Estimating the Magnitude and Characteristics of Prescription Opioid Injection Misuse and the Role of Syringe Services Programs in Response to the Opioid Crisis in the United States

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A Dissertation Submitted to

The Faculty of
The Milken Institute School of Public Health
of The George Washington University
in partial fulfillment of the requirements
for the degree of Doctor of Public Health

May 19, 2019

Dissertation directed by

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The Milken Institute School of Public Health of The George Washington University certifies that Christopher McCall Jones has passed the Final Examination for the degree of Doctor of Public Health as of February 4, 2019. This is the final and approved form of the dissertation.

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Abstract of Dissertation

Estimating the Magnitude and Characteristics of Prescription Opioid Injection Misuse and the Role of Syringe Services Programs in Response to the Opioid Crisis in the United States

The United States is experiencing an unprecedented crisis of prescription and illicit opioid misuse, addiction and overdose. In 2017, 47,600 Americans died from an overdose involving opioids, with 17,029 of these deaths involving prescription opioids (Centers for Disease Control and Prevention, 2018). In the same year, 11.1 million people aged 12 years and older reported misusing prescription opioids, and 1.7 million met diagnostic criteria for a past-year prescription opioid use disorder (SAMHSA, 2018). Coincident with the increase in opioid misuse and addiction in the U.S. over the past decade are rising rates of prescription opioid injection and transmission of infectious diseases such as hepatitis C virus (HCV) and endocarditis (Jones et al., 2017; Jones, 2018; Zibbell et al., 2018; Ronan & Herzig, 2016).

Following the 2015 HIV outbreak in Scott County, Indiana associated with injection of the prescription opioid oxymorphone, and a decade-long increase in viral hepatitis infection rates, especially in areas of the U.S. with long-standing prescription opioid misuse and addiction, policymakers, public health practitioners, and other stakeholders have become increasingly concerned about prescription opioid injection misuse and related harms. Studies indicate that people who inject prescription opioids have an elevated risk for HCV transmission and potentially other infectious disease transmission compared to people who inject drugs but not prescription opioids (Zibbell et al., 2014; Lankenau et al., 2015; Havens et al., 2013). This increased risk is thought to be the result of factors such as preparing oral prescription opioids for injection, high rates of

syringe sharing and reuse, sharing and injecting residual "washes", use of high dead space syringes, and engaging in multiple injections per injection episode and multiple injection episodes per day, that are not typically seen with other injected drugs (Zibbell, et al., 2014; Jones, 2018; Lankenau et al., 2015; Zule, et al., 2016; Broz, et al., 2018). Thus, a pressing public health policy concern is identifying and scaling up interventions to reduce prescription opioid injection and its associated harms.

Syringe Services Programs (SSPs) – evidence-based programs that provide sterile injection equipment and comprehensive infectious disease, substance use, and overdose prevention and treatment services – have been identified as a potential key intervention in response to the opioid crisis and increasing opioid injection. However, there is limited recent research characterizing the population of people injecting prescription opioids and other drugs that can help guide how to best position SSPs to reach and impact this population. Further, the policy environment for SSPs is rapidly evolving, with multiple states enacting laws, regulations, and policies in recent years to enable the establishment of SSPs. Collectively, the research gaps around prescription opioid injection and the changing policy environment for SSPs has created a critical need to better define the characteristics of people who inject prescription opioids, to identify the services and resources needed by this population, and to understand how SSPs are navigating the evolving policy environment in order to maximize their role in response to the opioid crisis.

This dissertation research aims, through the use of mixed methods, to address these knowledge and policy gaps through: 1) systematically reviewing the literature to synthesize what is known about the population of individuals who inject prescription

opioids in the U.S.; 2) estimating the magnitude of prescription opioid injection in the United States; 3) examining overall, sociodemographic, and substance use trends and correlates of prescription opioid injection among a nationally representative sample to identify populations at-risk for prescription opioid injection and related harms; and 4) using these quantitative findings to inform a qualitative exploration of SSPs' responses to the rapidly changing policy environment in the midst of the evolving opioid epidemic and how they can be further leveraged to reduce the harms associated with opioid injection. This dissertation accomplishes these aims through three separate, but related studies.

The first study provides a synthesis of the available peer-reviewed literature on the prevalence of prescription opioid injection misuse, the sociodemographic characteristics of people who inject prescription opioids, and the health outcomes associated with prescription opioid injection misuse in the U.S. based on a systematic review of the published literature from 2000 to 2017. The study also identifies areas for future research based on gaps identified during the systematic review.

Based on the systematic review, the prevalence of prescription opioid injection has increased significantly in the past decade, with an overall estimated prevalence of lifetime prescription opioid injection among people 12 years and older in the U.S. of approximately 0.3%, and a prevalence among people with opioid use disorder estimated at 16%-25%. The review also identified demographic, socioeconomic, and clinical characteristics that were consistently associated with prescription opioid injection. In addition, the study identified a significant increase in risk for risky injection practices such as syringe sharing and reuse and subsequent transmission of infectious disease among people who inject prescription opioids. The findings of this systematic review

have important implications for opioid prevention and treatment policy and clinical practice, including the need to expand opioid use disorder prevention and treatment services, to have access to preventive services, testing, and treatment for HIV and viral hepatitis, and to increase availability of SSPs that can provide comprehensive risk reduction services to people who inject drugs (PWID). Finally, the study concluded there is a pressing need for additional research on the prevalence and characteristics of people who inject prescription opioids and other drugs.

The second study provides the first nationally representative analysis of prescription opioid injection trends in the U.S. using data from the 2003-2014 National Surveys on Drug Use and Health. This study provides estimates on the magnitude of prescription opioid injection and identifies key correlates of prescription opioid injection, including quantifying the extent of unsafe injection practices and syringe sources for people who inject prescription opioids.

The study found that rates of prescription opioid injection misuse increased 65% among people 12 years or older during the study period. By 2012–2014, 710,100 people in the U.S. had reported ever injecting prescription opioids, an increase of more than 300,000 people since 2003–2005. The increase in prescription opioid injection misuse occurred across a broad range of demographic and substance using groups, with particularly large increases among women, non-Hispanic whites, and people aged 18–25 years. The study also found high rates of syringe reuse and sharing with nearly 60% of people who have ever injected prescription opioids reporting reuse of their own needle the last time they injected, and roughly 1 in 5 reporting reuse of someone else's needle as well as allowing someone else to reuse their needle. Only 2.3% of individuals reporting

lifetime prescription opioid injection reported getting their most recent syringe from an SSP. The study concluded that there is a critical need to bring to scale evidence-based interventions that prevent prescription opioid misuse, increase the provision of medication-assisted treatment for opioid use disorders, and expand access to comprehensive services such as those provided by SSPs that reduce injection-related harms.

The third study uses applied qualitative methods to explore and describe how SSPs are responding to the evolving opioid epidemic and rapidly changing policy environment. In addition, the study identifies barriers SSPs are facing, as well as facilitators, innovative collaborations, and successful strategies SSPs are pursuing to meet the needs of the expanding population of people injecting opioids and other drugs and address the evolving opioid crisis.

The study found that despite progress in expanding the number of SSPs in recent years, some participating programs are facing multiple legal, policy, funding, and community barriers. However, programs also described strategies they are deploying to address these barriers, taking into account how specific barriers were playing out in the state or local context of the program.

The study concluded that SSPs continue to encounter multiple barriers that are limiting the number, scope, and reach of SSPs. To counter these barriers, SSPs are employing multiple strategies to engage policymakers and communities, strengthen their funding base, and reach at-risk populations. Coupling these strategies with policy changes that address the underlying legal and financial barriers facing SSPs and strengthening efforts to combat stigma related to drug use and addiction can substantially

expand the role of SSPs as part of the public health response to the opioid crisis in the U.S.

The three studies conducted as part of this dissertation provide key insights into prescription opioid injection trends, demographic, socioeconomic, geographic, clinical characteristics, and health outcomes associated with prescription opioid injection, and the experiences of SSPs in the midst of the opioid crisis and a rapidly evolving policy environment. Taken together, the new knowledge produced from this dissertation can be used to inform the development, prioritization, and implementation of policies, programs, and practices that aim to reduce prescription opioid injection and its related harms and expand the role of SSPs in response to the U.S. opioid crisis.

Table of Contents

Abstract of Dissertation.....……....iv

List of Figures…….xi

List of Tables….……xii

Chapter 1: Introduction……1

Chapter 2: Prescription Opioid Injection Misuse in the United States:
A Narrative Review of the Literature…..……..29

Chapter 3: Trends and Key Correlates of Prescription Opioid Injection
Misuse in the United States……..……..68

Chapter 4: Syringe Services Programs: An Examination of Legal, Policy,
and Funding Barriers In the Midst of the Evolving Opioid Crisis in the U.S…….....91

Chapter 5: Conclusion……..142

References……154

Appendix A……..180

List of Figures

Figure 1…….....9

Figure 2……..10

Figure 3……..18

Figure 4……..19

Figure 5……..20

Figure 6……..23

Figure 7……..28

Figure 8……..33

Figure 9……..60

Figure 10……82

List of Tables

Table 1……6

Table 2……...11

Table 3……...22

Table 4……...34

Table 5……...41

Table 6……...49

Table 7……...56

Table 8……...76

Table 9……...80

Table 10……83

Table 11……98

Table 12……...100

Chapter 1: Introduction

The United States is in the midst of an unprecedented crisis of prescription and illicit opioid misuse, addiction, and overdose. Prescription opioid misuse and its associated health and social consequences have impacted the U.S. for more than a decade. In 2017, 47,600 Americans died from an overdose involving opioids, with 17,029 of these deaths involving prescription opioids (Centers for Disease Control and Prevention, 2018). In the same year, 11.1 million people aged 12 years and older reported misusing prescription opioids, and 1.7 million met diagnostic criteria for a past-year prescription opioid use disorder (SAMHSA, 2018).

Concerns related to rising rates of prescription opioid injection and related harms have emerged in recent years due to the 2015 outbreak of 181 HIV cases in Indiana associated with injection of the prescription opioid oxymorphone, stabilization of HIV rates since 2010 for nonurban and since 2012 for urban whites who inject drugs, and a decade of rising rates of HCV and HBV, especially in areas with long-standing prescription opioid misuse and addiction (Peters et al., 2016; Wejnert et al., 2016; Suryaprasad et al., 2014; Zibbell et al., 2015; Harris et al., 2016). Thus, a current pressing public health policy concern is to identify and scale up interventions that can reduce opioid injection misuse and related harms.

Syringe Services Programs (SSPs) – evidence-based programs that provide sterile needles and syringes, other injection equipment, and syringe disposal, as well as comprehensive infectious disease, substance use, and overdose prevention and treatment services – have been identified as a potential key intervention that can significantly impact the opioid epidemic and reduce the harms associated with opioid injection (World

Health Organization (WHO), 2004; Belani et al., 2012; Wilson et al., 2015; U.S. Department of Health and Human Services (DHHS), 2016). However, there is limited recent research characterizing the population of people injecting prescription opioids and other drugs that can help guide how to best position SSPs to reach and impact this population. Further, the policy environment for SSPs is rapidly evolving, with multiple states enacting laws, regulations, and policies in recent years to enable the establishment of SSPs. These knowledge and policy gaps have created a critical need to better define the characteristics of people who inject prescription opioids, to identify the services and resources needed by this population, and to understand how SSPs are navigating the evolving policy environment in order to maximize their role in response to the opioid crisis.

PRESCRIPTION OPIOID INJECTION AND HEALTH HARMS

Injection drug use is a highly efficient mechanism to transmit blood-borne infectious diseases such as HIV, HCV, and HBV as well as skin and soft tissue infections and infectious endocarditis (Gerberding, 1995; Lansky et al., 2014; Holtzman et al., 2009; Ronan & Herzig, 2016; Wurcel et al,, 2016). In the U.S., approximately 9% of new HIV infections are attributed to injection drug use (Wejnert et al., 2016), 16% of persons with acute HBV infections report injection drug use, (CDC, 2011) and nearly 70% of individuals reporting risk behaviors for HCV report engaging in injection drug use (CDC, 2015). People who inject drugs also are at increased risk for substance use disorders, drug overdose, and engaging in high-risk sexual behaviors (Degenhardt et al., 2010; Silva et al., 2013; Lake & Kennedy, 2016; Belani et al., 2012; Spiller et al., 2015; Zule et al., 2016).

Research indicates that people who misuse opioids over time often move from less dangerous routes, such as oral misuse, to more dangerous routes, such as injection (Black et al., 2013). Non-oral routes of misuse, especially injection misuse, provide faster drug delivery and onset compared to oral use, thereby intensifying the reinforcing, euphoric effects of opioids and increasing vulnerability to addiction (Compton & Volkow, 2006; Katz et al., 2008; Silva et al., 2013). Multiple qualitative studies have described a trajectory from oral opioid misuse to non-oral/non-injection routes to injection of prescription opioids and in some cases concurrent or subsequent injection of heroin or other illicit opioids (Lankenau et al., 2012; Pollini et al., 2011; Peavy et al., 2012; Mateu-Gelabert et al., 2014; Mars et al., 2014; Inciardi et al., 2009).

Injection may be the most dangerous route of misuse as it is associated with significant public health consequences, such as: increased risk of overdose, psychiatric comorbidity, right-sided endocarditis, increased emergency department visits, mortality, and the transmission of infectious diseases such as HIV and HCV due to sharing of syringes and other injection equipment (Black et al., 2013; Surratt et al., 2011; Havens et al., 2007; Young et al., 2010; Silva et al., 2013; Ronan & Herzig, 2016; Lankenau et al., 2015; Zibbell et al., 2014; Zibbell et al., 2015; Peters et al., 2016). Importantly, the risk for certain negative health effects may be higher for prescription opioid injection compared to injection of other drugs. Studies have found that prescription opioid injection remains a risk factor for HCV even after accounting for injection of other drugs, including heroin, likely as a result of factors such as the process of preparing oral prescription opioids for injection, sharing and injecting residual prescription opioid "washes", and use of high dead space syringes (Roy et al., 2011; Zibbell et al., 2014;

Lankenau et al., 2015; Zule et al., 2016). In addition, aspects of prescription opioid formulations, including other active and inactive ingredients such as talc, can increase risk for injection-related skin complications and infections (Lake & Kennedy, 2016; Roux et al., 2011; Roy et al., 2011; Katz et al., 2011).

Although recent research indicates that overall prescription opioid misuse appears to be stabilizing or declining, (Dart et al., 2015; SAMHSA, 2018) subsequent studies have found that the frequency and intensity of prescription opioid misuse use and opioid use disorders have increased among multiple demographic groups even as overall misuse has declined (Han et al., 2015; Jones, 2016). This suggests that more problematic use, including injection misuse, and associated morbidity and mortality will continue to increase. Further, the recent increases in heroin use and overdose linked to people who first misused prescription opioids before initiating heroin use, and the rapid proliferation of illicitly made fentanyl being mixed with or sold as heroin or other illicit drugs leading to high numbers of overdoses, point to the extraordinary urgency of preventing opioid misuse and opioid injection and reducing injection-related harms among people who already inject opioids (Jones, 2013; Jones et al., 2015; Gladden et al, 2016, Jones et al., 2018).

THE EVIDENCE FOR SYRINGE SERVICES PROGRAMS

The World Health Organization (WHO), HHS, CDC, and other scientific organizations have, at different points in time, reviewed the evidence on SSPs and stated that SSPs are an evidence-based approach to reducing injection-related risk behaviors and the transmission of infectious diseases such as HIV and HCV when implemented as part of a comprehensive strategy to address injection-related harms (WHO, 2004; DHHS,

1998; Belani et al., 2012; Institute of Medicine, 2002). A 2014 systematic review of SSPs found that the primary components of SSPs (syringe/needle exchange, provision of sterile drug preparation equipment, methadone and buprenorphine treatment for opioid use disorder, and risk reduction information, education, and counseling) were effective at reducing injection-related risk behaviors and transmission of HIV and HCV (MacArthur et al., 2014).

Research has consistently shown that SSPs are most impactful when they provide the full complement of risk reduction services including distribution of sterile syringes/needles and other injection equipment, risk reduction education, infectious disease testing, counseling and linkages to treatment, provision of or linkages to substance use treatment, in particular medication-assisted treatment for opioid use disorder, and overdose education and naloxone distribution (Degenhardt et al., 2010; MacArthur et al., 2014; Abdul-Quader et al., 2013; Belani et al., 2012; Hagan et al., 2011).

Impacts on Injection-related Risk Behaviors

A number of studies in the U.S. have examined the effectiveness of SSPs on injection-related risk behaviors (IRBs) such as syringe/needle sharing and reuse and sharing of other injection and drug preparation equipment. Among SSP users in Chicago, Ouellet et al., found significant reductions in IRBs among regular users of the SSP compared to nonusers (**Table 1**) (Ouellet et al., 2004).

Table 1. Injection Risk Practices Among SSP users compared to SSP Nonusers, Chicago, Illinois (Ouellet, 2004)

Injection Risk Practice	Adjusted Odds Ratio (95% CI)
Receptive needle sharing	0.30 (0.19-0.46)
Bleach needle before receptive sharing (among those who share receptively)	1.17 (0.57-2.41)
Always bleach needle before receptive sharing (among those who shared receptively)	3.63 (1.83-7.17)
Gave own used needle to someone	0.47 (0.31-0.71)
Backloaded	0.33 (0.22-0.52)
Shared cooker	0.39 (0.25-0.61)
Shared cotton	0.48 (0.32-0.72)
Shared water	0.41 (0.24-0.63)
Multiple injections with same needle	0.15 (0.08-0.27)

Findings of similar magnitude and direction for syringe/needle sharing and reuse behaviors have been reported in multiple studies in the U.S., although the findings related to reduced sharing of other injection equipment (cookers, cotton, washes) are more mixed. Among HIV-infected SSP users in Baltimore, between baseline and 6 month follow up, use of the SSP reduced lending syringes (34% vs 16%, $p<0.01$), using someone else's syringe (23% vs 11%, $p<0.01$), sharing cookers (70% vs 53%, $p<0.01$), sharing cotton (59% vs 39%, $p<0.01$), daily cooker sharing among those who did share (54% vs 22%, $p<0.01$), and daily cotton sharing among those who did share (41% vs 14%, $p<0.01$) (Vertfeuille et al., 2000).

Using data from four large U.S. cities between 1994 and 2004, Holtzman et al., found that recent SSP use was associated with significantly reduced odds of sharing

needles (aOR = 0.77; 95% = 0.67-0.88), but not sharing other injection equipment (aOR = 0.89; 95% CI = 0.77-1.04) (Holtzman et al., 2009). Bluthenthal et al., found SSP users were significantly less likely to share syringes compared to non-SSP users (aOR = 0.57; 95% CI = 0.46-0.72); however, they did not find a protective effect of SSPs on sharing of other injection equipment (aOR = 0.85; 95% CI = 0.68-1.07) (Bluthenthal et al., 1998). Similarly, among SSP users in Seattle, Hagan et al., reported that SSP use was associated with lower odds of injection with a used syringe (aOR = 0.7; 95% CI = 0.5-0.9), but not with cooker or cotton sharing (aOR = 0.8; 95% CI = 0.6-1.1) (Hagan et al., 2000).

The most recent data on IRBs come from the SSP implemented as part of the Scott County, Indiana HIV outbreak in 2015. Among SSP users, there were significant reductions between first visit to the SSP and most recent visit in sharing syringes to inject (34% vs 5%, $p=0.04$), median frequency of syringe reuse (4 vs 1, $p<0.001$), median number of syringes returned (0 vs 47, $p<0.001$), and median number of syringes given (35 vs 42, $p=0.004$). The researchers did not find significant reductions in sharing syringes to divide drugs (38% vs 10%, $p=0.17$) or sharing other injection equipment (44% vs 11%, $p=0.52$) (Patel et al., 2015).

Although sharing of other injection equipment did not reach statistical significance in several studies, there was consistency in the direction of the relationship. Research suggests the mixed findings related to sharing of other injection equipment is likely the result of a lack of focus on risk reduction messages for risks related to sharing equipment relative to messages for risks related to sharing of syringes/needles. This lack of focus on efforts to reduce sharing of other injection equipment stems from two primary issues. First, for both HIV and HCV, the sharing of used syringes/needles carries the

greatest risk for infectious disease transmission so the main focus has historically been on this behavior. Second, although the risk of transmission associated with the sharing of other injection equipment (cookers, cotton, washes) is lower than that for syringe/needle sharing, the risks for HIV and HCV transmission are not equal; the risk for transmission of HIV is much lower than that for HCV due to HCV's much greater ability to survive and persist in the environment. Thus, given this differential risk and the fact that HIV was the primary public health prevention concern for people who inject drugs for many years, there was less focus on educating these individuals about sharing other injection equipment relative to the sharing of syringes/needles (Ciesek et al., 2010; Hagan et al., 2001; Hagan et al., 2011).

Researchers have also examined the absence of SSPs on IRBs. After the closure of a SSP in Connecticut, researchers found that access to sterile syringes was significantly reduced. Prior to closure, 14% of survey respondents reported a non-sterile primary source for syringes; after closure this increased to 51% ($p<0.001$). In addition, respondents reported a 118% increase in syringe reuse and a 113% increase in syringe sharing after closure (Broadhead et al., 1999) Neaigus et al., compared IRBs in New York City, a city with SSPs, to Newark, New Jersey, a city without SSPs, and found that people who injected drugs in Newark, after controlling for potential city-level confounders, were less likely to obtain syringes from SSPs or pharmacies (aOR = 0.004; 95% CI = 0.001-0.01), more likely to obtain syringes from street sellers (aOR = 74.0; 95% CI = 29.9-183.2), more likely to inject with someone else's syringe (aOR = 2.3; 95% CI = 1.1-5.0), more likely to reuse syringes (aOR = 2.99; 95% CI = 1.63-5.50), and

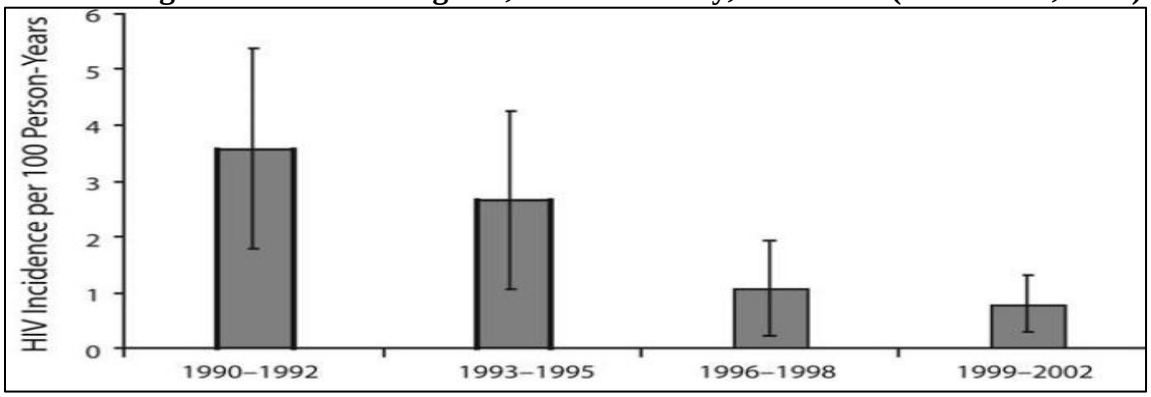
more likely to not always inject once only with a new, sterile syringe that had been sealed in a wrapper (aOR = 5.4; 95% CI = 2.9-10.3), (Neaigus et al., 2008).

Impacts on Transmission of HIV infection

The WHO states "there is compelling evidence that increasing the availability and utilization of sterile injecting equipment for both out-of-treatment and in-treatment injecting drug users contributes substantially to reductions in the rate of HIV transmission." (WHO, 2004). The CDC and DHHS also state that SSPs, as part of a comprehensive HIV prevention strategy, are an effective intervention to reduce the transmission of HIV (Belani et al., 2012; DHHS, 1998).

