharing partner (Peters, 2016). In addition, needle exchanges often provide testing for blood borne disease which can raise awareness in persons unaware they have been infected, and hopefully reduce further transmission of the disease (Des Jarlais, 2005; Cotter, 2018).

Research on needle exchanges, mainly from community outreach programs and exchanges outside of the U.S., have shown that they are associated with a 2 to 5-fold reduction in the transmission of HIV, HBV and HCV (Des Jarlais, 2005; Neaigus, 2008; Hagan, 2011; Potier, 2014; Aspinall, 2014; Abbasi, 2017). As stated earlier, most of these programs provide comprehensive equipment (swabs, filters, cookers) and referrals to SUD treatment services. After implementation of a national program for needle exchanges in Switzerland, risk of transmission of HIV, HBV and HCV was reduced by 80% among those who began injecting drugs in the new era with access to needle exchanges relative to those that began injecting before the national program was initiated (Somaini, 2000). A review by the CDC noted that substantial reductions in HIV and HCV can be achieved if 50% of the population injecting drugs are provided just 10 clean needles per year (Abdul-Quader, 2013). One cost analysis study showed that for each dollar invested in needle exchanges there is between $5 to $8 saved from preventing new HIV incident cases alone, which translates to $270 million USD saved in the US for every $50 million USD invested (Nguyen, 2014).

It is unclear why, but needle exchanges have been shown to be more effective at reducing the transmission of HIV than the transmission of HCV (Des Jarlais, 2005b; Abdul-Quader, 2013; Martin, 2013; Potier, 2014; Abbasi, 2017; NAS, 2017; Platt, 2017). However, a study found that combining antiviral treatment with MAT programs and needle exchanges can reduce HCV transmission by up to 50% (Martin, 2013). Another study showed that combining needle exchange programs with MAT programs were associated with reducing HCV transmission by more than half compared to programs that only provided clean needles/syringes (Turner, 2011).

Needle exchanges are also associated with a lower frequency of reusing needles (Pouget, 2005; Neaigus, 2008) and sharing needles (Turner, 2011). There is evidence that persons who inject drugs prefer getting needles and other equipment from community outreach organizations rather than pharmacies (Vorobjov, 2009; Craine, 2010), but this may be that the most vulnerable and highest risk groups of persons injecting drugs prefer the lower risk and stigma associated with fixed and mobile community based programs (Miller, 2002; Vorobjov, 2009). A large proportion of pharmacists are against policies that permit them to distribute clean needles and hold negative views of persons with SUDs (Wright-De Agüero, 1998; NAS, 2017), and less than one-third report being allowed to sell syringes by their managers despite it being legal (Wright-De Agüero, 1998).

However, even pharmacy programs show harm reduction benefits despite most pharmacy needle exchange programs providing fewer ancillary services and only providing needles/syringes instead of additional injection equipment (Sawangjit, 2017). Pharmacy needle exchange programs are shown to reduce needle sharing by half when compared to the absence of any needle exchange program (Gelghorn, 1995; Pouget, 2005; Neaigus, 2008; Sawangjit, 2017), but appear to be less effective at reducing needle sharing compared to community outreach needle exchange programs that provide more comprehensive services (Miller, 2002; Pouget, 2005; Craine, 2010; Sawangjit, 2017). It is also unclear if these pharmacy programs increase safe disposal of used equipment or reduce transmission of blood borne diseases (Neaigus, 2008; Vorobjov, 2009; Sawangjit, 2017).

In conjunction with needle exchanges, psychosocial interventions also prove effective in reducing needle sharing compared to controls with no intervention or among persons provided written materials alone (Gilchrist, 2017). These psychosocial programs involve multi-week educational programs, blood borne disease testing, counseling, behavioral and cognitive therapies, motivational interviewing, and/or contingency management interventions (programs that pay persons with SUDs to adhere to the program) (Gilchrist, 2017). Use of contingency management interventions – providing incentives to adhere to programs -- have been shown to be effective in improving retention in MAT programs (Rice, 2020) and reducing use of illicit opioids while in treatment (Griffith, 2000). However, there is inadequate evidence demonstrating positive effect of psychosocial interventions on other harm reduction behaviors or quality of life (Wild, 2021).

Access to Fentanyl Testing

A very important recent harm reduction strategy is the distribution of fentanyl test strips to persons using opioids regardless of type or mode of ingestion. Fentanyl has been repeatedly found in counterfeit prescription opioids, most heroin currently sold in the U.S., cocaine, other stimulants, and various other drugs sold illicitly (Peiper, 2019; Friedman, 2020; Karch, 2021; Oh, 2020). Some drug checking devices used on samples of seized street drugs in powder and pill form appear to have a low false negative rate of <4% for fentanyl, with a lower limit of detection around 1% of volume, even in samples with a higher percent of inert materials or adulterants (Canfield, 2020; Green, 2020; McCrae, 2020). Persons injecting drugs appear to overwhelming want to know if fentanyl is present and are concerned by the presence of fentanyl (Krieger, 2018; Allen, 2020).

Almost half of persons reporting injecting drugs in a sample from San Francisco had used a fentanyl test strip during the past year, with use of test strips being higher among younger persons, those that had witnessed an overdose, and persons who had received overdose training and naloxone (Oh, 2020). However, studies show that less than a quarter reported that they would dispose of the product that contained fentanyl instead of injecting it, and about half made no changes in dosage (Oh, 2020; Karamouzian, 2018). This coincides with findings showing that the majority of persons injecting drugs view fentanyl as unavoidable (Weicker, 2020).

Programs that have begun free distribution of fentanyl test strips report high utilization between 50-85% of persons provided test strips (Krieger, 2018; Goldman, 2019; Park, 2020; Park, 2021). Those provided test strips also reported taking more precautions during injecting drugs such as reducing dosage and having someone look after them (Krieger, 2018; Peiper, 2019; Goldman, 2019; Park, 2020; Park, 2021). Those that do reduce their dosage show a reduction in risk of overdose by almost half (Karamouzian, 2018). While utilization is high, those that test their product after consumption are far less likely to modify their dosage later compared to those that test prior to consumption (Peiper, 2019). The advent of fentanyl test strips and their distribution is relatively new which coincides with limited research on their efficacy, barriers to utilization and most importantly their impact on dose injected after a positive test result. As with other harm reduction strategies that distribute materials that are defined as drug paraphernalia by local or State laws, it is also important to remove legal barriers that discourage or criminalize the distribution, possession and use of fentanyl test strips.

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