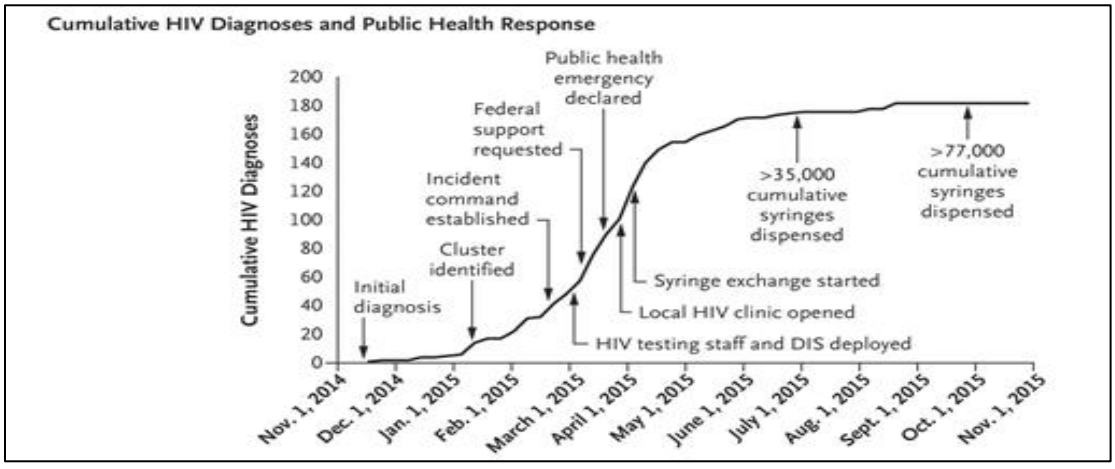
Studies in the U.S. consistently demonstrate positive effects of SSPs on HIV transmission. Des Jarlais et al., found that expansion of HIV prevention services, primarily through rapid scale-up of SSPs, in New York City was associated with a persistent decline between 1990 and 2002 in the annualized HIV incidence rate among people who inject drugs - declining from 3.55 (95% CI = 1.73-5.37) in 1990-1992 to 0.77 (95% CI = 0.28-1.26) in 1999-2002 ($p<0.0001$) (**Figure 1**). The HIV prevalence among people who inject drugs also declined during the study from 50% in 1990-1992 to 17% in 1999-2002 ($p<0.0001$) (Des Jarlais et al., 2005).

Figure 1. HIV Incidence Among Injection Drug Users Entering Beth Israel Medical Center Drug Detoxification Program, New York City, 1990-2002 (Des Jarlais, 2005)



Using HIV surveillance data for 1996 through 2011, Ruiz et al., demonstrated that expansion of SSPs due to a funding-related policy change in Washington, DC was associated with 120 averted HIV cases in the 24 months after the change (Ruiz et al., 2015). Neaigus et al., reported that people who live in Newark, New Jersey, a city without SSPs, who inject drugs were significantly more likely to test seropositive for HIV compared to people who inject drugs living in New York City, a city with SSPs, (aOR = 3.2; 95% CI = 1.6-6.1) (Neaigus et al., 2008). Assessing the impact of SSPs on HIV seroprevalence in 81 cities (54% of cities were in North America), Hurley et al., found that HIV seroprevalence, on average, increased by 5.9% per year in the 52 cities without SSPs compared to a decrease of 5.8% per year in the 29 cities with SSPs. In addition, the average annual change in HIV seroprevalence was 11% lower in cities with SSPs compared to those without SSPs ($p<0.004$) (Hurley et al., 1997). As demonstrated in **Figure 2**, the implementation of an SSP and rapid expansion of syringe distribution in Scott County, Indiana, coupled with substance use treatment and HIV treatment, was temporally associated with a bending of the HIV epidemic curve (Peters et al., 2016).

Figure 2. Cumulative HIV Diagnoses and Public Health Response, Scott County, Indiana, 2014-2015 (Peters, 2016)



Impact on transmission of viral hepatitis

HCV is the most common infectious virus associated with injection drug use. Hagan et al., found significantly reduced odds of HCV and HBV among SSP users compared to nonusers in Tacoma, Washington. Specifically, after adjusting for demographic characteristics and duration of injection drug use, odds for nonusers of the SSP were: HCV (aOR = 7.3; 95% CI = 1.6-32.8) and HBV (aOR = 5.5; 95% CI = 1.5-20.4) (Hagan et al., 1995). However, in a similar study comparing SSP users to nonusers in Seattle, Washington, Hagan et al., found no association between SSP use and HCV or HBV (**Table 2**) (Hagan et al., 1999). The authors posit that the difference in findings is likely due to dilution bias in that SSP nonusers may have had access to sterile syringes from other sources such as pharmacies or other community-based programs thus diluting the effect of the SSP as well as selection bias for SSP users in that those who were at higher risk for hepatitis may have been more likely to be SSP users, highly efficient transmission of hepatitis via syringes and needles as well as other injection equipment, and the higher background rate of hepatitis in the Seattle drug using population (Hagan et al., 1999, Hagan et al., 2000).

Table 2. HCV and HBV Seroconversion By SSP Use Status, Seattle, Washington (Hagan, 1999)

	HCV Seroconversion	**HBV Seroconversion**
SSP Use	**Adjusted Relative Risk (95% CI)**	**Adjusted Relative Risk (95% CI)**
Never	1.0	1.0
Current - Sporadic SSP Use	2.59 (0.79-8.5)	2.36 (0.86-6.47)
Current - Regular SSP Use	1.31 (0.79-2.19)	1.81 (0.69-4.77)

Examining HCV prevalence among people who inject drugs entering a large detoxification program in New York City, Des Jarlais et al., found a decline between 1990-1991 and 2000-2001 in HCV prevalence overall from 90% to 63% and from 80% to

59% among people who were HIV-negative. In addition, the authors found that HCV prevalence among new injectors (those injecting for 6 years or less) was 86% in 1990-1991 compared to 38% in 2000-2001. These declines correspond with a substantial expansion of SSPs in New York City which began in 1992 when approximately 250,000 syringes were distributed versus the approximately 3,000,000 syringes distributed in 2000-2001 (Des Jarlais et al., 2005). Comparing New York City to Newark, New Jersey, consistent with findings for higher risk for IRBs and HIV prevalence, Neaigus et al., reported significantly increased odds for having antibody to the HBV core antigen (aOR = 4.4; 95% CI = 2.8-6.9) and antibody to HCV (aOR = 3.0; 95% CI = 1.8-4.9) among people who inject drugs in Newark where there was no access to SSPs (Neaigus et al., 2008).

Impacts on drug use

Despite an evidence base supporting the effectiveness of SSPs, persistent concerns that SSPs will increase initiation into injection drug use, increase the duration or frequency of injection, and generally increase drug use have limited the number and role of SSPs in the U.S. Several studies have sought to address these important research questions. Fisher et al., using a randomized controlled trial design, found that use of an SSP was not associated with increased drug injection nor was it associated with more positive urine drug screens for morphine or amphetamine (a surrogate marker for increased drug use) (Fisher et al., 2003). Similarly, in a study comparing SSP users to nonusers in Chicago, Hou et al., reported that drug use frequency did not increase among SSP users during the study period compared to nonusers of SSPs (Hou et al., 2006).

Among people who inject drugs in Seattle, Hagan et al., found that drug use did not increase among SSP users and that people who had previously used the SSP compared to never users of the SSP were significantly more likely to reduce injection frequency (aRR = 2.85; 95% CI = 1.47-5.51), discontinue injection (aRR = 3.5; 95% CI = 2.1-5.9), and were 60% more likely to remain in methadone treatment at one year follow up (Hagan et al., 2000). SSPs serving as a bridge to substance use treatment was also found among SSP users in Baltimore where 19% of SSP users in the study were attending substance use treatment at 6 months follow up compared to 8% at baseline ($p<0.001$) (Vertefeuille et al., 2000).

Based on the totality of the available data, the WHO has stated "There is no convincing evidence of major unintended consequences of programs providing sterile injection equipment to injecting drug users, such as initiation of injecting among people who have not injected previously, or an increase in the duration or frequency of illicit drug use or drug injection." (WHO, 2004). Yet, despite this declaration from the WHO and the data from numerous studies showing no increase in risk behaviors among people who inject drugs accessing SSPs, there has been a persistent, and strongly held belief that SSPs encourage drug use and risk behaviors. This belief has been reflected in Federal, state, and local public health policy for many years, and has greatly limited the reach of SSPs as the opioid epidemic has evolved.

THE POLITICAL AND LEGAL HISTORY OF SSP IN THE UNITED STATES

Despite a robust evidence base, SSPs have been limited in scale and scope in the U.S. due to a number of persistent legal, policy, political, and funding issues (Lurie et al., 1997; Bramson et al., 2015; Des Jarlais et al., 2016; Weinmeyer et al, 2016). In the U.S.,

the first SSPs were implemented in the late 1980s in large urban centers such as San Francisco, New York, Tacoma, and Portland, each of which had a recognized injection drug use problem and the political capacity to implement SSPs (Clarke et al., 2016). However, unlike in many other developed countries where SSPs were being implemented broadly as a recognized evidence-based public health intervention, a lack of political support and opposition from substance use treatment providers, law enforcement, and many communities substantially limited implementation of SSPs more broadly in the U.S. (Lurie et al., 1997; Hurley et al., 1997).

In 1988, Congress prohibited the use of federal funds for SSPs due to concerns that funding would signal government endorsement of illicit drug use, contradict law enforcement efforts and messages, and imply to young people that drug use is acceptable. Many opponents also believed that funding SSPs would worsen the public health consequences of drug use by increasing illicit drug use and injection drug use in particular (Fisher et al., 2003; Lurie et al., 1997; Clarke et al.,2016). This lack of political support and explicit stigma towards drug use facilitated the implementation of an inefficient and uneven patchwork of laws, regulations and policies for SSPs around the country. In many areas, laws, regulations, and policies were enacted to criminalize possession of syringes, needles, and other injection equipment as well as directly outlaw the implementation of SSPs (Lurie et al., 1997; Bramson et al., 2015; Clarke et al., 2016; Weinmeyer et al., 2016). Operationally, this meant that many states did not implement SSPs and those that did either did so with little political support and limited resources or did so without explicit legal authorization.

The federal funding ban was lifted in the FY2010 Consolidated Appropriations Act and in July 2010, the U.S. Department of Health and Human Services issued guidelines for programs interested in using federal funds to support SSPs (DHHS, 2010; Fisher et al., 2016). This shift in policy was largely due to the change in Presidential Administrations and concurrent large democratic majorities in Congress which supported a shift in Federal drug policy from a criminal justice focus to a public health focus. However, this policy change was short-lived and the ban was subsequently reinstated in the FY2012 budget as part of a budget compromise between the Obama Administration and the new Republican-controlled Congress (Weinmeyer et al., 2016). In addition to being short-lived, a study of SSPs conducted while the ban was lifted found the HHS requirements for certification in order to receive federal funds were burdensome and that many SSPs anticipated significant challenges in receiving the funds. The authors concluded that "there may be legal, programmatic, implementation, political, and cultural challenges to seeking and complying with [HHS] requirements of federal funding. Lifting the federal funding ban will not improve funding prospects for [SSP] operations for programs without local health department connections, local support, and highly structured operations." (Green et al., 2012).

The reinstatement of the funding ban was criticized by many in the harm reduction and public health communities (Green et al., 2012, Weinmeyer et al., 2016), however, it occurred during a time when the impacts of the opioid epidemic in the U.S. and its connection with injection drug use were not fully appreciated. Since that time, there has been a growing recognition among the medical and public health communities,

policy-makers, and the general public that the U.S. is experiencing an unprecedented opioid crisis.

The fact that SSPs have historically been operated in large urban areas and mostly concerned with injection of illicit drugs such as heroin has limited the reach of SSPs both in terms of providing services to people injecting prescription opioids in urban communities, but also limited their reach in suburban and rural areas which have disproportionately been impacted by the opioid epidemic. Indeed, research has shown that SSPs are much less likely to be implemented in more rural and suburban areas of the U.S., especially those in the South or Midwest – areas that have been heavily impacted by prescription opioid misuse, including rising rates of prescription opioid injection (Zibbell et al., 2015; Suryaprasad et al., 2014; Des Jarlais et al., 2015). In fact, a recent study estimated that only 6.9% of syringes distributed through SSPs were distributed in rural areas of the U.S. (Des Jarlais et al., 2015) despite a 2015 study showing that rates of lifetime and past-year injection drug use increased as urbanicity decreased (Oster et al., 2015). Not surprisingly, a recent study that identified the 220 U.S. counties at highest risk for rapid dissemination of HIV or HCV infections among people who inject drugs were largely rural counties and counties in the South (Van Handel et al., 2016).

Recognizing these pressing concerns and despite lingering political and community opposition, on the heels of the 2015 HIV outbreak in Scott County, Indiana, a number of states, including Ohio, Kentucky, Indiana, and West Virginia – states with high rates of opioid morbidity and mortality – have passed laws or enacted regulations allowing for the implementation of SSPs under certain conditions (Ohio Amended Substitute House Bill 64, 2015; Kentucky Revised Statute, 2015; Indiana Senate Enrolled

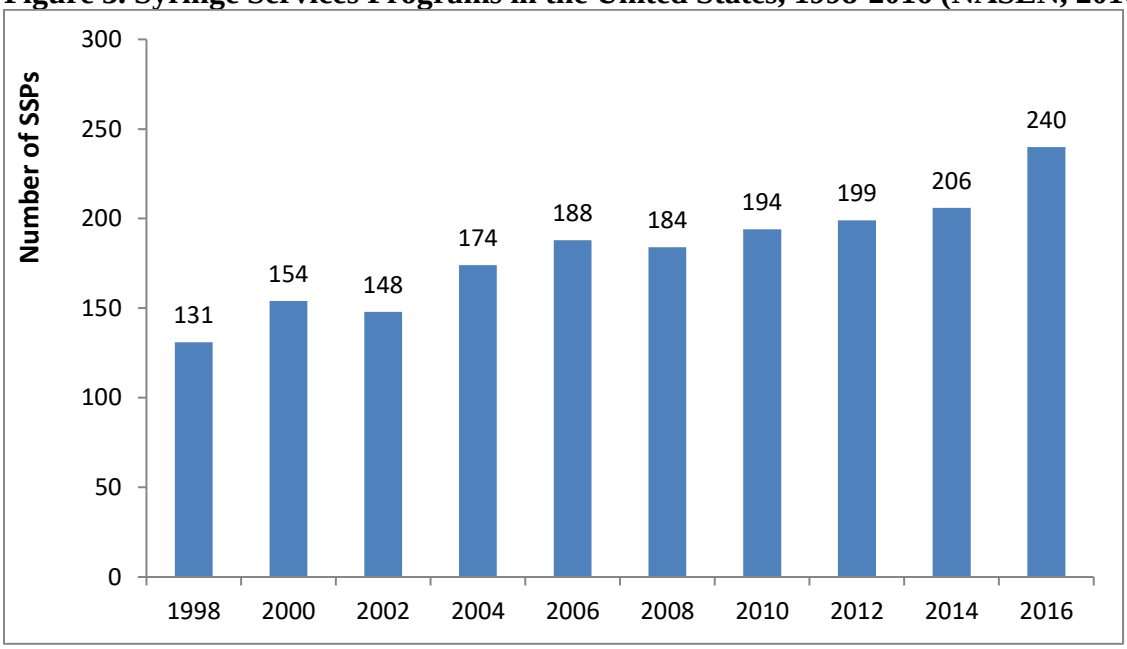
Act 461, 2015; City of Huntington, WV, 2016). Further, the U.S. Congress, in December 2015, through the FY2016 Consolidated Appropriations Act, partially lifted the ban on the use of Federal funds to support certain services offered by SSPs once specific criteria have been met (U.S. Congress Consolidated Appropriations Act, 2015). Specifically the law states:

> "Notwithstanding any other provision of this Act, no fund appropriated in this Act shall be used to purchase sterile needles or syringes for the hypodermic injection of any illegal drug: *Provided*, That such limitation does not apply to the use of funds for elements of a program other than making such purchases if the relevant State or local health department, in consultation with the Centers for Disease Control and Prevention, determines that the State or local jurisdiction, as applicable, is experiencing, or is at risk for, a significant increase in hepatitis infections or an HIV outbreak due to injection drug use, and such program is operating in accordance with State and local law."

CURRENT STATE OF SYRINGES SERVICES PROGRAMS

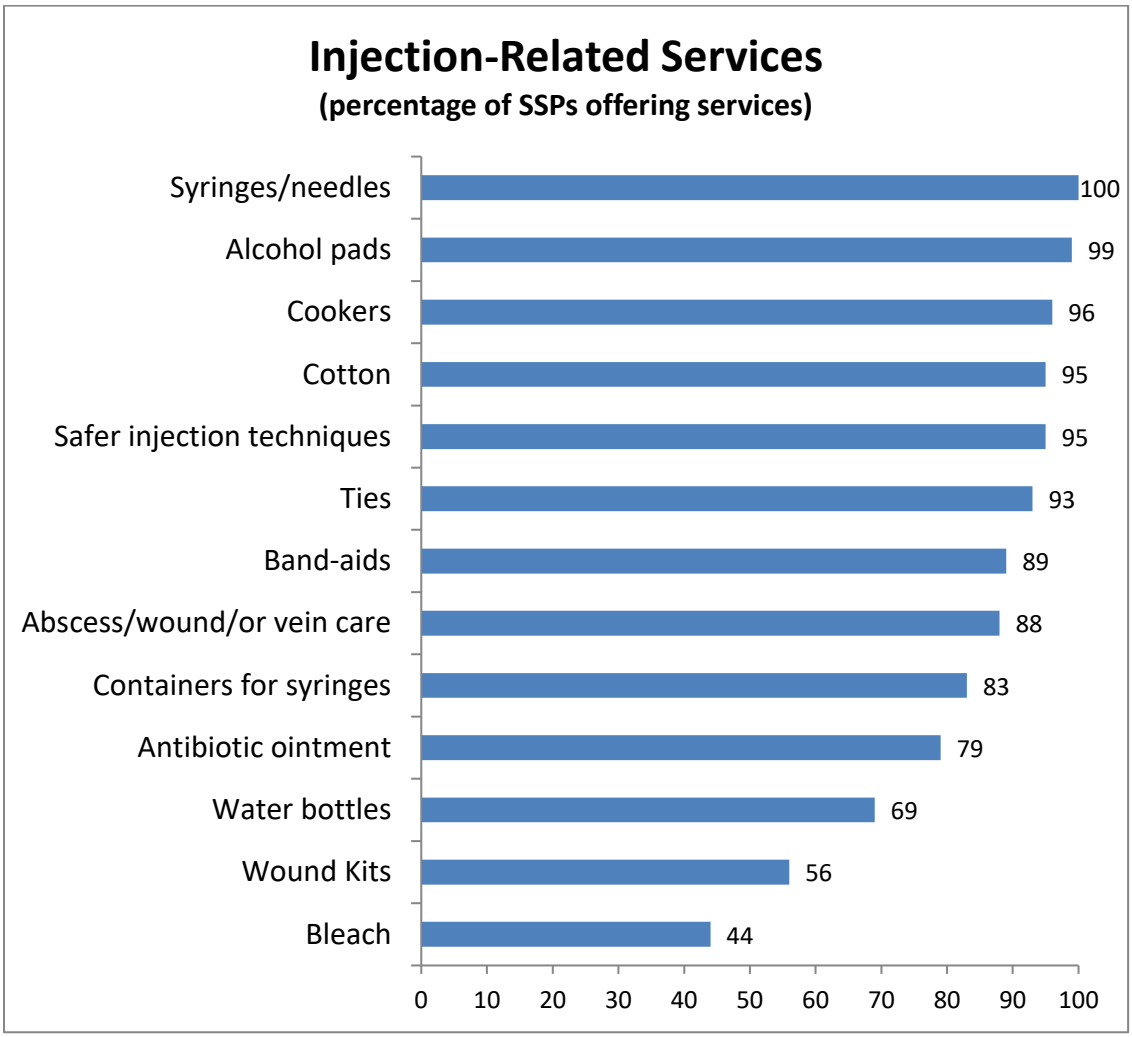
The number of SSPs has increased in recent years. According to the North American Syringe Exchange Network (NASEN, 2016), there were 240 known SSPs operating in the U.S. in 2016, an increase from 131 in 1998 (**Figure 3**). SSPs are typically free-standing, fixed-location programs that have pre-specified operating hours where syringes, needles, and other injection equipment, and other harm reduction activities are provided. Some programs are housed within or affiliated with larger medical programs such as Community Health Centers; others operate mobile van exchanges or utilize individuals to distribute or exchange syringes, needles and other injection equipment in locations known to people who inject drugs.

Figure 3. Syringe Services Programs in the United States, 1998-2016 (NASEN, 2016)



A 2014 survey of SSPs provides important insight into the injection-related services currently offered by these programs. All of the SSPs surveyed reported providing syringes and needles to individuals, and virtually all provided sterile injection equipment such as alcohol pads, cookers, cotton, and ties as well as education on safer injection techniques (**Figure 4**). Other commonly provided services included Band-Aids, abscess, wound, or vein care, containers for syringes, antibiotic ointment, water bottles, and wound kits. Bleach to clean injection equipment was provided by a large minority of programs (Des Jarlais et al., 2014).

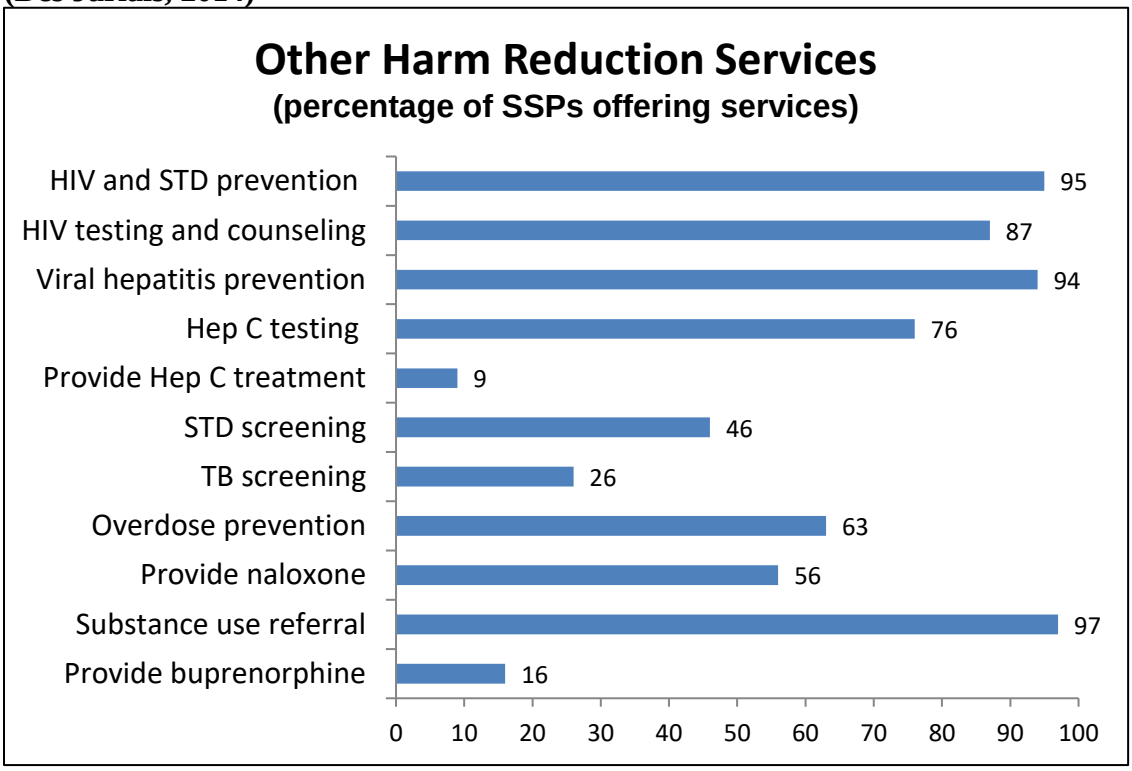
Figure 4. Injection Related Services Offered by Syringe Services Programs (Des Jarlais, 2014)



In addition to services related to injection practices and sterile injection equipment, SSPs offered other harm reduction services (**Figure 5**). The majority offered HIV, viral hepatitis, and STD prevention services such as education on risk reduction practices for HIV, viral hepatitis, and STDs; conducted HIV and HCV testing and counseling for individuals who expressed interest in receiving testing and counseling; provided referrals to substance use treatment as well as direct referrals to treatment providers affiliated with the SSP.

A smaller percentage of SSPs provided overdose education and naloxone distribution where individuals through one-on-one or group classes are trained in how to prevent, recognize, and respond to an opioid overdose, including the administration of naloxone. A minority of SSPs screened for other STDs such as gonorrhea and syphilis as well as screened for TB. A small minority of SSPs directly provided medical treatment for HCV or medication-assisted treatment for opioid use disorder with buprenorphine products (Des Jarlais et al., 2014).

Figure 5. Other Harm Reduction Services Offered by Syringe Services Programs (Des Jarlais, 2014)



CHALLENGES FACING SYRINGE SERIVCES PROGRAMS

Due to the worsening of the opioid overdose epidemic and corresponding increases in rates of HCV and concerns over HIV outbreaks associated with prescription opioid and heroin injection, a number of states have enacted legislation or regulations in recent years enabling the implementation of SSPs. For example, in the midst of the HIV

outbreak in Scott County in 2015, Indiana, first through emergency public health order, allowed Scott County, in collaboration with CDC, to open an emergency SSP in order to contain the spread of HIV. Indiana followed this emergency order with a state law allowing local implementation of SSPs under certain conditions. Kentucky and Ohio quickly followed with state legislation enabling SSPs, and West Virginia, through their public health regulatory authority, allowed SSPs under specific conditions. Despite these advances, implementation of SSPs has not been commensurate with potential need. A recent analysis found that 93% of the most vulnerable counties for the rapid dissemination of HIV or HCV due to injection drug use did not have an SSP (AMFAR, 2017). These findings underscore the disconnect between where SSPs and the critical services they offer are needed most and where they are currently available. Moreover, they highlight the need to understand how recent policy changes enabling the implementation of SSPs are being operationalized and how SSP implementation is being matched with populations in need.

In addition to variation across states, a 2015 study found that substantially fewer SSPs were located in rural and suburban areas compared to urban areas, and even when SSPs were located in rural and suburban areas, services offered by the SSPs were less robust compared to those offered in urban areas (**Table 3**) (Des Jarlais et al., 2015). For example, nearly 70 percent of SSPs in the U.S. are located in urban areas, and a much larger percentage of rural SSPs compared to urban SSPs are classified as small (distributing between 1-9,999 syringes). In addition, rural SSPs were more likely to report resource or funding challenges and have fewer full time paid staff, and they were less likely to report distribution of naloxone or referral to methadone or buprenorphine

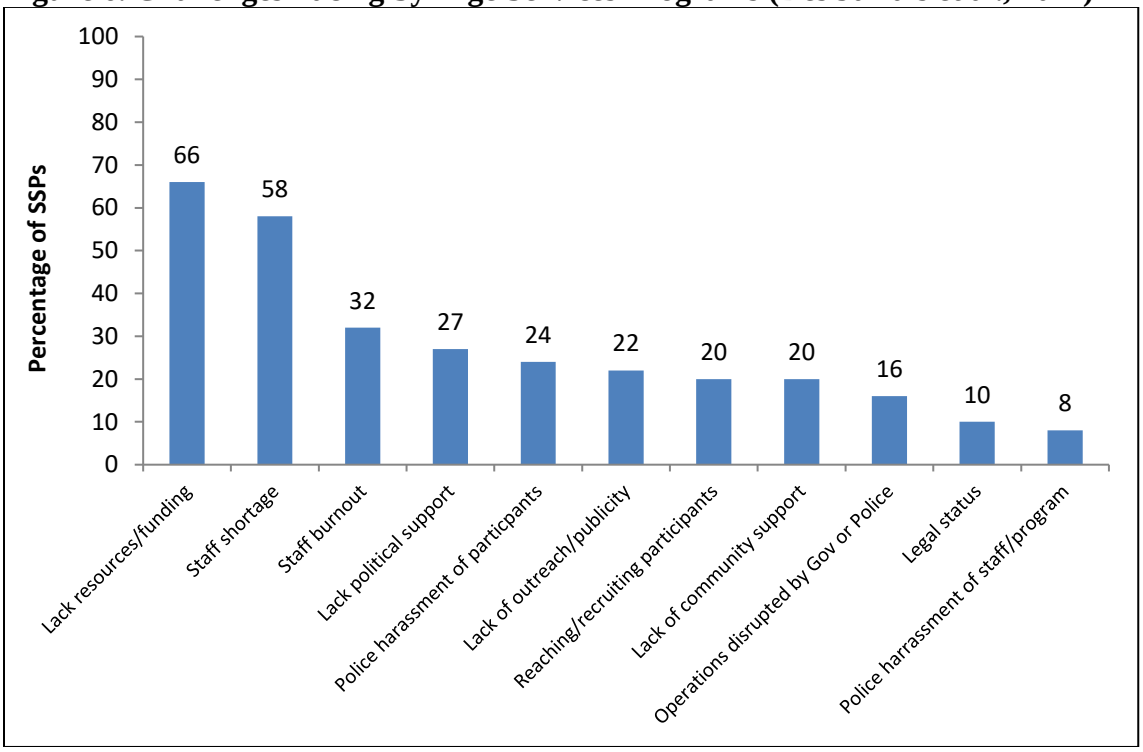
treatment for opioid use disorder. These findings are increasingly concerning given that prior research shows high rates of prescription opioid misuse and overdose, rising rates of HCV and HBV, and increases in heroin use linked to prior prescription opioid misuse among more rural and suburban populations (Hall et al., 2008; McDonald et al., 2014; Zibbell et al., 2014; Zibbell et al., 2015; Suryaprasad et al., 2014; Harris et al., 2016; Van Handel et al., 2016; Cicero et al., 2014).

Table 3. Select Characteristics of Syringe Services Programs in the United States, 2013

Program characteristic	**SSP location**		
	Rural	**Suburban**	**Urban**
	No. (%)	**No. (%)**	**No. (%)**
Region			
Midwest	6 (20)	1 (3)	23 (77)
Northeast	4 (9)	4 (9)	35 (81)
Puerto Rico	1 (20)	0 (0)	4 (80)
South	1 (7)	0 (0)	12 (86)
West	18 (30)	9 (15)	31 (51)
Total	**30 (20)**	**14 (9)**	**105 (69)**
Program size (no. of syringes distributed)			
Small (1–9,999)	5 (17)	1 (7)	6 (6)
Medium (10,000–55,000)	10 (33)	4 (29)	21 (20)
Large (55,001–499,999)	14 (47)	6 (43)	60 (57)
Very large (≥500,000)	0 (0)	3 (21)	16 (15)
None/unknown/missing	1 (3)	0 (0)	2 (2)
Operating Characteristic	**SEP location**		
	Rural	**Suburban**	**Urban**
	%	**%**	**%**
Syringes estimated to be distributed via secondary exchange, peer delivery services, both	30	28	20
SSPs encouraged secondary exchange	73	79	71
Mobile exchange	23	71	74
Experienced a lack of resources/funding	73	64	63
Experienced problems reaching, recruiting participants, or both	20	36	18
Full-time paid personnel	40	79	77
Former drug users as program personnel	50	86	70
Selected service			
HIV counseling and testing	87	71	90
HCV testing	67	79	78
Sexually transmitted diseases screening	40	29	50
HCV referral tracking	33	43	44
Distribution of food	33	29	54
Distribution of naloxone	37	57	61
Referral to methadone or buprenorphine	70	86	90
Adapted from Des Jarlais et al., 2015			

In addition to geographic variation and inadequate access, 66% of SSPs reported having a lack of resources or funding, 58% reported staff shortage, and 32% reported staff burnout. These challenges significantly limit the capacity and reach of SSPs. Additional external challenges that impact SSP operations such as a lack of political support, police harassment of participants or staff, and a lack of community support were also reported by SSPs. Of note, nearly 1 in 5 SSPs reported difficulty in reaching and recruiting participants (**Figure 6**) (Des Jarlais et al., 2014).

Figure 6. Challenges Facing Syringe Services Programs (Des Jarlais et al., 2014)



PURPOSE OF RESEARCH

The purpose of this research, using a mixed methods approach, is to address the knowledge and policy gaps described above through: 1) systematically reviewing the literature to synthesize what is known about the population of individuals who inject prescription opioids in the U.S.; 2) estimating the magnitude of prescription opioid

injection in the United States; 3) examining overall, sociodemographic, and substance use trends and correlates of prescription opioid injection among a nationally representative sample to identify populations at-risk for prescription opioid injection and related harms; and 4) using these quantitative findings to inform a qualitative exploration of how SSPs are responding to the rapidly changing legal, policy, and public health environment of the opioid epidemic and how they can be further leveraged to reduce the harms associated with opioid injection.

The first study will address a current gap in the literature by providing a synthesis of the available peer-reviewed literature on the characteristics of people who inject prescription opioids in the U.S., as well as identify areas for future research based on gaps identified during the systematic review. The second study, building on the systematic review conducted in study one, will provide the first nationally representative analysis of prescription opioid injection in the U.S. – providing estimates on the magnitude of prescription opioid injection and identifying key correlates of prescription opioid injection, including quantifying the extent of unsafe injection practices and syringe sources for people who inject prescription opioids and other drugs using a nationally representative sample. The third and final study, will build on studies one and two to document, using rich qualitative data, how SSPs are responding across multiple domains to the evolving opioid epidemic and rapidly changing policy environment. In addition, study three will identify barriers SSPs are facing and identify facilitators, innovative collaborations, and successful strategies SSPs are pursuing to meet the needs of the expanding service population and evolving opioid crisis.

Collectively, these findings provide new understanding on prescription opioid injection and SSPs that can directly inform opioid misuse prevention and treatment policy and programmatic development and implementation, including how best to target SSP implementation and service offerings to meet the needs of the expanding population of people who inject opioids and other drugs. Further, by providing estimates of the magnitude of prescription opioid injection in the U.S., the findings enable policy-makers to better determine resource needs. Finally, the findings will contribute to the national conversation on the role SSPs can play in addressing the evolving opioid epidemic and increasing opioid injection-related harms.

The results of these studies are presented in the next three chapters. For each chapter, the research is divided into the following sections: 1) background; 2) methods; 3) results; 4) discussion; 5) study limitations; and 6) study conclusion. The final chapter of this dissertation (Chapter 5) provides a synthesis of the three stand-alone studies in the broader opioid epidemic research and policy context, recommendations for future research, and final conclusions.

CONCEPTUAL FRAMEWORK

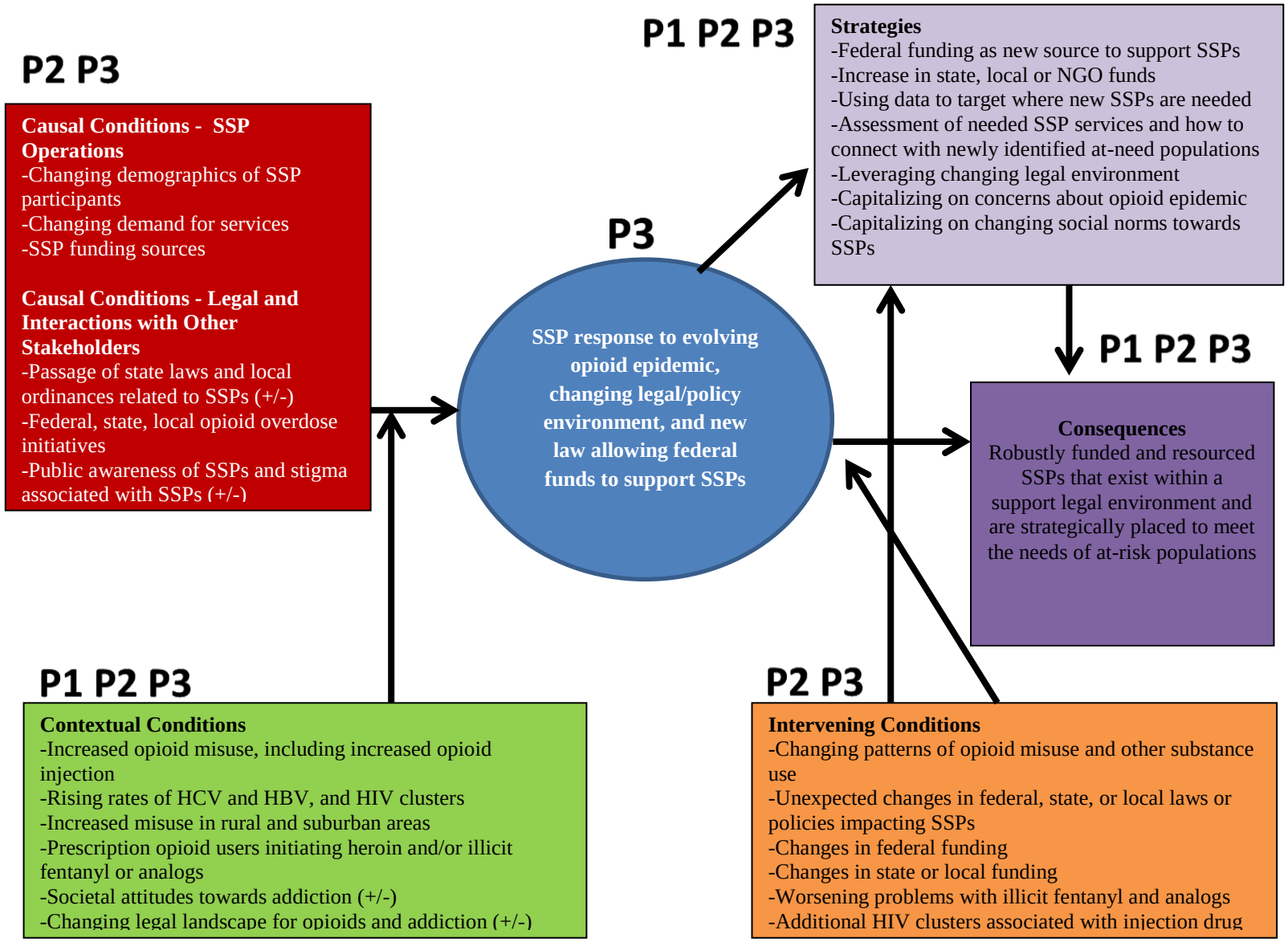
The conceptual framework underpinning this research is drawn from the Structured Approach developed by Strauss and Corbin (Strauss & Corbin, 1990). Although this framework is generally associated with Grounded Theory, it is also used to provide insight into problems that are not well understood or characterized. A similar approach has been taken in other health services and public health policy research (Fahim et al., 2014; Yamey et al., 2012).

Within the framework, Strauss and Corbin identify four areas that have interplay with the core phenomenon: 1) contextual and intervening conditions, 2) causal conditions, 3) strategies, and 4) consequences (**Figure 7**) For this analysis, the core phenomenon (blue oval) is to understand how SSPs are responding to the evolving opioid epidemic and changing legal and policy environment. The factors influencing this phenomenon are complex, and the proposed research will employ mixed methods to elucidate these factors in an effort to inform future SSP and opioid-related policy development and implementation. Quantitative methods in papers 1 and 2 will be used to estimate the magnitude of the problem and characterize the contextual, intervening and causal conditions and inform the strategies and consequences of the framework. Qualitative methods in paper 3, largely informed by the findings in papers 1 and 2, will be used to characterize causal and intervening conditions, inform strategies and consequences, and describe the core phenomenon.

Contextual conditions (green box), informed by papers 1 and 2, include increased opioid misuse, including increased opioid injection, rising rates of HCV and HBV, and HIV clusters associated with injection drug use, increased opioid misuse in rural and suburban areas, people who misuse prescription opioids initiating use of heroin and/or illicit fentanyl or analogs, societal attitudes towards addiction, and the changing legal landscape for opioids and addiction. Causal conditions (red box), informed by papers 1 and 2, include changing demographics of SSP participants, changing demands for specific services in SSPs, changing funding sources for SSPs, passage of state laws and local ordinances enabling SSP implementation, Federal, state, and local overdose prevention initiatives, and public awareness of SSPs and stigma associated with SSPs.

Strategies (lavender box), informed by papers 1, 2, and 3, which represent steps that can be taken based on the core phenomenon include new federal funding sources for SSP operations, increases in state, local or non-governmental funding for SSPs, using data to target where new SSPs are needed and better targeting of SSP services and how to connect with at-need populations, leveraging the changing legal environment, and capitalizing on concerns about the opioid epidemic and injection-related harms and changing social norms. Intervening conditions (orange box), informed by papers 2 and 3, include countervailing forces and organizations opposed to expanding SSPs, changing patterns of opioid misuse and other substance use, unexpected changes in federal, state, or local laws/policies impacting SSPs, changes in federal, state, or local funding, and worsening of problems associated with high-potency synthetic opioids such as illicitly manufactured fentanyl and fentanyl-analogs and additional clusters of HIV in different areas of the country associated with injection drug use. Finally, the consequence (purple box), informed by papers 1, 2, and 3, which represents the ideal end result of the framework, is the existence of robustly funded and resourced SSPs that exist within a supportive legal environment and are placed strategically to meet the needs of at-risk populations.

Figure 7. Conceptual Framework based on Strauss and Corbin's Structured Approach



Chapter 2: Prescription Opioid Injection Misuse in the United States: A Narrative Review of the Literature

This manuscript provides a synthesis of the available peer-reviewed literature on the prevalence of prescription opioid injection misuse, the sociodemographic characteristics of people who inject prescription opioids, and the health outcomes associated with prescription opioid injection misuse in the U.S. based on a systematic review of the published literature from 2000 to 2017. The study also identifies areas for future research based on gaps identified during the systematic review.

The United States has experienced an unprecedented increase in prescription opioid misuse, addiction, and overdose over the past 15 years. In 2016, more than 11.5 million people in the U.S. reported past-year misuse of prescription opioids and nearly 2 million met diagnostic criteria for a past-year prescription opioid use disorder (SAMHSA, 2017). In addition, 17,087 overdose deaths in the U.S. involved prescription opioids in 2016 (Jones et al., 2018). The economic cost of prescription opioid misuse in the U.S. is estimated at more than $70 billion annually (Florence et al., 2015).

Concerns about rising rates of prescription opioid injection and injection-facilitated transmission of HIV and hepatitis C virus (HCV) have increased in recent years due to the 2015 outbreak of HIV in Scott County, Indiana associated with injection of the prescription opioid oxymorphone and the decade-long increase in HCV rates in the U.S., especially in areas with high rates of prescription opioid misuse (Peters et al., 2016; Wejnert et al., 2016; Suryaprasad et al., 2014; Zibbell et al., 2015; Harris et al., 2016; Zibbell et al., 2018).

Although the connection between infectious disease transmission and injection drug use in general is well documented, emerging research indicates that people who inject prescription opioids are at elevated risk for infectious disease transmission even after accounting for injection of other drugs. This is likely a result of factors such as the process of preparing oral prescription opioids for injection, sharing and injecting residual prescription opioid "washes", using high dead space syringes, and engaging in multiple injections per injection episode and multiple injection episodes per day (Roy et al., 2011; Zibbell et al., 2014; Lankenau et al., 2015; Zule et al., 2016; Broz et al., 2018). In addition, PWID are at increased risk for substance use disorders, drug overdose, and engaging in sexual risk behaviors (Zule et al., 2016; Degenhardt et al., 2010; Silva et al., 2013; Lake & Kennedy, 2016; CDC, 2016; Spiller et al., 2015).

Despite growing concerns over increasing opioid injection and related harms, there is limited understanding about the population of people who inject prescription opioids in the U.S. To date, a review of the literature to synthesize what is known about the prevalence of prescription opioid injection in the U.S. and the risk factors for prescription opioid injection has not been conducted. This information gap constrains the ability of policymakers, public health practitioners, and clinicians to develop and implement informed and targeted policies and resource allocations that address the needs of this at-risk population. To address this gap, a narrative review of the literature was undertaken.

The research questions of interest included:

1. What is the prevalence of prescription opioid injection in the U.S.?

2. What is known about the demographic, socioeconomic, and geographic characteristics and risk factors for prescription opioid injection in the U.S.?
3. What is known about co-occurring substance use, mental health, and health-related outcomes among people who inject prescription opioids in the U.S.?
4. What other characteristics have been associated with prescription opioid injection in the U.S.?

METHODS

The literature review was conducted based on guidelines provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) group (Moher et al., 2009).

Databases Searched

After consultation with an academic librarian specializing in health literature databases, a comprehensive search strategy was developed to identify relevant research articles. To capture a broad range of medical, clinical, public health, and social science literature, PubMed, Scopus, and EMBASE databases were searched on July 7, 2017 to identify studies published since 2000 that provided information on the four key research questions of the review. A subsequent literature search using the same search parameters was conducted on January 17, 2018 to identify any relevant literature published since July 7, 2017.

The following combinations of search terms were used: “opioid analgesics” or “prescription opioid” or “opioid” or “prescription opiate” or “opiate” or “painkiller” or “pain killer” or “pain reliever” or “pain relievers” or “analgesic” AND “drug overdose” or “overdose” or “prescription drug misuse” or “nonmedical use” or “misuse” or

"abuse*" or "depend*" or "opioid use disorder" or "overdose" AND "substance abuse intravenous" or "injection drug use" or "intravenous drug use" or "intravenous" or "IV" or "injection" or "inject*".

Studies included in the review were English language papers published between 2000 and 2017. Eligible study designs included randomized controlled trials, non-randomized controlled trials, observational or other epidemiological studies, and studies reporting on surveys or interviews, including qualitative studies, of people who use drugs as long as they provided some quantitative information on prescription opioid injection. Only studies conducted in the U.S. were included due to differences in drug use patterns, drug markets, and policies related to drug use across countries. Studies reporting on injection drug use that did not distinguish prescription opioid injection from other drugs injected, i.e., reported history of drug injection but not prescription opioid injection or combined prescription opioid and heroin injection into a single category were excluded.

Data extraction and Analysis

Study specific information, including author, publication date, study year(s), study population, location, sample size, and outcomes relevant to the four key research questions, and study limitations were extracted from each study and entered into a Microsoft Excel spreadsheet. After all relevant information was extracted from included studies, a narrative synthesis was conducted for each of the four key research questions.

RESULTS

The database search identified 4,183 unique studies published between 2000 and 2017. Title review and study country narrowed the number of eligible studies to 971, and abstract review further narrowed the number to 101 studies for full text review. A final

sample of 58 studies (**Figure 8**) met the inclusion criteria, 55 from the initial literature search and 3 studies from bibliographic review of the full text articles (**Table 4**).

Figure 8. Article Selection Process

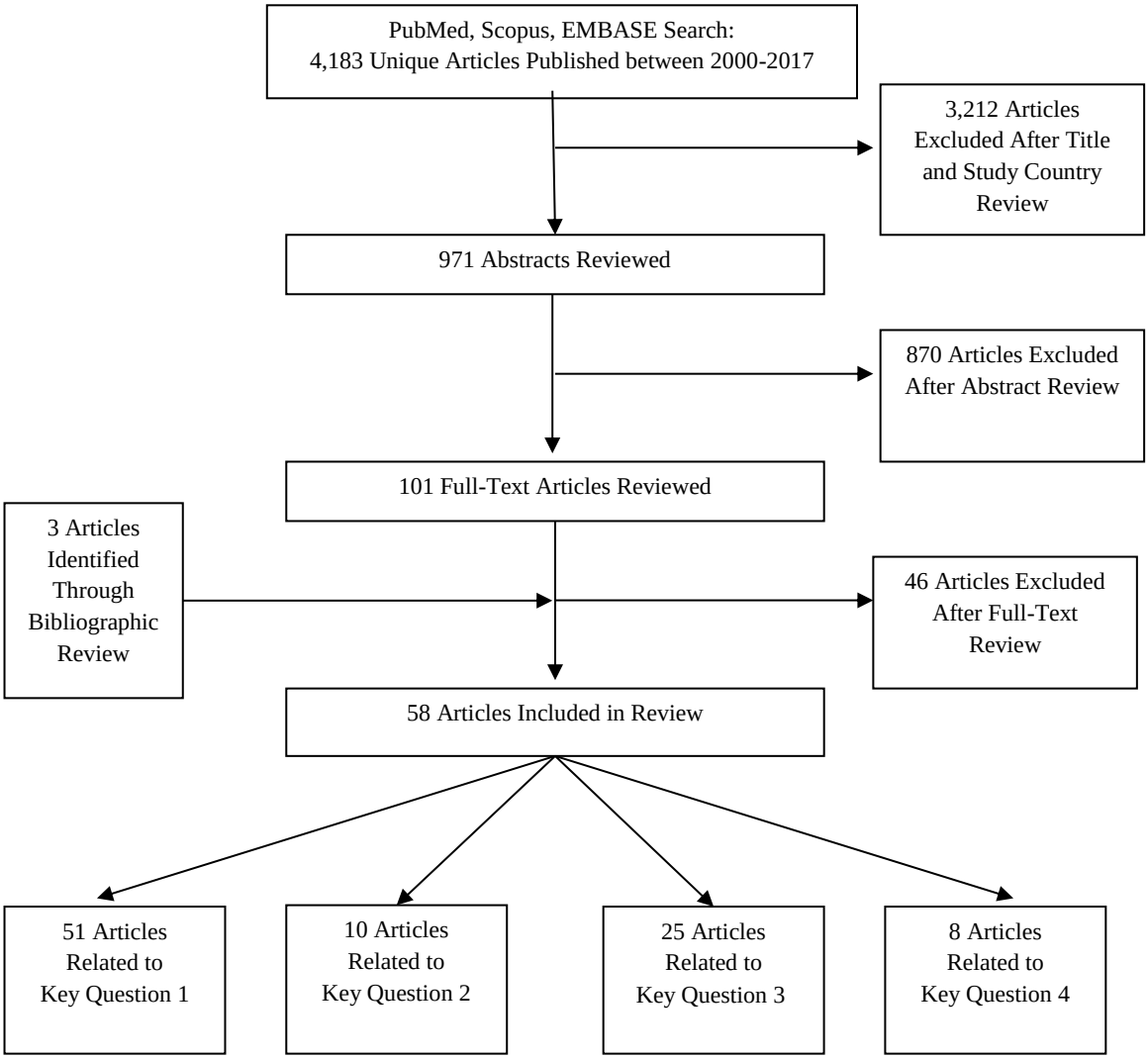


Table 4. Summary of 58 Studies Examining Prescription Opioid Injection in the United States Published Between 2000 and 2017

Lead Author, Year	Year(s) Studied	Study Population	Study Location	Sample Size	Provides Information on Key Questions			
					Question 1	Question 2	Question 3	Question 4
Passik, 2006	Not given	Individuals ≥18 seeking admission to an Addiction Treatment Unit in Kentucky with a chief complaint of prescription drug abuse	Lexington, KY	109	Select opioids	No	No	No
Sigmon, 2006	2002-2004	Individuals ≥18 with opioid use disorder in an outpatient methadone program	Burlington, VT	75	Yes	No	No	No
Carise, 2007	2001-2004	Individuals admitted to addiction treatment in 157 participating treatment programs	157 Treatment Programs in 22 states	27,816	OxyContin	No	No	No
Grau, 2007	2002	Individuals ≥16 years reporting nonmedical opioid use ≥1 time in past 30 days	Cumberland County, ME	237	OxyContin	No	No	No
Havens, 2007	2004-2005	Individuals reporting OxyContin use ≥1 time in past 3 years and reporting any opioid analgesic use (medically or nonmedically) in past 30 days	Rural Appalachian KY	184	Yes	No	Yes	Yes
McCabe, 2007	2005	Undergraduate students at a large public university	Midwestern U.S.	4,580	Yes	No	No	No
Rosenblum, 2007	2005	Individuals newly entering a methadone program who reported opioid abuse in past 30 days	72 Opioid Treatment Programs in 33 States	5,663	Yes	No	No	No
Davis, 2008	2004-2006	Individuals living on the streets who use drugs	New York City, NY	586	Select opioids	No	No	No
Green, 2009	2005-2008	Individuals ≥18 reporting past 30 day prescription opioid use among people assessed for treatment	222 Treatment Centers across U.S.	3,821	Yes	No	No	No
Subramaniam, 2009	2003-2006	Individuals aged 14-18 years with DSM-IV opioid, cannabis, and/or alcohol abuse or dependence and receiving treatment	Baltimore, MD	166	Yes	No	No	No

Butler, 2010	2005-2008	Individuals ≥18 reporting past 30 day prescription opioid abuse among people assessed for treatment	245 Treatment Centers in 27 states	5,686	Yes	Yes	Yes	No
Butler, 2010	2007	People reporting nonmedical use of prescription opioids who accessed Erowid.org online website	Web-based survey	469	Yes	No	No	No
Cicero, 2010	Not given	Individuals ≥18 entering treatment with DSM IV prescription opioid abuse or dependence and reporting use of prescription opioids to get high ≥1 time in past 30 days	Treatment Centers across U.S.	1,818	Yes	No	No	No
Young, 2010	2008-2009	Individuals reporting any past 30 days prescription opioid misuse and OxyContin use (medically or nonmedically) ≥1 time in past 3 years	Rural Appalachian KY and a Metro City in KY	212	Select opioids	Yes	No	No
Back, 2011	Not given	Individuals ≥18 not seeking treatment with DSM IV prescription opioid dependence in past 12 year	Not given	24	Yes	No	No	No
Church, 2011	2010	New HCV cases interviewed by Health Department	Massachusetts	28	Yes	No	No	No
Cicero, 2011	Not given	RADARS SKIP - Individuals ≥18 with opioid dependence and entering treatment South Florida - Individuals ≥18 reporting misuse of ≥1 prescription drug ≥5 times in past 90 days and whose most frequently misused drug was an opioid	Treatment Centers across U.S. (RADARS); South Florida	1,983 (RADARS) 782 (SF)	Yes	No	No	Yes
Havens, 2011	2001-2004	Felony probationers participating in an HIV prevention trial	Rural Appalachian KY	800	Yes	No	No	No
Havens, 2011	2008-2010	Individuals ≥18 reporting use of prescription opioids, heroin, crack/cocaine, or methamphetamine to get high in past 30 days	Rural Appalachian KY	400	Yes	No	Yes	No

Jenkins, 2011	2009	Individuals who were clients of syringe exchange programs run by the local health department	Seattle, King County, WA	443	Yes	No	Yes	No
Jones, 2011	2009	Individuals aged 21-60 years currently misusing oxycodone via intranasal or intravenous routes and not seeking treatment for substance use	New York City, NY	50	No	Yes	Yes	No
Surratt, 2011	Not given	Individuals ≥18 reporting abuse of psychoactive prescription drugs ≥5 times in past 90 days.	South Florida	791	Yes	Yes	Yes	Yes
Young, 2011	2008-2010	Individuals ≥18 reporting use of prescription opioids, heroin, crack/cocaine, or methamphetamine to get high in past 30 days	Rural Appalachian KY	503	Yes	No	No	No
Lankenau, 2012	2008-2009	Individuals aged 16-25 engaging in misuse of prescription drugs ≥3 times in past 90 days and reporting injection drug use in past 90 days	New York City, NY and Los Angeles, CA	50	Yes	Yes	Yes	No
Stanley, 2012	2010	New HCV cases interviewed by Health Department	Wisconsin	17	Yes	No	No	No
Black, 2013	2007-2011	Individuals ≥18 reporting past 30 days prescription opioid abuse among people assessed for treatment	540 Treatment Centers in 35 states	29,459	Yes	Yes	Yes	No
Butler, 2013	2009-2012	Individuals ≥18 reporting past 30 days prescription opioid abuse among people assessed for treatment	357 Treatment Centers in the U.S.	26,413	Select opioids	No	No	No
Cicero, 2013	Not given	Individuals ≥18 entering treatment with DSM-IV prescription opioid abuse and reporting past 30 day use of prescription opioids to get high	160 Treatment Centers across U.S.	3,520	Select opioids	No	No	No
Havens, 2013	2008-2010	Individuals ≥18 reporting use of prescription opioids, heroin, crack/cocaine, or methamphetamine to get high in past 30 days	Rural Appalachian KY	392	Yes	No	Yes	Yes
Johnson, 2013	2008-2009	Individuals aged 16-25 engaging in misuse of prescription drugs ≥3 times in past 90 days and	New York City, NY and Los Angeles, CA	40	No	No	Yes	Yes

		reporting lifetime injection of a prescription drug						
Jones, 2013	2002-2010	Individuals ≥12 years participating in the National Survey on Drug Use and Health (NSDUH)	United States	Not given	No	No	Yes	No
Marder, 2013	2012	Patients with Thrombotic Thrombocytopenic Purpura (TTP)-like illness and matched controls	Tennessee	43	No	No	Yes	No
Silva, 2013	2009-2011	Individuals aged 16-25 engaging in misuse of prescription drugs ≥3 times in past 90 days	New York City, NY and Los Angeles, CA	596	Yes	No	Yes	No
Cassidy, 2014	2008-2011	Individuals ≥18 reporting past 30 days prescription opioid abuse among people assessed for treatment	437 Treatment Centers in 37 states	232,874	Select opioids	No	No	No
Cicero, 2014	2008-2013	Individuals ≥18 entering treatment with DSM-IV prescription opioid abuse and reporting past 30 day use of prescription opioids to get high	160 Treatment Centers across U.S.	10,568	Buprenorphine	No	No	No
Lavonas, 2014	2010-2012	Individuals ≥18 years old entering substance abuse treatment	125 Treatment Centers in 50 states and 79 Opioid Treatment Programs in 34 states	4,669	Buprenorphine	No	No	No
Miller, 2014	2012-2014	Individuals with suspected diagnosis of thrombotic microangiography or thrombotic thrombocytopenic purpura	Rural NC	15	No	No	Yes	No
Vietri, 2014	2012	Individuals ≥18 years participating in the online U.S. National Health and Wellness Survey	United States	25,864	Yes	No	No	No
Zibbell, 2014	2012	Individuals ≥18 years old with a history of injection drug use in past 12 months	Cortland County, NY	123	Yes	No	Yes	No
Conrad, 2015	2014-2015	Individuals with newly diagnosed HIV	Scott County, IN	135	No	No	Yes	Yes
Heimer, 2015	2008-2012	Individuals ≥18 years old reporting injection drug use in past 30 days	Suburban CT	456	Yes	No	Yes	No

Lankenau, 2015	2009-2011	Individuals aged 16-25 engaging in misuse of prescription drugs ≥3 times in past 90 days	New York City, NY and Los Angeles, CA	162	Yes	Yes	Yes	No
Mateu-Gelabert, 2015	2012-2013	Individuals aged 18-32 reporting nonmedical use of prescription opioids	New York City, NY	46	Yes	No	Yes	No
Meyer, 2015	2007-2009	Individuals ≥18 years old with DSM IV opioid dependence, opioid positive urine drug screen, and report primary drug of use as prescription opioids	Burlington, VT	89	Yes	No	No	No
Setnik, 2015	2011	Individuals aged 18-55 not dependent on opioids but reporting recreational use on ≥10 occasions in the past year and ≥1 occasion in past 12 weeks	Salt Lake City, UT	80	Yes	No	No	No
Cicero, 2016	2009-2014	Individuals ≥18 years old with primary diagnosis of opioid abuse and opioid use in past 30 days	>125 Treatment Centers across U.S.	152	OxyContin, Opana ER	No	No	No
Peters, 2016	2014-2015	Individuals with newly diagnosed HIV	Scott County, IN	181	Oxymorphone, Oxycodone	No	Yes	No
Zule, 2016	2005-2008	Individuals reporting drug use, having sex with men (+/- drug use), and sex partners of people using drugs (+/- drug use)	Two urban and two rural counties in NC	1,985	No	No	No	Yes
Bennett, 2017	2014-2015	Military veterans reporting past 30 day use of opioids (prescription or illicit)	New York City, NY	218	Yes	No	Yes	No
Cassidy, 2017	2012-2015	Individuals ≥18 years old and adolescents aged 13-18 being assessed for treatment and reporting past 30-day prescription opioid use.	831 Treatment Centers in 45 states (adults) and 180 Centers in 26 states (adolescents)	226,357; 12,906	Hydrocodone	No	No	No
Eckhardt, 2017	2005-2012	Individuals aged 18-35 reporting injection drug use in past 30 days or individuals injecting for <5 years and reporting injection drug use in past 30 days	New York City, NY	714	Yes	No	Yes	No
Green, 2017	2006-2014	Single opioid intentional abuse poison control center exposure calls among people ≥12 years	Poison Control Centers in U.S.	6,107	Yes	No	Yes	No

Hoffman, 2017	2006-2009; 2014-2015	Patients receiving treatment at nonprofit substance abuse treatment facilities	Northern FL	1,043	Yes	No	No	No
Jones, 2017	2003-2014	Individuals ≥12 years participating in the National Survey on Drug Use and Health (NSDUH)	United States	Not given	Yes	Yes	Yes	Yes
Jones, 2017	2004-2013	Treatment admissions for primary prescription opioid abuse among people ≥12 years to state-licensed or certified treatment centers that receive federal funding.	United States	1,260,151	Yes	Yes	Yes	No
Liebling, 2017	2015-2016	Individuals aged 18-29 not currently in substance use treatment reporting past 30 day nonmedical use of prescription opioids	Rhode Island	199	Select opioids	No	No	No
Surratt, 2017	2011-2014	Individuals aged 18-39 years reporting use of illicit club drugs ≥3 times in past 3 months, reporting nonmedical use of a psychoactive prescription medication ≥1 time in past 3 months, sexual intercourse in past 3 months, and attendance at large local nightclubs ≥1 time per month	Miami-Dade County, Florida	323	Yes	No	No	No
Zibbell, 2017	2004-2014	Treatment admissions reporting injection drug use among treatment admission of people ≥12 years to state-licensed or certified treatment centers that receive federal funding.	United States	20,623,517	Yes	Yes	No	No

Key Question 1: What is the prevalence of prescription opioid injection in the U.S.?

Fifty-one studies provided information on the prevalence of prescription opioid injection in the U.S. Twenty-four studies examined prevalence of prescription opioid injection in non-treatment seeking populations (Zibbell et al., 2014; Lankenau et al., 2015; Silva et al., 2013; Havens et al., 2007; McCabe et al., 2007; Davis & Johnson, 2008; Butler et al., 2010; Back et al., 2011; CDC, 2011; Havens et al., 2011a; Havens et al., 2011b; Jenkins et al., 2011; Laneknau et al., 2012; CDC, 2010; Havens et al., 2013; Vietri et al., 2014; Heimer et al., 2015; Mateu-Gelabert et al., 2015; Setnik et al., 2015; Bennett et al., 2017; Eckhardt et al., 2017; Green et al., 2017; Jones, 2018; Surratt et al., 2017), 12 studies examined prevalence in populations seeking or receiving treatment (Zibbell et al., 2018; Sigmon et al, 2006; Rosenblum et al., 2007; Green et al., 2009; Subramaniam et al., 2009; Butler et al., 2010; Cicero et al., 2010; Cicero et al., 2011; Surratt et al., 2011; Black et al., 2013; Meyer et al., 2015; Hoffman et al., 2017; Jones et al., 2017), and 17 studies reported prevalence of injection of specific opioids (Peters et al., 2016; Davis & Johnson, 2008; CDC, 2012; Green et al, 2009; Passik et al., 2006; Carise et al., 2007; Grau et al., 2007; Young et al., 2010; Young & Havens, 2012; Butler et al., 2013; Cicero et al., 2013; Cassidy et al., 2014; Cicero et al., 2014; Lavonas et al., 2014; Cicero et al., 2016; Cassidy et al., 2017; Leibling et al., 2018)). Among the 24 studies examining prevalence in non-treatment seeking populations, three studies provided prevalence estimates of prescription opioid injection among general populations and 23 provided prevalence estimates among people reporting recent drug use.

Using data from the National Survey on Drug Use and Health (NSDUH), a nationally representative annual survey of people aged 12 years and older in the U.S., the

prevalence of lifetime prescription opioid injection increased from 0.16% of people aged 12 and older in 2003-2005 to 0.27% in 2012-2014. This equated to an estimated 710,000 people aged 12 and older in the U.S. in 2012-2014 reporting lifetime injection of prescription opioids – an increase of more than 300,000 people compared to 2003-2005 (Jones, 2018). Vietri et al., using data from a nationally representative internet survey in 2010, found that 0.4% of adults 18 or older reported injection of prescription opioids in the past 90 days (Vietri et al., 2014). Among undergraduates at a large public university in the Midwest, McCabe et al., found that 0.1% of students had ever injected prescription opioids (McCabe et al., 2007).

Prevalence estimates for prescription opioid injection among non-treatment seeking populations reporting recent drug use, among individuals seeking or receiving treatment, and for specific opioids are found in **Table 5**. There was substantial heterogeneity across studies and populations resulting in wide variation in prevalence estimates. For example, prevalence of lifetime prescription opioid injection among non-treatment seeking individuals reporting recent drug use ranged from a low of 0.3% among 18 to 39 year olds reporting illicit club drug use in Miami, Florida to a high of 88.7% of adults 18 or older in Appalachian Kentucky who reported drug use in the past 30 days. Among adults seeking or receiving treatment, prevalence estimates were more consistent across studies. For example, past 30 day prescription opioid injection or reporting prescription opioid injection as the preferred route of use at treatment ranged from 12.0% to 41.0% across included studies, and prevalence of lifetime injection ranged from 32.9% to 69.0%. Estimates of recent prescription opioid injection were most

consistent across studies that included large, geographically diverse populations of people with opioid use disorders, with prevalence between 16% to 25%.

Prevalence estimates for injection of specific opioids varied widely depending on factors such as the population included in the study, local drug markets, and the ease with which a particular opioid can be prepared for injection, and study time frame. For example, prevalence of lifetime injection of Dilaudid (hydromorphone) ranged from a low of 0.6% among street drug users in New York City to a high of 11.6% of 18 to 29 year olds reporting recent drug use living in Rhode Island.

Table 5. Prevalence Estimates for Prescription Opioid Injection from Included Studies

Non-Treatment Seeking Individuals Reporting Recent Drug Use		
Lead Author, Year	**Study Population**	**Prevalence Estimate(s) for Prescription Opioid Injection**
Havens, 2007	Individuals reporting OxyContin use ≥1 time in past 3 years and reporting any opioid analgesic use (medically or nonmedically) in past 30 days	• 35.3% reported lifetime injection • 15.0% reported past 30 day injection
McCabe, 2007	Undergraduate students at a large public university in the Midwest	• 0.5% of reported lifetime injection
Davis, 2008	Street drug users	• 4.4% reported lifetime injection
Butler, 2010	People reporting nonmedical use of prescription opioids who accessed the Erowid.org online website	• 7.2% reported injection as preferred route
Back, 2011	Individuals ≥18 not seeking treatment with DSM IV prescription opioid dependence in past 12 year	• 29.2% reported injection
Church, 2011	New HCV cases interviewed by the Health Department	• 30.0% reported past 6 month injection
Havens, 2011	Felony probationers participating in an HIV prevention trial	• 13.1% reported lifetime injection
Havens, 2011	Individuals ≥18 reporting use of prescription opioids, heroin, crack/cocaine, or methamphetamine to get high in past 30 days	• 68.8% reported lifetime injection
Jenkins, 2011	Individuals who were clients of syringe exchange programs run by the local health department	• 7.7% reported injection
Lankenau, 2012	Individuals aged 16-25 engaging in misuse of prescription drugs ≥3 times in past 90 days and injection drug use in past 90 days	• 80.0% reported lifetime injection

Stanley, 2012	New HCV cases interviewed by the Health Department	• 47.1% reported lifetime injection
Havens, 2013	Individuals ≥18 reporting use of prescription opioids, heroin, crack/cocaine, or methamphetamine to get high in past 30 days	• 88.7% reported lifetime injection • 68.4% reported past 6 month injection • 61.7% reported initiating injection with opioids
Silva, 2013	Individuals aged 16-25 engaging in misuse of prescription drugs ≥3 times in past 90 days	• 25.8% reported lifetime injection
Vietri, 2014	Individuals ≥18 years old participating in the internet U.S. National Health and Wellness Survey	• 37.4% reported past 90 day injection
Zibbell, 2014	Individuals ≥18 years old with a history of injection drug use in past 12 months	• 57.7% reported past year injection
Heimer, 2015	Individuals ≥ 18 years old reporting injection drug use in past 30 days	• 48.3% with chronic pain reported lifetime injection • 36.7% without chronic pain reported lifetime injection • 16.8% with chronic pain reported past 30 day injection • 13.7% without chronic pain reported past 30 day injection
Lankenau, 2015	Individuals aged 16-25 engaging in misuse of prescription drugs ≥3 times in past 90 days	• 72.2% reported lifetime injection
Mateu-Gelabert, 2015	Individuals aged 18-32 years old reporting nonmedical use of prescription opioids.	• 46.6% reported lifetime injection
Setnik, 2015	Individuals aged 18-55 not dependent on opioids but reporting recreational use on ≥10 occasions in the past year and ≥1 occasion in past 12 weeks	• 1.3% reported past year injection
Bennett, 2017	Military veterans reporting past 30 day use of opioids (prescription or illicit)	• 7.0% reported past 30 day injection • 2.0% reported injecting ≥15 days in past 30 days
Eckhardt, 2017	Individuals aged 18-35 reporting injection drug use in the past 30 days or injecting for <5 years and injecting in past 30 days	• 13.7% reported lifetime injection
Green, 2017	Single opioid intentional abuse poison control center exposure calls among people ≥12 years	• 3.8% of all opioid-related intentional abuse exposure calls involved injection • 6.7% of all single substance opioid-related intentional abuse exposure calls involved injection
Surratt, 2017	Individuals aged 18-39 reporting use of illicit club drugs ≥3 times in past 3 months, reporting nonmedical use of a psychoactive prescription medication ≥1 time in past 3 months, sexual intercourse in past 3 months, and attendance at large local nightclubs ≥1 time per month.	• 0.3% reported lifetime injection
Individuals Seeking or Receiving Treatment		
Lead Author, Year	**Study Population**	**Prevalence Estimate**

Sigmon, 2006	Individuals ≥18 with opioid use disorder in an outpatient methadone program	• 69.0% reported lifetime injection • 41.0% reported injection as preferred route
Rosenblum, 2007	Individuals newly entering a methadone program who reported opioid abuse in the past 30 days	• 32.9% reported lifetime injection
Green, 2009	Individuals ≥18 reporting past 30 day prescription opioid abuse among people assessed for substance abuse treatment	• 20.6% of men reported past 30 day injection • 18.4% of women reported past 30 day injection
Subramaniam, 2009	Individuals aged 14-18 with DSM-IV opioid, cannabis, and/or alcohol abuse or dependence and receiving treatment	• 4.3% reported past 30 day injection
Butler, 2010	Individuals ≥18 reporting past 30 day prescription opioid abuse among people assessed for substance abuse treatment	• 20.2% reported past 30 day injection
Cicero, 2010	Individuals ≥ 18 entering treatment with DSM IV prescription opioid abuse or dependence and reporting using prescription opioids to get high ≥1 time in past 30 days	• 12.0%-14.0% reported injection as preferred route
Cicero, 2011	RADARS SKIP - Individuals ≥18 with opioid dependence and entering treatment South Florida - Individuals ≥18 reporting misuse of ≥1 prescription drug ≥5 times in past 90 days and whose most frequently misused drug was an opioid	• RADARS SKIP, 25.3% reported past 30 day injection • South Florida, 21.4% reported past 90 day injection
Surratt, 2011	Individuals ≥18 reporting abuse of psychoactive prescription drugs ≥5 times in past 90 days.	• 23.8% reported past 90 day injection
Black, 2013	Individuals ≥18 reporting past 30 days prescription opioid abuse among people assessed for substance abuse treatment	• 16.0% reported past 30 day injection
Meyer, 2015	Individuals ≥ 18 years old with DSM IV opioid dependence, opioid positive urine drug screen, and reporting primary drug of abuse as prescription opioids	• 17.0% reported prescription injection as preferred route
Hoffman, 2017	Patients receiving treatment at nonprofit substance abuse treatment facilities	• 44.7% in 2014-2015 reported injection compared to 10.3% in 2006-2009 • 51.0% of daily prescription opioid users in 2014-2015 reported injection compared to 12.0% in 2006-2009
Jones, 2017	Treatment admissions for primary prescription opioid abuse among people ≥12 years to state-licensed or certified treatment centers that receive federal funding	• 18.1% of treatment admissions for prescription opioid abuse reported injection as usual route in 2013 compared to 11.7% in 2004
Zibbell, 2017	Treatment admissions reporting injection drug use among treatment admission of people ≥ 12 years to state-licensed or certified treatment centers that receive federal funding	• 2.2% of all treatment admissions reported injection in 2014 compared to 0.6% in 2004
Studies Providing Estimates for Specific Opioids		

Lead Author, Year	Study Population	Prevalence Estimate
Passik, 2006	Individuals ≥18 seeking admission to an Addiction Treatment Unit in Kentucky with a chief complaint of prescription drug abuse	Among people using the specific opioid • 23.1% reported lifetime injection of OxyContin • 10.0% reported lifetime injection of Lortab • 20.0% reported lifetime injection of Percocet • 75.0% reported lifetime injection of morphine • 100% reported lifetime injection of Dilaudid
Carise, 2007	Individuals admitted to addiction treatment in 157 participating treatment programs	• 17% reported lifetime injection of OxyContin
Grau, 2007	Individuals ≥16 years reporting nonmedical opioid use ≥1 time during past 30 days	• 51.5% reported past 30 day injection of OxyContin • 44.1% reported past 30 day injection of other opioids
Rosenblum, 2007	Individuals newly entering a methadone program who reported opioid abuse in past 30 days	Among people using the specific opioids • 35.4% reported lifetime injection of any oxycodone • 38.4% reported lifetime injection of OxyContin • 14.8% reported lifetime injection of IR oxycodone • 7.6% reported lifetime injection of hydrocodone • 11.5% reported lifetime injection of methadone • 85.0% reported lifetime injection of morphine • 89.8% reported lifetime injection of hydromorphone • 57.1% reported lifetime injection of fentanyl • 37.5% reported lifetime injection of other opioids
Davis, 2008	Street drug users	• 1.8% reported lifetime injection of morphine • 1.4% reported lifetime injection of OxyContin • 0.6% reported lifetime injection of Dilaudid
Young, 2010	Individuals reported any past 30 days prescription opioid misuse and OxyContin use (medically or nonmedically) ≥1 time in past three years	• 3.0% reported lifetime injection of buprenorphine • 14.9% reported lifetime injection of fentanyl • 21.8% reported lifetime injection of hydromorphone • 1.0% reported lifetime injection of methadone

		• 33.7% reported lifetime injection of morphine • 44.6% reported lifetime injection of OxyContin • 3.0% reported lifetime injection of other oxycodone
Young, 2011	Individuals ≥18 reporting use of prescription opioids, heroin, crack/cocaine, or methamphetamine to get high in past 30 days	Among those reporting injection drug use • 62.4% initiated injection with prescription opioids • 48.2% initiated with OxyContin injection • 14.2% initiated with other prescription opioids
Lankenau, 2012	Individuals aged 16-25 engaging in misuse of prescription drugs ≥3 times in past 90 days and reporting injection drug use in past 90 days	• 36.0% reported OxyContin as first opioid injected • 14.0% reported Dilaudid as first opioid injected • 12% reported morphine as first opioid injected • 18% reported other opioids as first opioid injected
Butler, 2013	Individuals ≥18 reporting past 30 days prescription opioid abuse among people assessed for substance abuse treatment	• 35.7% of people abusing OxyContin reported past 30 day injection before OxyContin reformulation compared to 15.9% after reformulation • 8.6% of people abusing ER oxymorphone reported past 30 day injection before OxyContin formulation compared to 15.6% after reformulation • 45.7% of people abusing ER morphine reported past 30 days injection before OxyContin formulation compared to 46.0% after reformulation
Cicero, 2013	Individuals ≥18 entering treatment with DSM-IV prescription opioid abuse and reporting past 30 day use of prescription opioids to get high	• 4.2% of people abusing hydrocodone reported past 30 day injection • 21.1% of people abuse oxycodone reported past 30 day injection
Cassidy, 2014	Individuals ≥18 reporting past 30 days prescription opioid abuse among people assessed for substance abuse treatment	Among people who reported only prescription opioid injection in past 30 days • 50.9% reported past 30 day oxycodone ER injection prior to OxyContin reformulation compared to 41.5% after reformulation • 0.7% reported past 30 day oxymorphone ER injection prior to OxyContin reformulation compared to 5.3% after reformulation • 14.8% reported past 30 day morphine ER injection prior to OxyContin reformulation compared to 25.2% after reformulation

		• 2.1% reported past 30 day buprenorphine injection prior to OxyContin reformulation compared to 13.0% after reformulation
Cicero, 2014	Individuals ≥18 entering treatment with DSM-IV prescription opioid abuse and reporting past 30 day use of prescription opioids to get high	• 34.4% of people misusing buprenorphine prior to treatment reported past 30 day injection
Lavonas, 2014	Individuals ≥18 years old entering substance abuse treatment	• 25.4% of people abusing buprenorphine reported past 30 day injection
Cicero, 2016	Individuals ≥18 years old with a primary diagnosis of opioid abuse and reporting opioid abuse in the past 30 days	• 42.7% of those abusing OxyContin reported injection prior to reformulation compared to 21.4% after reformulation • 60.% of those abusing Opana ER reported injection prior to reformulation compared to 51.4% after reformulation
Peters, 2016	Individuals with newly diagnosed HIV	• 87.8% reported injection of oxymorphone in past year • 1.2% reported injection of oxycodone in past year
Cassidy, 2017	Individuals ≥18 years old and adolescents aged 13-18 being assessed for treatment and reporting past 30 day prescription opioid abuse	• 1.5% of adults abusing hydrocodone reported past 30 day injection
Liebling, 2017	Individuals 18-29 years old not currently enrolled in treatment reporting past 30 day nonmedical use of prescription opioids	• 17.6% reported lifetime injection of oxycodone • 11.6% reported lifetime injection of hydromorphone

Key Question 2: What is known about the demographic, socioeconomic, and geographic characteristics and risk factors for prescription opioid injection in the U.S.?

Ten studies provided information on demographic, socioeconomic, or geographic characteristics associated with prescription opioid injection in the U.S. (Zibbell et al., 2018; Lankenau et al., 2015; Lankenau et al, 2012; Jones, 2018; Butler et al., 2010; Surratt et al., 2013; Black et al., 2013; Jones et al., 2017; Young et al., 2010; Jones et al.,

2011) Two studies used national data from the Treatment Episode Data Set (TEDS) to assess prescription opioid injection trends among different demographic groups. Jones et al., examined the percentage of treatment admissions reporting prescription opioid injection as the preferred route of use among people with prescription opioid use disorders between 2004 to 2013 In the study, significant increases in the percentage of admissions reporting prescription opioid injection were found among males (12.8% in 2004 to 18.7% in 2013); females (10.4% in 2004 to 17.5% in 2013); 18-24 year olds (15.0% in 2004 to 22.4% in 2013); 25-34 year olds (13.1% in 2004 to 20.5% in 2013); 35-44 year olds (9.5% in 2004 to 14.6% in 2013); non-Hispanic whites (11.9% in 2004 to 19.3% in 2013); people living in the South (15.8% in 2004 to 27.3% in 2013); in the Midwest (14.9% in 2004 to 18.6% in 2013); and in the Northeast (7.0% in 2004 to 10.8% in 2013) (Jones et al., 2017).

Zibbell et al., examining prescription opioid injection among all admissions for substance use treatment in the TEDS data from 2004 to 2014, found significant increases in the percentage of treatment admissions who reported prescription opioid injection for the following groups: males (0.6% in 2004 to 1.1% in 2014); females (0.8% in 2004 to 2.9% in 2014); 12-17 year olds (0.1% in 2004 to 0.2% in 2014); 18-29 year olds (0.4% in 2004 to 3.5% in 2014); 30-39 year olds (1.0% in 2004 to 2.8% in 2014); 40-49 year olds (0.6% in 2004 to 1.1% in 2014); non-Hispanic whites (0.9% in 2004 to 3.2% in 2014); non-Hispanic blacks (0.1% in 2004 to 0.2% in 2014); and among Hispanics (0.1% in 2004 to 0.7% in 2014) (Zibbell et al., 2018).

Nine studies provided data on demographic, socioeconomic, and geographic factors associated with prescription opioid injection in bivariable or multivariable

analyses (**Table 6**). One study examined these factors among a nationally representative population (Jones, 2018), three studies included large and geographically diverse populations seeking or receiving treatment (Butler et al., 2010; Black et al., 2013; Jones et al., 2017) and five studies reported on specific populations in different geographic locations – Kentucky (Young & Havens, 2010), New York City (Jones et al., 2011), New York and Los Angeles (Lankenau et al., 2015; Lankenau et al., 2012), and south Florida (Surratt et al., 2011).

Demographic factors associated with increased likelihood of prescription opioid injection in bivariable and/or multivariable analyses included male sex, White race, young to middle-aged adults, and initiating prescription opioid misuse at an earlier age. Socioeconomic factors associated with increased likelihood of prescription opioid injection included lower educational attainment, being unemployed or less than full-time employed, being homeless, having a lower annual household income, being uninsured, and receiving Medicaid. Data on the association between geographic factors and risk for prescription opioid injection were more limited. Jones et al., found that prescription opioid injection was more likely in the Midwest and South compared to the Northeast (Jones et al., 2017). Young et al., reported that prescription opioid injection was more common in rural Kentucky compared to urban Kentucky (Young & Havens, 2010). Jones found that among people 12 and older who had misused opioids in their lifetime the odds of prescription opioid injection was higher in smaller metro and non-metro areas compared to large metro areas (Jones, 2018).

Table 6. Demographic, Socioeconomic, and Geographic Characteristics Associated with Prescription Opioid Injection

Lead Author, Year	Demographic Characteristics	Socioeconomic Characteristics	Geographic Characteristics
Butler, 2010	Increased odds of prescription opioid injection • Male vs female, aOR = 1.17 (95% CI: 1.02-1.34)[b] • White vs nonwhite, aOR = 1.93 (95% CI: 1.44-2.58)[b] Decreased odds of prescription opioids injection • As age increases, aOR = 0.96 (95% CI: 0.96-0.97)[b]	Decreased odds of prescription opioid injection • As years of education increase, aOR = 0.95 (95% CI: 0.92-0.99)[b]	
Young, 2010			• Prescription opioid injection more common in rural vs urban areas[a]
Jones, 2011	• Oxycodone injectors more likely to be White vs Black[a]	• Oxycodone injectors more likely to be unemployed vs employed[a]	
Surratt, 2011	Increased odds of prescription opioid injection • White vs African American, OR = 17.30 (95% CI: 6.30-47.62)[a] • Hispanic vs African American, OR = 5.97 (95% CI: 1.96-18.12)[a] • 18-24 vs ≥45 years old, OR=8.39 (95% CI: 4.34-16.25)[a] • 25-34 vs ≥45 years old, OR=5.53 (95% CI: 2.91-10.55)[a] • 35-44 vs ≥45 years old, OR=4.16 (95% CI: 2.09-8.27)[a] • Public treatment vs street drug use, OR = 3.69 (95% CI:1.63-8.34)[a] • Private treatment vs street drug use, OR = 6.63 (95% CI:3.04-14.46)[a] • Methadone vs street drug use, OR = 6.55 (95% CI:3.01-14.24)[a]		
Lankenau, 2012	• Mean age at prescription opioid injection = 17.7 years		

Black, 2013		Increased odds of prescription opioid injection • Unemployed vs employed, OR = 1.19 (95% CI: 1.09-1.31)[b] • Homeless vs not homeless, OR = 1.27 (95% CI: 1.15-1.41)[b]	
Lankenau, 2015	Increased incidence rate ratio (IRR) for prescription opioid injection • White vs other race, IRR = 1.39 (95% CI: 1.10-1.77)[a]		

Key Question 3. What is known about co-occurring substance use, mental health, and health-related outcomes among people who inject prescription opioids in the U.S.?

Twenty-five studies assessed co-occurring substance use, mental health, or health-related outcomes among people who inject prescription opioids (Peters et al., 2016; Zibbell et al., 2014; Lankenau et al., 2015; Silva et al., 2013; Havens et al., 2007; Havens et al., 2011b; Jenkins et al., 2011; Lankenau et al., 2012; Havens et al., 2013; Heimer et al., 2015; Mateu-Gelabert et al., 2015; Bennett et al., 2017; Eckhardt et al., 2017; Green et al., 2017; Jones, 2018; Surratt et al., 2017; Butler et al., 2010; Black et al., 2013; Jones et al., 2017; Jones et al., 2011; Johnson et al., 2013; Jones, 2013; CDC, 2013, Miller et al., 2014; Conrad et al., 2015).

Eight studies provided prevalence estimates of other substance injection or substance use among people who inject prescription opioids. Black et al., found that 10.3% of their sample of people misusing prescription opioids being assessed for treatment had injected prescription opioids and at least one other substance in the past 30 days (Black et al., 2013). Havens et al., reported that 23.1% of people who had injected prescription opioids in an Appalachian Kentucky sample had ever injected heroin, 12.1% had ever injected cocaine, 67.7% reported past 30 day misuse of benzodiazepines, 46.2% reported past 30 day use of marijuana, 24.6% reported past 30 day use of cocaine or crack, and 9.2% reported past 30 day use of methamphetamine (Havens et al., 2007). Johnson et al., reported among their cohort of young, urban individuals who injected prescription opioids, 93% had injected heroin, 90% had injected cocaine, 50% had injected methamphetamine, 33% had injected ketamine, and 30% had injected prescription stimulants (Johnson et al., 2013). Among people in New York City who

reported injection of oxycodone, Jones et al., reported that 100% used at least one other substance with 96% using heroin, 24% misusing other prescription opioids, 16% using cocaine, 12% using marijuana, 8% using benzodiazepines, and 8% using alcohol (Jones et al., 2011).

Three studies reported on the relationship between prescription opioid injection and heroin injection. Lankenau et al., reported that 50% of their cohort of young, urban individuals who inject drugs reported injecting heroin before injecting prescription opioids and 30% reported injecting prescription opioids prior to heroin injection (Lankenau et al., 2012). Mateu-Gelabert et al., reported only 8.7% of their young adult cohort in New York City injected prescription opioids prior to heroin use (Mateu-Gelabert et al., 2015). Bennet et al, found that 18% of people who reported occasional heroin use also reported injecting prescription opioids at least once in the past 30 days whereas 60% of people who frequently used heroin reported injecting prescription opioid at least once in the past 30 days, and 33% of people who frequently used heroin reported injecting prescription opioids on at least 15 days in the past 30 days (Bennett et al., 2017).

Nineteen studies examined the relationship between prescription opioid injection and substance use, mental health, and health-related outcomes using bivariable or multivariable methods (**Table 7**). Eight studies provided data on substance use (Lankenau et al., 2015; Jones, 2018; Surratt et al., 2017; Butler et al., 2010; Black et al., 2013; Jones et al., 2017; Jones et al., 2011; Jones, 2018); two studies provided data on mental health outcomes (Lankenau et al., 2015; Black et al, 2013); and sixteen reported on associations with health-related outcomes (Havens et al., 2007 ; Havens et al., 2011; Jenkins et al.,

2011; Black et al., 2013; Havens et al., 2013; Marder et al., 2013; Silva et al., 2013; Miller et al., 2014; Zibbell et al., 2014; Conrad et al., 2015; Heimer et al., 2015; Lankenau et al., 2015; Peters et al., 2016; Eckhardt et al., 2017; Green et al., 2017; Jones, 2018).

Using the national TEDS treatment admission data, Jones et al., found that prescription opioid injection was significantly associated with heroin, cocaine, marijuana, and methamphetamine use at treatment admission (Jones et al., 2017). Lankenau et al., also found a significant associated between prescription opioid injection and heroin and cocaine use as well as with having a history of being prescribed tranquilizers (Lankenau et al., 2015). Although Surrat et al., found a significant association between heroin use and prescription opioid injection, they found that cocaine use was negatively associated with prescription opioid injection among their population of individuals using drugs in South Florida (Surratt et al., 2017). In addition to substance use, several studies found a positive association between substance use disorders and prescription opioid injection. Jones found having a heroin use disorder or cocaine use disorder in the past year was associated with prescription opioid injection (Jones, 2018). Surratt et al., and Jones found increased odds of prescription opioid injection among people with prescription opioid use disorders (Surratt et al., 2017; Jones, 2018). Increasing years of opioid use (Butler et al., 2010), having a history of sniffing opioids (Lankenau et al., 2015), having a history of substance use treatment (Lankenau et al., 2015; Jones et al., 2017; Jones, 2018), and living with someone who uses alcohol or drugs (Black et al., 2013) were positively associated with prescription opioid injection.

Five studies identified an increased risk for HCV infection among people who inject prescription opioids (Zibbell et al., 2014; Lankenau et al., 2015; Havens et al., 2007; Havens et al., 2013; Eckhardt et al., 2017)); however, although Eckhardt found a positive association at the bivariable level, the relationship was not statistically significant at the multivariable level (Eckhardt et al., 2017). Two studies investigating the HIV outbreak in Scott County, Indiana in 2015 found a significant relationship between prescription opioid injection, primarily injection of oxymorphone, and HIV infection (Conrad et al., 2015; Peters et al., 2016). A nationally representative study found that people who injected prescription opioids had higher odds of HIV compared to people who injected other drugs but not prescription opioids (Jones, 2018). Black et al., found no statistically significant association between prescription opioid injection and diagnosis of HIV among their large study of individuals being assessed for substance use treatment (Black et al., 2013).

Black et al., found that prescription opioid injection was positively associated with liver disease, having a recent ED visit, recent treatment for pain, and receiving treatment for a nonfatal overdose (Black et al., 2013). Three additional studies found an increased risk of nonfatal overdose among people who inject prescription opioids (Havens et al., 2011; Jenkins et al., 2011; Silva et al., 2013), although this relationship was not statistically significant in multivariable analyses in two of the studies (Jenkins et al., 2011; Silva et al., 2013). Similar to Black et al., Heimer et al., found a significant positive association between having chronic pain and reporting prescription opioid injection (Heimer et al., 2015). Green et al., reported that prescription opioid injection was associated with an increased risk for death or other major outcome compared to oral

opioid misuse among poison control center exposure calls (Green et al., 2017). Lankenau et al., found that having a history of psychiatric hospitalization and a history of incarceration were positively associated with prescription opioid injection (Lankenau et al., 2015). Black et al., also found a significant association between psychiatric severity score and prescription opioid injection (Black et al., 2013). Two studies reported on the strong positive association between oxymorphone injection and the development of thrombotic thrombocytopenic purpura (TTP)-like illness (Marder et al., 2013; Miller et al., 2014).

Table 7. Substance Use, Mental Health, and Health Outcomes Associated with Prescription Opioid Injection

Substance Use • Heroin use (Jones 2011[a], Surratt, 2011[a]; Lankenau, 2015[a]; Jones, 2017[b]) • Cocaine use (Lankenau, 2015[a]; Jones, 2017[b]) • Marijuana use (Jones, 2017[b]) • Methamphetamine use (Jones, 2017[b]) • Frequent prescription opioid misuse (Jones, 2013[b]) • Years of opioid misuse (Butler, 2010[b]) • History of sniffing prescription opioids (Lankenau, 2015[a]) • History of being prescribed tranquilizers (Lankenau, 2015[a]) • Living with someone who uses alcohol or drugs (Black, 2013[b]) Substance Use Disorders • Prescription opioid use disorder (Surratt, 2011[a]; Jones, 2017[b]) • Cocaine use disorder (Jones, 2017 [b]) • Heroin use disorder (Jones, 2017 [b]) Substance Use Treatment • History of substance use treatment (Lankenau, 2015 [a]; Jones, 2017 [b]; Jones, 2017 [b]) Mental Health • History of psychiatric hospitalization (Lankenau, 2015[a]; Black, 2013[b]) Other Outcomes • History of incarceration (Lankenau, 2015[a])
Health Outcomes

• Hepatitis C virus infection (Havens, 2007 [a]; Havens, 2013[b]; Zibbell, 2014[a,b]; Lankenau, 2015[a]; Eckhardt, 2017[a]) • Liver disease (Black, 2013[b]) • HIV infection (Conrad, 2015 [a]; Peters, 2016[a]; Jones, 2018[b]) • Having a recent ED visit (Black, 2013 [b]) • Non-fatal overdose (Havens, 2011[a,b]; Jenkins, 2011[a]; Black, 2013[b]; Silva, 2013[a]) • Recent treatment for pain/chronic pain (Black, 2013[b]; Heimer, 2015[a,b]) • Thrombotic thrombocytopenic purpura (TTP)-like illness [specific to oxymorphone injection] (Marder, 2013[b]; Miller, 2014[a]) • Death or other major outcome (Green, 2017[a])
a Based on bivariable analysis
b Based on multivariable analysis

Key Question 4. What other characteristics have been associated with prescription opioid injection in the U.S.?

Eight studies provided information related to key research question four (Zule et al., 2016; Havens et al., 2007; Havens et al., 2013; Jones, 2018; Surratt et al., 2017; Cicero et al., 2011; Johnson et al., 2013; Conrad et al., 2015). One study provided data on the source for injected prescriptions (Cicero et al., 2011)), one study provided data on sexual risk behaviors among people who inject prescription opioids (Johnson et al., 2013), and seven studies reported on injection practices among people who inject prescription opioids (Havens et al., 2007; Havens et al., 2013; Johnson et al., 2013; Conrad et al., 2015; Zule et al., 2016; Surratt et al., 2017; Jones, 2018).

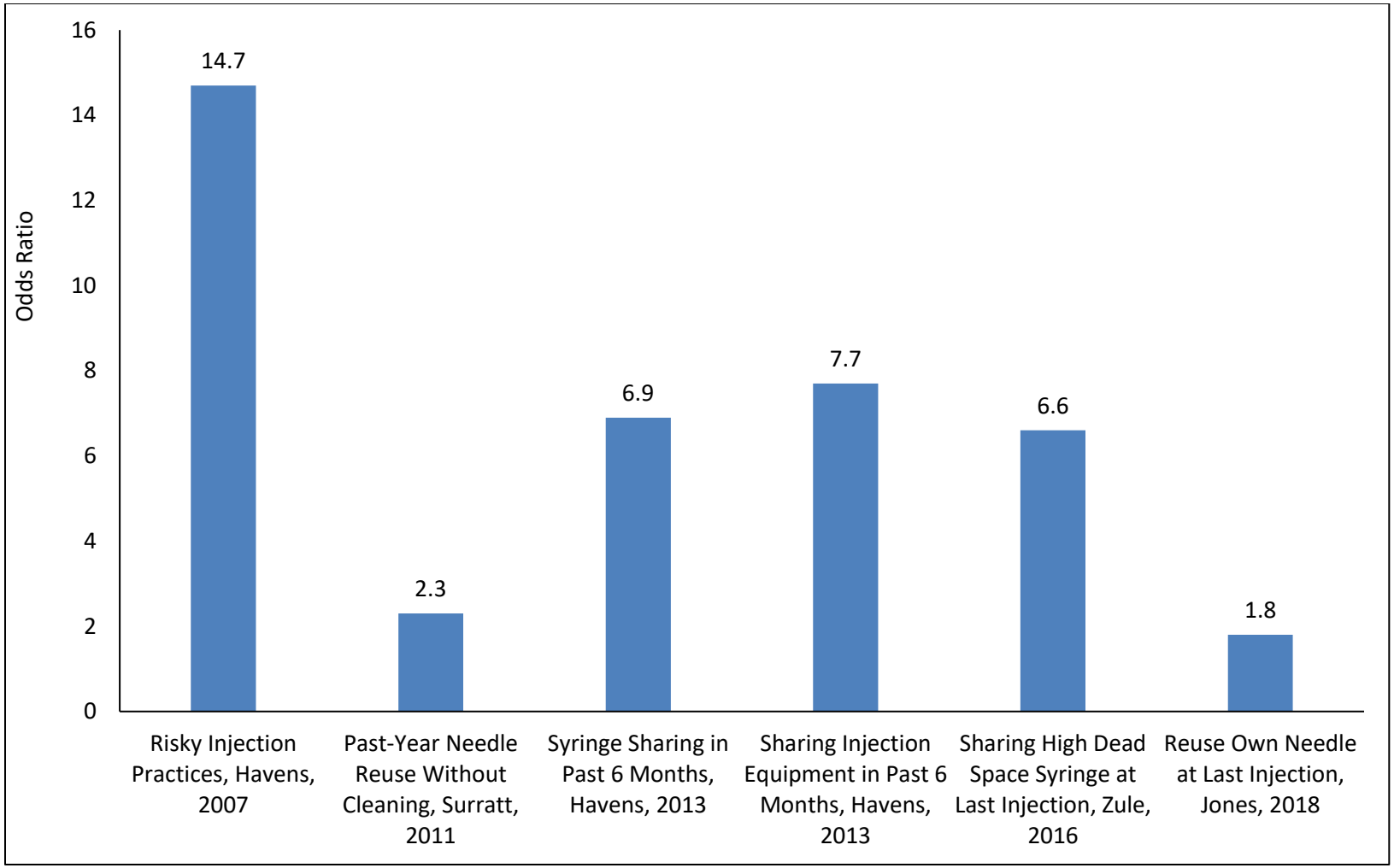
Cicero et al., found, among a sample of people entering treatment for opioid use disorder, that drug dealers and theft were the most likely sources of opioids for individuals who misused prescription opioids and medical sources were least likely among people who inject opioids compared to those who do not inject. In the same study, among a sample of people who used drugs in South Florida, drug dealers, theft, and

medical sources of opioids were all more likely to be a source for opioids for people who injected opioids compared to those who do not inject (Cicero et al., 2011). Johnson et al., found that 75% of their cohort of young urban individuals who inject prescription opioids reported engaging in risky sexual behaviors such as having sex without a condom while under the influence of a misused prescription drug (Johnson et al., 2013).

Engaging in injection practices that increase risk for transmission of infectious diseases was common among people who inject prescription opioids in the studies that examined this outcome. Jones, using data from a nationally representative sample, found that 57.2% of people reporting lifetime prescription opioid injection reused their own needle the last time they used a needle to inject drugs, 19.5% reused someone else's needle, 21.2% reported someone else reused their needle, and 26.8% reported cleaning their needle with bleach the last time they injected (Jones, 2018). This study also found that people who injected prescription opioids were significantly less likely to receive syringes from a syringe services program (SSP) compared to people who had injected other drugs but not prescription opioids. Havens et al., found that among people who inject prescription opioids in Appalachian Kentucky, 10.5% reported receptive needle sharing, 26.3% reported distributive needle sharing, 42.1% reported sharing other injection equipment such as cottons or cookers, 52.6% very often cleaned their needles with water only, and 10.5% reported very often using bleach to clean their needle (Havens et al, 2007). Johnson et al., found that 58% of their sample of people who inject prescription opioids engaged in risky injection behaviors such as sharing of syringes or other injection equipment (Johnson et al., 2013). Conrad et al., reported that among a cohort of recently diagnosed HIV cases, the average number of syringe-sharing partners

was nine, and that individuals reported between one and six injection partners per injection event and engaged in between four to 15 injection events per day (Conrad et al., 2015). Five studies found consistently elevated odds of risky injection behaviors or sharing of syringes or injection equipment among people who inject prescription opioids compared to people who inject drugs but not prescription opioids (Havens et al., 2007; Surratt et al., 2011; Havens et al., 2013; Zule et al., 2016; Jones, 2018) (**Figure 9**).

Figure 9. Odds of Risky Injection Practices Associated with Prescription Opioid Injection



DISCUSSION

Out of more than 4,000 potential articles identified in the literature search, 58 addressed one or more of the four key research questions on prescription opioid injection in the U.S. Based on these data, the overall estimated prevalence of lifetime prescription opioid injection is approximately 0.3% among people 12 years and older in the U.S. The prevalence of prescription opioid injection among people seeking or receiving treatment for opioid use disorder was substantially higher – with 16%-25% reporting recent prescription opioid injection in the studies that included large, geographically diverse populations.

Importantly, general population studies as well as studies of people seeking or receiving treatment indicate that prescription opioid injection has significantly increased in the past decade. The prevalence of prescription opioid injection increased 65% between 2003-2005 and 2012-2014 among people 12 years and older in a nationally representative study. Similarly, the prevalence among treatment admissions with prescription opioid use disorders increased 55% between 2004 and 2013. These findings parallel increases in injection-related health harms such as viral hepatitis and endocarditis during the same time period (Suryaprasad et al., 2014; Harris et al., 2016; Zibbell et al., 2018; Ronan & Herzig, 2016).

Although there was substantial heterogeneity across the reviewed studies, a number of demographic, socioeconomic, and clinical characteristics were associated with an increased risk of prescription opioid injection in at least two of the reviewed studies. Demographic characteristics included male sex, non-Hispanic white race, age 18 to 44 years, and living in a rural area. Socioeconomic factors included lower educational

attainment, being homeless, being unemployed, having a low annual household income, being uninsured, and receiving Medicaid. Clinical characteristics included initiating prescription opioid misuse at an earlier age, having a prescription opioid use disorder, using heroin or having a heroin use disorder, using cocaine or having a cocaine use disorder, prior receipt of substance use treatment, experiencing a nonfatal overdose, having chronic pain, and having a history of psychiatric illness or high severity of psychiatric problems. These findings underscore the complex clinical and social challenges facing individuals who are injecting prescription opioids, and point to the importance of implementing clinical interventions that address underlying opioid misuse and co-occurring substance use and mental disorders along with policies that address the underlying social determinants of health, such as stable and affordable housing, education and employment opportunities, and insurance coverage and access to care, that are critical to improve the health of people who inject prescription opioids and other drugs.

The findings of this review have important implications for opioid prevention and treatment policy, clinical practice, and future research. In the area of opioid prevention, several studies found earlier age of initiation of prescription opioid misuse and increasing years of misuse are associated with increased risk of prescription opioid injection. These findings highlight the importance of broad implementation of strategies to prevent or delay the onset of prescription opioid misuse among youth. This includes community and school-based prevention programs as well as efforts to curb inappropriate opioid prescribing in order to reduce the direct exposure of opioids through prescribing to youth and indirectly through environmental availability of opioids that can be diverted for misuse. Preventive interventions have demonstrated long-term effectiveness in reducing

opioid misuse among youth with protective effects into early adulthood in multiple randomized controlled trials (Spoth et al., 2013).

The significantly elevated risk of prescription opioid injection among people with a prescription opioid use disorder and among those using heroin or with a heroin use disorder coupled with the increased risk for overdose associated with prescription opioid injection highlight the pressing need to rapidly expand access to medication-assisted treatment (MAT) for opioid use disorder. MAT, with methadone or buprenorphine in particular, reduces opioid use, opioid-related mortality, and the transmission of infectious diseases such as HIV and HCV (Mattick et al., 2009; Mattick et al., 2014; Lee et al., 2016; Tsui et al., 2014; Krupitsky et al., 2011; Schwartz et al., 2013). The increased overdose risk also underscores the importance of access to overdose prevention education and naloxone among people who inject prescription opioids.

The high prevalence of risky injection practices among people who inject prescription opioids provides insight into the underlying mechanisms contributing to elevated HCV infection risk among people who inject prescription opioids. These findings, coupled with data indicating people who inject prescription opioids are less likely to get syringes from a SSP (Jones,2018) and often lack awareness of these programs and the services they offer (Mateu-Gelabert, 2015), lend empirical support for initiatives to educate this at-risk population about safer injection techniques and harm reduction service availability, as well as efforts to expand the availability of comprehensive SSPs. Scaling these interventions is acutely needed in rural areas of the U.S. and in the South and Midwest where access to these interventions is particularly limited and prescription opioid misuse, including prescription opioid injection, as

identified in this review, is disproportionately high (Jones, 2018; Jones et al., 2017; Des Jarlais et al., 2015; Van Handel et al., 2016).

STUDY LIMITATIONS

This literature review is subject to limitations. First, among the included studies, only two used nationally representative samples, the remainder examined prescription opioid injection among different geographic populations often using convenience samples; thus, many of the findings may not be generalizable to all people who inject prescription opioids. Second, a majority of the studies only provided information on overall prevalence and did not provide data on other key research questions of interest. Third, only a minority of articles included prescription opioid injection as a specific aim of the study. Fourth, many of the studies were based on data from the same database or study population, although in some cases the time period was different. Six studies were based on data from the National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO) database; six studies used data from the Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS) system; six studies included people in rural Appalachian Kentucky; and four studies used data from the same sample of young, urban individuals who use drugs. This further limits the representativeness of included studies. Fifth, only a minority of studies examined the association between various demographic or other factors and prescription opioid injection using multivariable methods to control for other variables that might influence prescription opioid injection. Sixth, included studies were cross-sectional; no studies were randomized or prospective, therefore precluding causal inferences from observed associations. Seventh, many of the studies used some form of survey or interview to capture

prescription opioid injection and other data from participants; thus, the reliability of the study findings is dependent on the accuracy and honesty of reporting among the participants and are subject to recall and social desirability bias. Eight, only 12 studies included data from 2014 or more recently. New patterns or correlates of prescription opioid injection may have emerged since that time. Ninth, the majority of studies were among individuals seeking or receiving treatment. This population may not be representative of all people who inject prescription opioids; thus, this review may not identify important risk factors and relevant policy interventions for prescription opioid injection. Tenth, the review itself is subject to publication bias as studies that found no significant effects might not have been pursued for publication or published. Finally, despite a structured and systematic approach to the literature search, it is possible that relevant articles were not identified with the search strategy used for this review.

Future research should attempt to address these limitations and build on the gaps identified in this review. For example, the most recent estimate of population-level prevalence is based on data from 2014. Since that time, the opioid epidemic has evolved considerably, including a decline in the prescribing of opioid analgesics (Guy et al., 2017), continued increases in heroin use (SAMHSA, 2017), and the emergence of highly potent synthetic opioids such as illicitly made fentanyl and fentanyl analogs that are substantially shifting the illicit drug market in the U.S. (Jones et al., 2018; Drug Enforcement Administration, 2017). How these changes are influencing the prevalence of prescription opioid injection and correlates of prescription opioid injection has not been explored in the literature. By design, this review focused on identifying the prevalence of prescription opioid injection in the U.S. and the characteristics of individuals who inject

prescription opioids. The review did not explore questions related to the impacts of opioid-related prevention or treatment policies or programs; future research should assess these important research questions. Finally, although this study was not specifically focused on the qualitative experiences of people who inject prescription opioids, the literature review uncovered few studies that specifically explored the attitudes, beliefs, preferences, and experiences of people who inject prescription opioids. Future research should prioritize the study of this population, including treatment and non-treatment seeking populations, in order to better inform the development of policies and programs that meet the needs of this at-risk, vulnerable population. Finally, included studies were cross sectional and asked about drug use behaviors retrospectively; future studies should employ prospective designs to provide insights into the trajectories and substance use patterns of people who have not yet initiated prescription opioid injection.

CONCLUSION

Despite the substantial published literature on prescription opioid misuse, use disorder, and overdose, only a small proportion provided information on the four key research questions of this review. The alarming trends of escalating overdose deaths and rising rates of opioid injection and infectious disease transmission demand that policymakers, public health practitioners, and clinicians take actions to expand opioid use disorder prevention and treatment services, access to preventive services, testing, and treatment for HIV and viral hepatitis, and availability of SSPs that can provide comprehensive risk reduction services to PWID. There is a pressing need for additional research on the prevalence and characteristics of people who inject prescription opioids and other drugs.

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Jones CM. Trends and Key Correlates of Prescription Opioid Injection Misuse in the United States. Addictive Behaviors. 2018 Mar;78:145-152.

Chapter 3: Trends and Key Correlates of Prescription Opioid Injection Misuse in the United States

[Published in Addictive Behaviors: 2018 Mar;78:145-152]

This manuscript describes the findings from an analysis of data from the 2003 to 2014 National Surveys on Drug Use and Health. This study provides the first nationally representative analysis of prescription opioid injection in the U.S. – providing estimates on the magnitude of prescription opioid injection and identifying key correlates of prescription opioid injection, including quantifying the extent of unsafe injection practices and syringe sources for people who inject prescription opioids and other drugs.

Injection drug use is a highly efficient mechanism to transmit blood-borne infectious diseases such as human immunodeficiency virus (HIV), hepatitis C virus (HCV), and hepatitis B virus (HBV) (CDC, 2011; CDC, 2015; Wejnert et al., 2016). People who inject drugs (PWID) also are at increased risk for other injection-related infections such as endocarditis, substance use disorders, and drug overdoses (Degenhardt et al., 2010; Lake & Kennedy, 2016; Ronan & Herzig, 2016; Wurcel et al., 2016).

In the U.S., over the past decade there has been an increased focus from federal and state policymakers to expand efforts to reduce unprecedented increases in prescription opioid misuse, use disorder, and overdose (White House Office of National Drug Control Strategy, 2010; HHS, 2015; National Governors Association, 2016). More recently, concerns from policymakers, clinicians, and the public health community have centered on emerging data indicating an increase in harms related to prescription opioid injection misuse (Strathdee & Beyer, 2015; Suryaprasad et al., 2014).

Research shows that people who misuse opioids often progress over time from less dangerous routes, such as oral misuse, to more dangerous routes, such as injection

(Harocopos et al., 2016; Jones et al. 2011; Mars et al., 2014; Syvertsen et al., 2017). Injecting provides faster drug delivery and onset compared to oral administration, thereby intensifying the reinforcing effects of opioids and increasing addiction vulnerability (Black et al., 2013; Compton & Volkow, 2006). Recent research shows that while overall prescription opioid misuse has declined or stabilized in the U.S., the prevalence of high-risk use – frequent misuse and opioid use disorder – have increased (Han et al., 2015), and both have been associated with injection misuse (Black et al., 2013; Jones, 2013). Taken together, these findings suggest that injection misuse has been increasing.

Additional indicators suggesting an increase in prescription opioid injection misuse include the significant rise in injection-related infections associated with opioid hospitalizations between 2002 and 2012 (Ronan & Herzig, 2016). Since the mid-2000s, rates of HCV infection have been increasing, especially in areas with high rates of prescription opioid misuse (Suryaprasad et al., 2014; Zibbell et al., 2015). An analysis in Kentucky, Tennessee, Virginia, and West Virginia found that as opioid treatment admissions reporting injection misuse increased so did rates of HCV between 2006 and 2012 (Zibbell et al., 2015). In addition, after several years of declines, the stabilization of HIV diagnoses since 2010 for nonurban and since 2012 for urban whites who inject drugs is thought to be related to the ongoing prescription opioid and heroin crisis (Wejnert et al., 2016). Concerns over prescription opioid injection were acutely brought to national attention during the 2015 outbreak of 181 HIV cases in Indiana associated with injection of prescription opioids, especially oxymorphone (Peters et al., 2016).

These trends are concerning given research showing that prescription opioid injection remains a risk factor for HCV even after accounting for injection of other drugs

including heroin. This increased risk is likely a result of unique factors such as the process of preparing prescription opioids for injection, sharing and injecting residual prescription opioid "washes", and use of high dead space syringes (Lankenau et al., 2015; Roy et al., 2011; Zibbell et al., 2014). Research also indicates other unique harms for prescription opioid injection misuse such as the development of thrombotic thrombocytopenic purpura-like illness and acute kidney injury associated with the injection of excipients included in prescription opioid formulations (Ambruzs et al., 2014; CDC, 2013). In addition, studies demonstrate that people who inject prescription opioids often engage in risky injection practices (Havens et al., 2007; Johnson et al., 2013; Surratt et al., 2011). Johnson et al., found that > 50% of the urban 16–25 year olds in their study who injected prescription opioids engaged in sharing of syringes or injection equipment (Johnson et al., 2013). In Appalachian Kentucky, Havens et al., 2007, found that 10.5% of people who injected prescription opioids engaged in receptive needle sharing, 26.3% reported distributive needle sharing, and 52.6% very often cleaned their injection equipment with water only.

Despite growing concerns over prescription opioid injection misuse, little recent research is available on the magnitude, characteristics, injection practices, and syringe sources for people who inject prescription opioids. To address these information gaps and inform targeted prevention, treatment, and risk reduction efforts, this study examines nationally representative data from 2003 to 2014 to estimate trends in prescription opioid injection, identify demographic and substance use characteristics associated with prescription opioid injection, and examine injection practices and syringe sources for people who inject prescription opioids.

METHODS

Data source

Data are from the 2003–2014 National Surveys on Drug Use and Health (NSDUH). NSDUH, an annual survey conducted by the Substance Abuse and Mental Health Services Administration, provides national estimates of the use of illicit drugs, including misuse of certain prescription drugs, alcohol, and tobacco among the U.S. civilian, noninstitutionalized population aged 12 years and older (Substance Abuse and Mental Health Services Administration (SAMHSA, 2016). NSDUH employs a state-based design with an independent, multistage area probability sample within each state and the District of Columbia. In addition, sensitive questions in the NSDUH are completed using audio computer-assisted survey interviewing which has been shown to increase honest, accurate reporting. The annual weighted interview response rate for NSDUH during the study period ranged from 71%–79%. Additional details on NSDUH methodology can be found elsewhere (SAMHSA, 2016).

Substance use measures

In NSDUH, prescription opioid misuse (nonmedical use) is defined as using a prescription opioid without a prescription or use [even with a prescription] simply for the experience or feeling the drug causes. Respondents who report misuse are classified as having any lifetime misuse, past-year misuse, or past-month misuse based on the recency of misuse. Respondents are also asked to report their age of first prescription opioid misuse. For this analysis, age of first misuse is categorized as: 14 years or younger, 15–17, 18–20, 21–25, and 26 or older. Consistent with prior research, (Muhuri et al., 2013) a binary variable was created to identify recent initiates for prescription opioid misuse;

defined as respondents who reported their first misuse of prescription opioids within the five years before participation in the survey. The same was done for recent initiates of cocaine, heroin, and stimulants.

NSDUH respondents are asked about injection drug use. For this study, prescription opioid injection misuse was identified based on response to the question "Have you ever, even once, used a needle to inject any other drug/any drug that was not prescribed for you or that you took only for the experienced or feeling it caused?" Respondents who answered yes to this question are then asked to list the drug(s) they injected. Individuals reporting any prescription opioid for this question were classified as having lifetime prescription opioid injection misuse. Respondents are asked separate questions to determine if they have ever injected heroin, cocaine, or stimulants. For this analysis, respondents are classified into the following binary variables: ever injected any drug, ever injected any opioid (prescription opioids and/or heroin), ever injected prescription opioids, ever injected heroin, ever injected cocaine, and ever injected stimulants.

NSDUH estimates past-year use disorders (abuse or dependence) for specific substances based on assessments of diagnostic criteria contained in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (American Psychiatric Association, 1994). For this study, past-year use disorders for prescription opioids, heroin, cocaine, stimulants, and sedatives (sedatives and/or tranquilizers) were included.

Injection practices and syringe/needle sources

Respondents are asked a series of questions about their injection practices and syringe sources related to the last time they used a needle to inject drugs. Injection

practices are categorized into four groups: 1) reused a needle respondent had used before; 2) used a needle respondent knew or suspected someone else had used before; 3) someone else used needle after respondent; 4) cleaned needle with bleach before use. Syringe source is categorized into the following: 1) syringe services program (SSP); 2) pharmacy; 3) given by/stolen from someone; 4) other (e.g., bought on street, got in shooting gallery, from drug dealer, from trash, some other way).

Health and healthcare-related outcomes

The following binary variables are assessed: ever received drug or alcohol treatment, ever having HIV, ever having hepatitis, and ever having a sexually transmitted disease (STD).

Demographic measures

Demographic data include: sex; age (12–17, 18–25, 26 or older); race/ethnicity (non-Hispanic white, other race/ethnicity); place of residence (residence in a Core-Based Statistical Area (CBSA) with ≥ 1 million population, residence in CBSA with < 1 million population, and residence not in CBSA); annual household income (<$20,000, $20,000–$49,999, $50,000 or more); and insurance status (uninsured, Medicaid, or private or other insurance).

Data analysis

Annual NSDUH data were pooled into four time periods containing 3 years of data for each time period: 2003–2005, 2006–2008, 2009–2011, 2012–2014. Pooling data improves the precision of estimates, reduces estimate suppression, and enables statistical comparisons across demographic groups. Estimates are presented as annual average rates.

To assess trends in injection drug use during the study period, annual average rates were computed for each time period. First, to assess trends in any lifetime injection drug use and for lifetime injection of specific substances among the overall population, rates of injection per 1000 population aged 12 years or older were calculated for any drug, any opioid, prescription opioids, heroin, cocaine, and stimulants. Second, to assess trends in lifetime injection of specific substances among people 12 years and older who reported lifetime misuse of prescription opioids, use of heroin, use of cocaine, or misuse of stimulants, rates of injection per 1000 users of each specific substance were calculated for any opioid, prescription opioids, heroin, cocaine, and stimulants. Third, to assess how injection of specific substances has changed over time among people who initiated use (misuse) of the specific substance within the five years before participation in the survey (i.e., recent initiates), rates of injection per 1000 recent initiates were calculated for prescription opioids, heroin, cocaine, and stimulants. Finally, to assess trends in lifetime injection of prescription opioids among people who have ever injected drugs and among people who inject other specific drugs, rates of prescription opioid injection per 1000 injectors were calculated for any drug, heroin, cocaine, and stimulants. Finally, to examine trends only among people misusing prescription opioids, rates of lifetime prescription opioid injection per 1000 people reporting lifetime misuse of prescription opioids by select demographic measures were calculated.

Two-sided *t* -tests were used to assess statistically significant differences between 2012–2014 annual average rates and earlier time periods. To assess statistically significant changes in trends, bivariate logistic regression models were applied to test p-

values of beta coefficients of the year variable. A p value of < 0.05 was considered statistically significant.

To compare injection practices and syringe sources for people reporting prescription opioid injection to PWID but not prescription opioids, annual average percentages for 2012–2014 were calculated for each injection practice and syringe source. Two-sided *t* -tests were used to assess statistically significant differences between the two groups; a p value < 0.05 was considered statistically significant.

Finally, three logistic regression models were developed to identify demographic and substance use characteristics, injection practices and syringe/needle sources, and health and healthcare-related outcomes associated with prescription opioid injection. The first model assessed the relationship between lifetime prescription opioid injection misuse and demographic and substance use characteristics among the overall population of people 12 years or older. The second model assessed the relationship between lifetime prescription opioid injection misuse and demographic and substance use characteristics, but was limited to people who had ever misused prescription opioids. The final model assessed the relationship between lifetime prescription opioid injection and demographic, substance use, health-related outcomes, injection practices, and syringe/needle sources among people who had ever injected any drug. Associations are reported as adjusted odds ratios with 95% confidence intervals.

STATA (version 14.2, Stata Corp. College Station, Texas) survey procedures were used to account for the complex sample design and sampling weights of the NSDUH data.

RESULTS

Prescription opioid injection misuse increased significantly during the study period (**Table 8**). Among people 12 years or older, the rate of prescription opioid injection increased from 1.6 per 1000 in 2003–2005 to 2.7 per 1000 in 2012–2014 (p value for trend < 0.05). This equates to an annual average of 710,100 individuals who had ever injected prescription opioids in 2012–2014 compared to 393,300 in 2003–2005. Rates of any opioid injection and heroin injection also increased significantly. Rates of any opioid injection increased from 7.3 per 1000 in 2003–2005 to 10.0 per 1000 in 2012–2014 (p value for trend < 0.05). For heroin, rates increased from 6.5 per 1000 in 2003–2005 to 8.9 per 1000 in 2012–2014 (p value for trend < 0.05). Trends for any drug, cocaine, and stimulant injection did not significantly change during the study period.

Table 8. Trends in Injection Drug Use, 2003–2005 to 2012–2014.

	2003–2005 Rate (95% CI)	2006–2008 Rate (95% CI)	2009–2011 Rate (95% CI)	2012–2014 Rate (95% CI)	Percent change 2003–2005 to 2012–2014	p value for trend [a]
Rate per 1000 population [b]						
Any drug	15.0 (13.9–16.0) *	16.4 (15.4–17.5)	14.8 (13.6–16.1)	16.7 (15.4–18.1)	11.7%	0.175
Any opioid	7.3 (6.6–8.1) *	8.5 (7.8–9.3) *	7.8 (6.9–8.6) *	10.0 (9.0–11.0)	37.0%	< 0.05
Prescription opioid	1.6 (1.3–2.0) *	1.9 (1.6–2.3) *	2.2 (1.8–2.7)	2.7 (2.2–3.2)	65.4%	< 0.05
Heroin	6.5 (5.8–7.3) *	7.6 (6.8–8.3) *	6.7 (5.9–7.5) *	8.9 (8.0–9.9)	36.5%	< 0.05
Cocaine	8.4 (7.6–9.3)	9.1 (8.2–10.0)	8.5 (7.5–9.4)	8.8 (7.8–9.7)	3.7%	0.909
Stimulants	6.6 (5.9–7.3)	6.7 (6.0–7.4)	6.4 (5.6–7.1)	7.5 (6.6–8.3)	12.9%	0.171
Rate per 1000 users [c]						
Any opioid	52.4 (47.1–57.8) *	59.0 (53.8–64.1) *	53.7 (48.1–59.4) *	69.6 (62.9–76.2)	32.7%	< 0.05
Prescription opioid	11.2 (9.0–13.4) *	12.3 (10.0–14.6) *	15.2 (12.4–18.0)	19.2 (15.8–22.6)	71.5%	< 0.05
Heroin	457.9 (419.9–495.9)	492.8 (451.3–534.3)	421.6 (388.9–454.2) *	479.0 (444.2–513.7)	4.6%	0.991
Cocaine	58.8 (53.4–64.3)	62.2 (56.2–68.2)	56.9 (51.0–62.8)	59.7 (53.9–65.5)	1.5%	0.837
Stimulants	75.3 (66.8–83.8) *	81.0 (72.9–89.1)	80.9 (71.2–90.5)	93.0 (82.6–103.4)	23.5%	< 0.05
Rate per 1000 recent initiates [d]						
Prescription opioid	2.6 (1.7–3.4) *	3.3 (2.0–4.6) *	6.2 (4.7–7.8)	7.7 (5.4–10.0)	200.0%	< 0.05
Heroin	313.2 (265.2–361.2) *	333.2 (285.7–380.8) *	338.7 (298.6–378.9) *	406.4 (368.5–444.3)	29.8%	< 0.05
Cocaine	19.2 (14.8–23.7)	20.6 (15.8–25.4)	20.5 (15.1–25.8)	21.5 (16.7–26.3)	11.7%	0.570
Stimulants	36.0 (26.4–45.7)	25.5 (19.2–31.8) *	27.8 (21.1–34.6)	39.2 (29.3–49.1)	8.8%	0.611
Rate of prescription opioid injection per 1000 injectors [e]						
Any drug	109.2 (87.1–131.4) *	116.8 (95.4–138.1) *	150.8 (124.1–177.6)	161.8 (134.5–189.0)	48.1%	< 0.05
Heroin	129.2 (92.6–165.9)	127.6 (90.0–165.1)	169.2 (133.6–204.9)	178.1 (142.2–214.0)	37.8%	< 0.05

	2003–2005 Rate (95% CI)	2006–2008 Rate (95% CI)	2009–2011 Rate (95% CI)	2012–2014 Rate (95% CI)	Percent change 2003–2005 to 2012–2014	p value for trend [a]
Cocaine	134.8 (103.6–166.1)	145.1 (113.5–176.6)	166.9 (128.9–204.8)	182.4 (146.5–218.2)	35.3%	< 0.05
Stimulants	116.8 (86.3–147.3)	137.8 (102.5–173.1)	165.2 (116.3–214.1)	166.8 (121.9–211.6)	42.8%	0.050

∗ Rate is statistically significantly different than 2012–2014 rate; $p < 0.05$.

a To assess statistically significant changes in trends, bivariate logistic regression models were applied to test p-values of beta coefficients of the year variable across the study period.

b Numerator is number of people reporting lifetime injection of any drug [or lifetime injection of a specific substance and denominator is number of people aged 12 years and older.

c Numerator is number of people reporting lifetime injection of a specific substance and denominator is number of people aged ≥12 reporting lifetime use (misuse) of specific substance.

d Numerator is number of recent initiates for specific substance reporting lifetime injection of specific substance and denominator is number of recent initiates for that specific substance.

e Numerator is number of people reporting lifetime injection of prescription opioids and denominator is the number of people reporting lifetime injection of any drug or a specific drug

When rates were calculated per 1000 people using each substance, significant increases in trends were found for prescription opioid injection, any opioid injection, and stimulant injection. Rates of prescription opioid injection increased from 11.2 per 1000 people misusing prescription opioids in 2003–2005 to 19.2 in 2012–2014 (p value for trend < 0.05). Any opioid injection increased from 52.4 in 2003–2005 to 69.6 in 2012–2014 (p value for trend < 0.05). Stimulant injection increased from 75.3 in 2003–2005 to 93.0 in 2012–2015 (p value for trend < 0.05). Trends for heroin and cocaine injection did not change significantly.

Among recent initiates, rates of prescription opioid injection increased from 2.6 per 1000 recent initiates in 2003–2005 to 7.7 in 2012–2014 (p value for trend < 0.05). In addition, heroin injection among recent heroin initiates increased from 313.2 in 2003–2005 to 406.4 in 2012–2014 (p value for trend < 0.05). Trends in cocaine and stimulant injection did not change significantly.

Prescription opioid injection increased among PWID. Specifically, prescription opioid injection increased from 109.2 per 1000 PWID in 2003–2005 to 161.8 in 2012–2014 (p value for trend < 0.05). Significant increases in prescription opioid injection also were found among people injecting heroin, from 129.2 per 1000 in 2003–2005 to 178.1 in 2012–2014 (p value for trend < 0.05) and among people injecting cocaine, from 134.8 in 2003–2005 to 182.4 in 2012–2014 (p value for trend < 0.05). No significant change occurred among people injecting stimulants.

Among people who had ever misused prescription opioids, multiple demographic groups experienced significant increases in prescription opioid injection trends (**Table 9**). Among females, rates increased from 7.9 per 1000 in 2003–2005 to 15.8 in 2012–2014 (p

value for trend < 0.05). For males, rates increased from 13.9 in 2003–2005 to 21.9 in 2012–2014 (p value for trend < 0.05). Significant increases in rates also were found among 18–25 year olds (p value for trend < 0.05), people 26 years and older (p value for trend < 0.05), non-Hispanic whites (p value for trend < 0.05), people living in CBSA with ≥ 1 million population (p value for trend < 0.05), CBSA < 1 million population (p value for trend < 0.05), and in non-CBSAs (p value for trend < 0.05), people with annual household incomes between $20,000–$49,999 (p value for trend < 0.05), and $50,000 or more (p value for trend < 0.05), the uninsured (p value for trend < 0.05), and people with private or other insurance (p value for trend < 0.05).

Table 9. Trends in rates [+] of prescription opioid injection misuse among people who have ever misused prescription opioids, 2003–2005 to 2012–2014.

	2003–2005 Rate (95% CI)	2006–2008 Rate (95% CI)	2009–2011 Rate (95% CI)	2012–2014 Rate (95% CI)	Percent change 2003–05 to 2012–14	p value for Trend [a]
Sex						
Female	7.9 (5.4–10.4) [*]	12.0 (8.2–15.8)	13.2 (9.3–17.0)	15.8 (12.5–19.2)	100.5	< 0.001
Male	13.9 (10.4–17.4) [*]	12.5 (9.1–16.0) [*]	16.8 (12.7–20.9)	21.9 (16.4–27.3)	57.3	0.005
Age, y						
12–17	[*]	[*]	[*]	[*]	--	0.617
18–25	8.4 (6.3–10.6) [*]	8.2 (5.8–10.7) [*]	13.9 (11.2–16.7) [*]	20.3 (16.7–24.0)	140.7	< 0.001
26 and older	13.4 (10.3–16.6) [*]	15.0 (11.7–18.3)	16.8 (12.9–20.7)	20.2 (15.8–24.5)	50.7	0.010
Race/Ethnicity						
Other race/ethnicity	4.7 (7.2–8.6)	7.0 (2.5–11.5)	6.4 (3.3–9.5)	6.7 (4.0–9.5)	44.2	0.535
Non-Hispanic white	13.2 (10.6–15.8) [*]	14.0 (11.4–16.6) [*]	18.1 (14.4–21.9) [*]	24.2 (19.7–28.7)	83.1	< 0.001
Place of residence						
CBSA with ≥ 1 million pop	9.6 (6.6–12.6) [*]	9.1 (6.0–12.2) [*]	10.1 (7.2–13.0) [*]	16.7 (12.0–21.3)	73.9	0.010
CBSA with < 1 million pop	11.9 (8.7–15.1) [*]	15.3 (11.2–19.5)	19.4 (13.7–25.1)	20.3 (16.2–24.5)	70.5	0.001
Non-CBSA	[*]	[*]	30.7 (11.6–49.7)	38.1 (18.0–58.2)	--	0.013
Annual household income						
<$20,000	18.3 (11.4–25.2) [*]	24.6 (16.4–32.8)	19.1 (12.7–25.5) [*]	29.7 (23.3–36.2)	62.2	0.069
$20,000–$49,999	10.6 (7.5–13.7) [*]	12.4 (8.5–16.4) [*]	18.0 (11.1–24.8)	22.4 (16.9–27.8)	111.3	< 0.001
$50,000 or more	8.2 (5.3–11.2)	6.9 (4.5–9.3) [*]	11.3 (8.2–14.4)	12.2 (8.2–16.2)	48.0	0.033
Insurance status						
Uninsured	18.5 (12.7–24.3) [*]	22.4 (15.5–29.3) [*]	21.2 (11.8–30.6)	33.0 (25.2–40.7)	77.9	0.010
Medicaid	[*]	23.8 (14.1–33.6)	19.7 (11.7–27.7)	26.9 (18.5–35.2)	--	0.168

	2003–2005 Rate (95% CI)	2006–2008 Rate (95% CI)	2009–2011 Rate (95% CI)	2012–2014 Rate (95% CI)	Percent change 2003–05 to 2012–14	p value for Trend [a]
Private or other insurance	8.2 (6.1–10.3) *	7.3 (5.6–9.0) *	12.1 (9.3–14.9)	13.1 (9.1–17.1)	59.8	0.004

CBSA = Core-Based Statistical Area.

Rate is statistically significantly different than 2012–2014 rate;*p < 0.05.

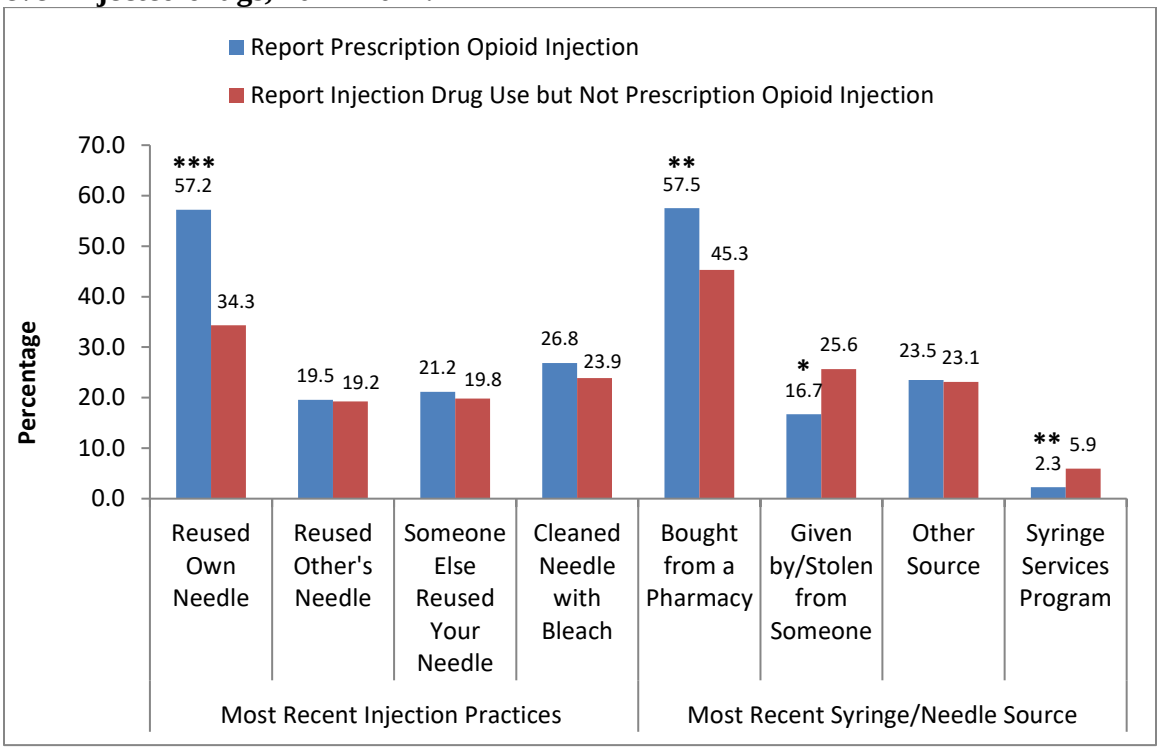
± Rate is per 1,000 persons for each analytic group (among people who have ever misused a prescription opioid).

a To assess statistically significant changes in trends, bivariate logistic regression models were applied to test p-vales of beta coefficients of year variable across the study period.

∗ Estimate is suppressed based on pre-specified suppression criteria.

In 2012–2014, 57.2% of those who had ever injected prescription opioids reported reusing their own needle the last time they used a needle to inject drugs compared to 34.3% among PWID but not prescription opioids ($p < 0.05$) (**Figure 10**). There was no difference between the two groups for reusing someone else's needle, someone else reusing their needle, or cleaning their needle with bleach. A greater percentage of people who had ever injected prescription opioids reported getting their most recent syringe/needle from a pharmacy compared to PWID but not prescription opioids, 57.5% versus 45.3%; $p < 0.05$. A smaller percentage of people who had ever injected prescription opioids reported their most recent syringe/needle was given by or stolen from someone (16.7% versus 25.6%; $p < 0.05$) or from a SSP (2.3% versus 5.9%; $p < 0.05$).

Figure 10. Injection practices and syringe/needle sources among people who have ever injected drugs, 2012–2014.



Percent is statistically significantly different, *p<0.05, **P<0.01, ***P<0.001

Results of the three multivariable logistic regression models are contained in **Table 10**. Among the overall population aged 12 years and older, the odds of prescription opioid injection were significantly higher in 2012–2014 compared to 2003–2005. Groups with increased odds of prescription opioid injection included: males, non-Hispanic whites, having an annual household income less than $50,000, the uninsured, people with Medicaid, and people with past-year use disorders for cocaine, heroin, or prescription opioids.

Table 10. Characteristics associated with prescription opioid injection misuse.

	Overall population	**People ever misusing prescription opioids**	**People ever injecting drugs**
Characteristic	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)
Year			
2003–2005	Ref	Ref	Ref
2006–2008	1.15 (0.85–1.57)	1.09 (0.81–1.47)	1.00 (0.72–1.39)
2009–2011	1.24 (0.92–1.66)	1.22 (0.92–1.62)	1.18 (0.86–1.63)
2012–2014	1.44 (1.07–1.95)	1.48 (1.10–1.98)	1.30 (0.94–1.79)
Sex			
Female	Ref	Ref	Ref
Male	1.61 (1.26–2.06)	1.16 (0.90–1.49)	0.71 (0.55–0.92)
Age, y			
12–17	0.06 (0.04–0.11)	0.09 (0.05–0.15)	0.23 (0.13–0.41)
18–25	Ref	Ref	Ref
26 or older	1.19 (0.99–1.43)	2.36 (1.94–2.87)	0.58 (0.47–0.71)
Race/ethnicity			
Other	Ref	Ref	Ref
Non-Hispanic white	4.32 (3.21–5.80)	3.14 (2.39–4.12)	1.94 (1.42–2.65)
Place of residence			
CBSA ≥ 1 million pop	Ref	Ref	Ref
CBSA < 1 million pop	1.20 (0.98–1.47)	1.32 (1.09–1.60)	1.15 (0.94–1.40)
Non-CBSA	1.39 (0.91–2.10)	2.01 (1.37–2.96)	1.78 (1.16–2.74)
Annual household income			
<$20,000	1.77 (1.40–2.24)	1.60 (1.26–2.04)	0.94 (0.72–1.22)
$20,000–$49,999	1.34 (1.08–1.66)	1.33 (1.07–1.66)	0.97 (0.77–1.24)
$50,000 or more	Ref	Ref	Ref
Insurance status			
Uninsured	2.98 (2.32–3.83)	1.57 (1.24–1.99)	1.20 (0.95–1.52)

	Overall population	People ever misusing prescription opioids	People ever injecting drugs
Medicaid	2.77 (2.10–3.66)	1.69 (1.29–2.22)	0.92 (0.68–1.25)
Private or other insurance	Ref	Ref	Ref
Past year substance use disorders			
Cocaine use disorder	2.05 (1.23–3.42)	1.34 (0.92–1.95)	0.80 (0.59–1.08)
Heroin use disorder	15.47 (9.76–24.53)	9.21 (6.43–13.18)	1.54 (1.11–2.14)
Prescription opioid use disorder	11.32 (7.97–16.09)	3.14 (2.39–4.12)	3.21 (2.28–4.51)
Stimulant use disorder	1.94 (0.84–4.47)	1.46 (0.75–2.82)	0.86 (0.50–1.49)
Sedative use disorder	1.29 (0.61–2.76)	1.10 (0.64–1.90)	1.09 (0.63–1.87)
Age first opioid nonmedical use, y			
14 or younger		Ref	
15–17		0.75 (0.54–1.06)	
18–20		0.41 (0.32–0.53)	
21–25		0.43 (0.30–0.61)	
26 or older		0.19 (0.13–0.28)	
Health-related outcomes			
Treatment for alcohol or drugs			1.33 (1.07–1.65)
HIV			3.16 (1.56–6.41)
Hepatitis			1.10 (0.84–1.43)
STD			1.65 (1.20–2.27)
Most recent injection practices			
Reused own needle			1.84 (1.45–2.34)
Reused other's needle			0.86 (0.57–1.29)
Someone else reused your needle			0.98 (0.68–1.40)
Cleaned needle with bleach			0.93 (0.71–1.21)
Most recent syringe/needle source			
Syringe services program			Ref
Pharmacy			2.08 (1.26–3.45)
Given by/stolen from someone			1.17 (0.71–1.94)
Other source			1.73 (0.97–3.08)
CBSA = Core-Based Statistical Area.			

Among people who had ever misused prescription opioids, the odds of prescription opioid injection were significantly elevated in 2012–2014 compared to 2003–2005. Groups with elevated odds of prescription opioid injection included: people 26 years or older, non-Hispanic whites, people living in a CBSA with < 1 million population or non-CBSAs, having an annual household income less than $50,000, the uninsured, people with Medicaid, people with past-year use disorders for heroin or prescription opioids, and people who initiated prescription opioid misuse before the age of 18.

When limited to PWID, the following groups had increased odds of prescription opioid injection: non-Hispanic whites, people living in non-CBSAs, and people with a past-year use disorder for heroin or prescription opioids. Males, people aged 12–17 and 26 or older had lower odds of prescription opioid injection. People who had ever injected prescription opioids compared to those who had injected other drugs but not prescription opioids had increased odds of ever receiving drug or alcohol treatment, ever having HIV, ever having an STD, reusing their own syringe/needle, and getting their most recent syringe/needle from a pharmacy.

DISCUSSION

This study found significant increases in prescription opioid injection misuse trends during the study period. Rates increased 65% among people 12 years or older, and the magnitude of the increase was greater when prescription opioid injection was examined among people who misuse prescription opioids – increasing 72% among people who have ever misused prescription opioids and 200% among recent prescription opioid misuse initiates. By 2012–2014, 710,100 people had reported ever injecting

prescription opioids, an increase of > 300,000 people since 2003–2005. These increases occurred across a broad range of demographic and substance using groups, with particularly large increases among women, non-Hispanic whites, and people aged 18–25 years. Importantly, these increases are consistent with other indicators of opioid-related harms identified in other studies during the study period (Ronan & Herzig, 2016; Han et al., 2015; Zibbell et al., 2015; Compton et al., 2016; Suryaprasad et al., 2014).

The strong association between prescription opioid injection misuse and both prescription opioid use disorder and heroin use disorder in the multivariable models support prior research documenting the intertwined nature of prescription opioid misuse and heroin use and stress the importance of reducing prescription opioid misuse as a key strategy to prevent future heroin use and overdose. Multiple studies have found that prescription opioid misuse typically preceded heroin initiation among current heroin users in the U.S. (Carlson et al., 2016; Cicero et al., 2014; Jones, 2013). Carlson et al., 2016, found that people who misused prescription opioids by non-oral routes, including injection misuse, were significantly more likely to initiate heroin use over a three year period compared to those who reported oral misuse.

Nearly 60% of people ever injecting prescription opioids reported reusing their own needle the last time they injected, and roughly 1 in 5 reported reusing someone else's needle as well as allowing someone else to reuse their needle – findings consistent with prior smaller studies (Havens et al., 2007; Johnson et al., 2013; Peters et al., 2016; Surratt et al., 2011). The small percentage of people obtaining syringes from SSPs is concerning. Many areas of the U.S. lack access to SSPs, especially more suburban and rural areas where the burden of prescription opioid misuse is disproportionately high (Des

Jarlais et al., 2015). The finding that 58% of people ever injecting prescription opioids obtained their most recent syringe/needle from a pharmacy is encouraging and presents opportunities to reach at-risk populations (Janulis, 2012). Additional research is needed to determine how pharmacies are implementing services for PWID, including what services such as HIV or HCV testing and linkages to medical and substance use treatment are being provided in addition to selling syringes and needles.

The finding that people who initiated prescription opioid misuse before the age of 18 were more likely to report injection misuse emphasizes the importance of prevention among adolescents. This includes broader implementation of evidence-based prevention programs (Spoth et al., 2013) and efforts to reduce inappropriate opioid prescribing to reduce unnecessary exposure to opioids and to limit environmental availability of prescription opioids for diversion and misuse.

Increasing rates of prescription opioid injection misuse, high prevalence of risky injection practices, and inadequate access to sterile syringe sources in this study coupled with coincident increases in rates of opioid use disorders, overdose deaths, and HCV highlight the need for broad availability of medication-assisted treatment with methadone, buprenorphine, or naltrexone for opioid use disorder and comprehensive risk reduction services such as those provided by SSPs. These interventions have been shown to reduce opioid use, overdose, and the transmission of infectious diseases (Belani et al., 2012; Wurcel et al., 2016). Scaling-up these interventions is acutely needed in rural areas of the U.S. where access is particularly limited (Des Jarlais et al., 2015; Van Handel et al., 2016). Rural areas in this study had higher rates and elevated odds of prescription opioid injection misuse compared to more urban areas, and overall use of SSPs was

significantly lower among people reporting ever injecting prescription opioids compared to those who had injected other drugs but not prescription opioids. Recent changes in federal funding and federal and state law have created a more supportive environment for broader implementation of these critical services (HHS, 2016), but research is needed to understand implementation efforts and to determine which at-risk populations are able to access them.

STUDY LIMITATIONS

This study is subject to several limitations. First, NSDUH data are self-reported, and their value depends on the truthfulness and accuracy of individual survey respondents; under- or over-reporting of drug use might occur. Second, because NSDUH is cross-sectional and different individuals were sampled each year, it is not possible to infer causality from the observed associations. Third, NSDUH captures only noninstitutionalized civilians; it excludes active duty military personnel, homeless people not living in shelters, incarcerated populations, and persons in residential treatment. Thus, rates in this study likely underestimate the full extent of injection drug use in the U.S. Fourth, NSDUH only includes information on most recent injection and syringe/needle sources. An individual's behavior during their most recent injection may not represent their usual or most common injection practices or syringe/needle sources.

CONCLUSIONS

Consistent with other indicators of prescription opioid-related morbidity and mortality, this study found significant increases in prescription opioid injection misuse in the U.S. over the past decade. These findings underscore the need to bring to scale evidence-based interventions that prevent prescription opioid misuse, increase the

provision of medication-assisted treatment for opioid use disorders, and expand access to comprehensive services such as those provided by SSPs that reduce injection-related harms.

Chapter 4: Syringe Services Programs: An Examination of Legal, Policy, and Funding Barriers in the Midst of the Evolving Opioid Crisis in the U.S.

This manuscript describes the findings from a qualitative study based on interviews of individuals running SSPs. The study explored the experiences of SSPs across multiple domains in the midst of the evolving opioid epidemic and rapidly changing policy environment. The study aimed to identify barriers SSPs are facing and identify facilitators, innovative collaborations, and successful strategies they are deploying to meet the needs of individuals who inject opioids and other drugs.

The United States is in the midst of a decades-long crisis of prescription and illicit opioid misuse, addiction, and overdose (SAMHSA, 2017; Jones et al., 2018). Coincident with the increase in opioid misuse and addiction are rising rates of prescription opioid injection and transmission of infectious diseases such as hepatitis C virus (HCV) and endocarditis (Jones et al., 2017; Jones, 2018; Zibbell et al., 2018; Suryaprasad et al., 2014; Ronan & Herzig, 2016). The 2015 outbreak of more than 180 HIV cases in Scott County, Indiana, associated with injection of the prescription opioid oxymorphone, brought national attention to the intersection of the opioid crisis, increasing prescription opioid injection, and infectious disease transmission (Peters et al., 2016).

Studies indicate that people who inject prescription opioids have an elevated risk for HCV and potentially other infectious disease transmission compared to people who inject drugs but not prescription opioids (Zibbell et al., 2014; Lankenau et al., 2015; Havens et al., 2013). This increase in risk is thought to be the result of factors such as preparing oral prescription opioids for injection, high rates of syringe sharing and reuse, sharing and injecting residual “washes”, use of high dead space syringes, and engaging in

multiple injections per injection episode and multiple injection episodes per day that are not typically seen with other injected drugs (Zibbell, et al., 2014; Jones, 2018; Lankenau et al., 2015; Zule, et al., 2016; Broz, et al., 2018).

In addition to focusing attention on the infectious disease risks associated with prescription opioid injection, the Scott County, Indiana outbreak uncovered a population of people who were injecting drugs that were not being reached by evidence-based interventions such as Syringe Services Programs (SSPs) that can reduce injection-related harms. Further, research published in late 2016 identified hundreds of additional counties in the U.S. that are vulnerable to the rapid dissemination of HIV or HCV due to risky injection drug use (Van Handel et al., 2016). Common among these counties are high rates of opioid use and related mortality and an absence of SSPs, with 93% of the vulnerable counties having no SSP (AMFAR, 2017).

SSPs have been shown to reduce injection-related risk behaviors and to decrease HIV, HCV, and hepatitis B virus (HBV) transmission (Macarthur et al., 2014; WHO, 2004, Belani et al., 2012; Patel et al., 2015; HHS, 1998). SSPs directly lower risk of injection-related harms by decreasing needle sharing and reuse, reducing the prevalence of blood-borne infectious agents in needles available for reuse, and reducing the sharing of injection-related equipment. Indirectly, SSPs lower risk of injection-related harms by linking individuals to substance use treatment, providing harm reduction education services, testing, counseling, and linkage to treatment for infectious diseases, safe sexual education and condoms, and in some SSPs directly providing treatment for HIV and HCV, as well as medication-assisted treatment for opioid use disorder (Hurley et al., 1997; WHO, 2004; Belani et al., 2012; Des Jarlais et al., 2015).

Despite the evidence demonstrating their effectiveness, SSPs have been limited in number, scale, and scope in the U.S. due to persistent legal, policy, political, social, and funding barriers (Lurie & Drucker, 1997; Bramson et al., 2015; Des Jarlais et al., 2016; Weinmeyer et al., 2016). In the U.S., the first SSPs were implemented in the late 1980s in a small number of large cities; however, a lack of political support and opposition from substance use treatment providers, law enforcement, and communities substantially limited implementation of SSPs in most areas of the U.S. (Clark et al., 2016; Lurie & Drucker, 1997; Hurley et al., 1997). Further, in 1988, Congress prohibited the use of federal funds to support SSPs due to concerns this would signal government endorsement of drug use, increase use and injection, and contradict law enforcement efforts (Lurie & Drucker, 1997; Clarke et al., 2016). This lack of political support and explicit stigma towards drug use and people who inject drugs led to the implementation of an inefficient and uneven mix of laws, regulations and policies related to SSPs across the country. In many states, laws were enacted to criminalize possession of syringes, needles, and other injection equipment, as well as directly outlaw the implementation of SSPs (Lurie & Drucker, 1997; Bramson et al., 2015; Clarke et al., 2016; Weinmeyer et al., 2016). Operationally, this meant many states did not implement SSPs and those that did either did so with little political support and limited resources or did so without explicit legal authorization. This has significantly limited the scope and reach of SSPs – both in terms of providing services to people injecting drugs in urban areas and reaching populations in suburban and rural areas, areas disproportionately impacted by the opioid crisis (Jones, 2018; Des Jarlais et al., 2015).

In recent years, recognizing the urgent need to address increasing rates of opioid injection, overdose, and infectious disease transmission, and spurred by the 2015 HIV outbreak in Indiana, a number of states and local jurisdictions have enacted laws or policies to enable implementation or expansion of SSPs (Ohio, 2015; Kentucky, 2015; Indiana, 2015; City of Huntington, WV, 2016). In addition, in December 2015, the U.S. Congress *partially* lifted the ban on Federal funds to support certain SSP services such as HIV testing and naloxone for overdose reversal, once jurisdictions have provided evidence to the Centers for Disease Control and Prevention (CDC) that they are experiencing or are at risk for significant increases in hepatitis infections or an HIV outbreak due to injection drug use. However, the ban on using Federal funds to purchase syringes or needles remained. (U.S. Congress, 2015).

These statutory and regulatory changes at the state and Federal level have resulted in an increase in the number of SSPs in a relatively short period of time under a variety of state and local regulations and policies. These policy changes, along with a growing population of people injecting prescription opioids and other drugs (Jones, 2018) and the rapid proliferation of highly potent synthetic opioids such as illicit fentanyl that are fueling a sharp increase in opioid overdoses (Jones et al., 2018), create a pressing need to understand how SSPs are responding to the evolving opioid crisis and policy environment. The aim of this study is to describe the experiences of SSPs as they navigate the evolving policy environment and to identify strategies SSPs are pursuing to maximize the role they can play in response to the opioid crisis in the U.S.

METHODS

This study used an applied qualitative approach to design and conduct the study. Given the research focus on capturing the first-hand experiences of individuals running SSPs, in-depth, semi-structured key informant interviews were conducted to explore the current experiences of SSPs in the midst of a rapidly changing policy environment in the context of the U.S. opioid crisis.

Participant recruitment

Between December 2017 and April 2018, in-depth, semi-structured interviews were conducted with individuals running SSPs (for the purpose of this study termed SSP program administrators). A purposive sample of SSP program administrators using maximum variation sampling was selected to capture a full range of perspectives from: 1) new SSPs (defined as in operation for 36 months or less), as well as established SSPs; 2) urban and rural SSPs; 3) SSPs housed in health departments and those not affiliated with a health department; and 4) SSPs from the four U.S. census regions. Study subjects were recruited from a list of potential respondents using the list of known SSPs maintained by the North American Syringe Exchange Network (NASEN, 2017). Direct email correspondence with SSP program administrators was the sole method of recruitment for this study. A total of 25 administrators representing 23 SSPs (9.0% of the 268 listed SSPs at the time of study recruitment) participated in the study.

Interview procedures

The interview guide was developed based on a review of the scientific literature and discussions with key thought leaders involved in national and state-level harm reduction policy and SSP implementation. The interview guide was designed to elicit responses in the following domains: 1) changing legal/policy environment; 2) funding

sources for programs; 3) population served and how it has changed; 4) program operations and services provided; 5) affiliations and interactions with state or local government; 6) interactions with law enforcement; 7) collaborations with the public health and substance abuse communities; and 8) engagement with state or local opioid misuse prevention task forces (see Appendix for interview guide).

All interviews were conducted via telephone and lasted approximately 60 minutes. The interview format was flexible, allowing the interviewer and interviewees to introduce or elaborate on different topics relevant to the research domains. Each interview was audio-recorded for accuracy and ease of transcription. All audio-recordings were transcribed verbatim into standard word-processing files. All transcriptions were compared to the audio-recording to ensure accuracy. These files were then uploaded into NVivo qualitative software (NVivo v12, QSR International, Burlington, MA) for analysis. Verbal informed consent was obtained from participants before each interview. Interviews occurred between December 2017 and April 2018. This study was exempted from Institutional Review Board review by the George Washington University Office of Human Research

Data Analysis

A thematic content analysis, using both inductive and deductive coding, was conducted to identify and group key themes across the domains of interest and to identify and summarize similarities and differences across SSPs. The first step in the coding process involved familiarization with the interviews by reading and rereading each of the transcripts and listening to the audio-recordings to identify codes consistent with the interview guide domains as well as to identify emerging codes not explicitly captured by

the guide domains. This was followed with line-by-line coding of the text. The coding process was iterative as new interviews were conducted and reviewed, leading to refinement of the initial codes and coding framework. Once all transcripts were coded, the codes were reviewed, refined, grouped, and placed into themes. The matrices and frequency query functions in NVivo software were used to facilitate theme identification and to identify connections of codes and themes across different SSPs characteristics. During this process, a second coder analyzed a 30% sample of interviews to validate and refine codes and themes. The two coders met to discuss codes and potential themes and revisions to those themes. Once themes were finalized, representative quotes were identified and extracted.

RESULTS

Characteristics of SSPs

A total of 23 SSPs were included in the study; five were in the Northeast, eight in the Midwest, eight in the South, and two in the West; 11 were in rural areas and 12 in urban areas; 11 were new programs and 12 established programs (**Table 11**). The mean and median time of SSP operation was 92.7 months and 36 months, respectively, with a range of 1-348 months. Among SSPs, 14 were operating in states where SSPs were legal, 7 in states that locally permitted SSPs or had no specific law prohibiting SSPs, and 2 in states where SSPs were illegal. Ten SSPs, mostly new programs, were part of the health department. The number of days an SSP was open and the hours they operated, on average, per day per site varied across programs. A large minority of programs, 43.5%, were open 1 day per week and 40.9% were open for 3 hours or less on the days the program was open. Approximately 30% of programs offered mobile syringe services.

Finally, all but four programs were located in states that had expanded Medicaid at the time of the study interview.

Table 11. Characteristics of Syringe Services Programs Participating in Qualitative Interviews.

Program	Census Region	Rural-Urban Status	Program Type	Time in Operation (months)	Legal Status of SSPs[a]	Part of Health Dept	# of Fixed Sites	Avg. # Days Open/Week Per Site	Avg. # Open Hours/Day Per Site	Mobile Syringe Services	Medicaid Expansion State
SSP1	MW	Urban	Establ.	36	Legal at state level	No	3	1	3	Yes	Yes
SSP2	NE	Urban	Establ.	240	Legal at state level	No	4	5	8	Yes	Yes
SSP3	South	Rural	New	30	Locally permitted or no law exists addressing SSPs	Yes	1	1	5	No	Yes
SSP4	West	Rural	Establ.	54	Legal at state level	No	1	5	3.8	No	Yes
SSP5	MW	Rural	New	36	Legal at state level	Yes	1	5	3.6	Yes	Yes
SSP6	MW	Rural	Establ.	60	Legal at state level	Yes	1	1	3	No	Yes
SSP7	MW	Rural	New	1	Legal at state level	Yes	1	5	8	No	Yes
SSP8	West	Urban	Establ.	348	Locally permitted or no law exists addressing SSPs	No	2	3.5	4.4	No	Yes
SSP9	South	Rural	New	6	Locally permitted or no law exists addressing SSPs	Yes	1	1	2	No	Yes
SSP10	MW	Urban	Establ.	216	Locally permitted or no law exists addressing SSPs	No	2	3.5	6.3	Yes	Yes
SSP11	NE	Urban	Establ.	240	Legal at state level	Yes	1	5	7.5	No	No

SSP12	South	Urban	Establ.	48	Legal at state level	No	1	5	8	Yes	No
SSP13	MW	Rural	Establ.	60	Locally permitted or no law exists addressing SSPs[b]	No	1	2	3	No	Yes
SSP14	NE	Rural	Establ.	192	Legal at state level	No	3	1	3.7	Yes	Yes
SSP15	MW	Urban	New	18	Legal at state level	Yes	1	1	4	No	Yes
SSP16	South	Rural	New	18	Legal at state level	No	1	6	5.2	Yes	No
SSP17	NE	Urban	Establ.	276	Locally permitted or no law exists addressing SSPs	No	3	1	2.3	No	Yes
SSP18	South	Urban	New	12	Illegal	No	1	1	2	No	No
SSP19	MW	Urban	New	18	Illegal	No	3	3	d	No	Yes
SSP20	NE	Rural	Establ.	144	Legal at state level	No	2	1.5	2	No	Yes
SSP21	South	Urban	New	30	Legal at state level	Yes	1[c]	6	4.3	No	Yes
SSP22	South	Urban	New	27	Locally permitted or no law exists addressing SSPs	Yes	1	1	2	No	Yes
SSP23	South	Rural	New	21	Legal at state level	Yes	1	1	1	No	Yes

a Legal status at time of interview

b Program operating underground without any local legal protection

c Program has 4 additional outreach locations

d Varies given illegal status of program

The key informant interviews covered a broad range of topics across the eight domains included in the interview guide; however, the most salient themes related to how SSPs are responding to the evolving opioid crisis and rapidly changing policy environment revolved around four domains: 1) legal and policy barriers; 2) funding challenges; 3) changing drug use trends and illicit drug supply, and 4) strategies SSPs are pursuing to overcome barriers and challenges (**Table 12**).

Table 12. Domains and Themes Identified in Qualitative Interview

Domain	**Themes**
Legal and Policy Barriers	• SSPs are operating in a fragile legal environment • Community resistance as a non-legal barrier • Pervasive stigma fuels legal and policy barriers
Funding Challenges	• SSPs are currently operating with a patchwork of funding • The Federal funding ban is preventing SSP implementation and growth • Perceptions of funding opportunities vary across programs • Stigma perpetuates SSP funding challenges
Changing Drug Use Trends and Illicit Drug Supply	• The expanding number of people injecting drugs and seeking services at SSPs • The emergence of illicit fentanyl has amplified the challenges faced by SSPs • A resurgence of methamphetamine is further challenging SSPs
Strategies SSPs are Pursuing to Overcome Barriers and Challenges	• Advocacy and engagement in the policy process to remove legal and policy barriers • Capitalizing on all potential funding sources • Expanding the reach of SSPs

1.0 Legal and Policy Barriers

1.1. SSPs are operating in a fragile legal environment

SSP program administrators across nearly all programs described a number of legal and policy barriers that resulted in SSPs operating in a fragile legal environment and constrained their ability to operate SSPs to maximal impact. Although there were differences in how these barriers were operationalized across jurisdictions, programs described them as significantly limiting their ability to establish new SSPs and expand existing programs, creating uncertainty about the long-term viability of SSPs, and constraining the ability of SSPs to reach at-risk populations. In contrast, when laws and policies were supportive, SSPs flourished.

For two programs, the fundamental legal barrier was that SSPs were explicitly prohibited by state law. These programs were operating either completely underground or with agreement that local law enforcement would not take action against them. An additional SSP operating in a state where local jurisdictions could sanction SSPs was operating underground due to a lack of approval of SSPs in the local area. These prohibitions created the most fragile legal environment and uncertainty among the SSPs interviewed.

> "We're seeing entire communities that need our services; we're only in these three communities [due to an implicit agreement with local law enforcement not to pursue legal action], but it would be really ideal to be able to operate in the western parts of the state as well." [SSP 19]

> "I supply syringes and stuff other people need. There are really still a lot of people that don't believe in what I do or what groups like me do. It's really hard to operate anywhere like that in a small town without going to court every other day." [SSP 13]

For other programs, the legal status of SSPs was ambiguous – either state law did not expressly prohibit or authorize SSPs or the determination was the responsibility of the local jurisdiction.

> "In our state, SSPs have been neither prohibited nor allowed, explicitly allowed...If I had actual legal authorization, explicit legal authorization at the state level that would really help the program…The prosecuting attorney assured us that what we were doing was not prohibited by law. That's not the way I read the law, and I am certain that that's an interpretation that could change with an administrative change. That makes the service fragile. I would like explicit authorizing language." [SSP 3]

Among the programs where the authority lies with the local government, SSPs detailed convoluted regulatory hurdles that were required before SSPs could be implemented. These hurdles were seen as significant barriers for implementation and expansion.

> "We recognize we should be in more places than we are, but we are just really limited by the city, and by neighborhoods who don't want to have needle exchanges in them. In order for us to set up a syringe exchange site, we have to get community buy in from that neighborhood. Then we have to take that to the board of health, who will approve it, and then we have to take that board of health approval to the city council. Then, they approve it, and then we have to take it back to the board of health one more time. We have to get city council member approval, and we have to get community approval. That is a huge obstacle for us. It just feels really sad knowing that neighborhoods that are across the bridge, that are like an hour bus ride from one of our syringe exchange sites, are seeing three times the amount of fatal overdoses than what we are seeing where our syringe exchange is. That's just hard because that, obviously, says that we're not in the places where we need to be." [SSP 17]

Even in states where the law explicitly authorized SSPs, how the law was operationalized and the policy and regulatory requirements to open, maintain, and expand SSPs often were not conducive to easily establishing SSPs. For some states, local elected officials such as county commissioners or city council members or the board of health had to approve the SSP.

> "They [state legislature] revised the law. Now it is harder to establish an SSP. We only have 7% of the counties in our state [with SSPs]. That's because they made it more difficult now. Thankfully, we have a year under our belt. The county

commissioners [who have to vote to approve or renew the SSP every 2 years] saw that it worked, so for us it was okay, but for a lot of other counties, it's going to be really hard for them now to establish [an SSP]…That's unfortunate because we're in a crisis." [SSP 15]

In some states, local elected officials do not play a formal role in approving SSPs; however, regulatory requirements issued by state entities such as the health department have to be met before an SSP can be implemented.

"Since we are part of public health we did not have the challenges that people will have if they're not public health. That's because we already have, you have to have [per state guidelines] a medical director, so we already have a medical director. You have to have biohazard waste disposal services, we already have that. For us, the [required state plan to establish an SSP] was easier because we didn't have to jump through as many hoops as somebody that is not part of public health [will have to do]." [SSP 8]

In addition to laws or policies enabling the distribution of sterile syringes and needles, the majority of programs raised the need for broader drug paraphernalia laws that cover more than sterile syringes and needles, as used syringes with drug residue on them and other injection equipment were often not covered or exempted under current statutes. This resulted in individuals not returning syringes to SSPs, not disposing of them properly in the community, and reluctance to engage in the program for fear of arrest.

> "Disposal has proven to be one of our biggest challenges. What that legislation [new drug paraphernalia law] did was protect syringe services providers, so staff, volunteers, outreach workers, that kind of thing, from prosecution. But our participants can still get in legal trouble for having a used syringe on their person. There is a lot of resistance still to bringing back syringes for safe disposal." [SSP 4]

Although the vast majority of states described a complex patchwork of legal and policy barriers that had to be navigated when establishing and operating SSPs, two states described positive impacts that resulted after their state laws were modified to either explicitly legalize SSPs or to address other legal barriers like drug residue on syringes and drug paraphernalia laws.

> "Our state [several years ago] decriminalized drug residue on the ends of needles if you're returning your needles to a syringe exchange on the day of the exchange. That just happened in our neighboring state this year. This is really the first year where the laws are actually conducive to opening syringe exchange in that state. Now exchange programs are popping up." [SSP 20]

> "I think [legalizing SSPs] gives the people that we serve a level of comfortability, a level of safety maybe because they know that they're protected. Quite frankly, I think it also gave us a little push to be more aggressive in the number of business

cards that we give, encouraging people to reach out to other folks because we're no longer at risk of arrest either." [SSP 16]

1.2. Community resistance as a non-legal barrier

Programs acknowledged that resistance from communities and elected officials was often a barrier to establishing or expanding SSPs, even when the legal environment was supportive.

"A lot of the challenge is the community itself. There are still a lot of people that don't have anything to do with drugs…they're very critical of us…they want us to go away. We have to convince, every year, [county] commissioners, and we're very worried about this upcoming renewal that will take place this year, whether or not we will be getting [the SSP] renewed again. Because there is so much critical publicity and people saying, 'If you're up for re-election, and you are supporting a needle exchange I'm not going to vote for you.' We've got politicians that want to keep their jobs…We know what we're doing is working, it's just convincing everyone to continue to let us work." [SSP 5]

The power of community resistance was further captured by several programs that stated that even though they could implement an SSP without approval by local elected officials, they would not pursue opening an SSP if the community was not supportive. This resulted in a delay and in some cases a missed opportunity to implement an SSP, even in communities where there was a clear need for services.

> "We're looking to open new syringe exchanges in the state. It's hard though because the boards of the towns are kind of blocking it. Although, technically you can go ahead and do it anyway, I would prefer to get a good community advisory group and go from there with the support of the community." [SSP 20]

1.3. Pervasive stigma fuels legal and policy barriers

Programs, both new and established and across geographic areas, stated that the underlying stigma of addiction and drug use, and the notion that SSPs condone or increase drug use, was the most significant obstacle to overcoming legal and policy barriers. Programs characterized stigma as existing at all levels in the community and that combating stigma was a substantial challenge.

> "A lot of our folks in the community, especially our elected officials, they'll have that mentality that this is a choice, that this is not a disease, that if we participate in buying clean syringes or supplies, that we are enabling people to continue in this destructive behavior. They don't see it that we are empowering them to make a healthier life eventually." [SSP 16]

> "People are pretty stuck in their beliefs, even though science has largely disproven that. I think there's still just a lot of stigma against the programming…We were told in one city that – we went to them and said, 'hey look, your hepatitis C and HIV rates from injection drug use are three times the counties or cities surrounding you. Can you consider this type of programming?'

> They told us that people in their city do not inject drugs. That a program like ours wasn't right for their community." [SSP 10]

2.0. Funding Challenges

2.1. SSPs are currently operating with a patchwork of funding

Programs commonly cited inadequate funding as a primary barrier to establishing new programs or expanding the number of SSPs or services offered by SSPs. It was typical for programs to depict a patchwork of funding, including from foundations, individual donations, merchandise sales, and to a much lesser extent government funding. For many programs, this funding was not stable from year to year and often had restrictions on how the money could be used (e.g., foundations would fund naloxone distribution but not purchase of syringes or needles).

> "Our primary sources of funding are- it's really a split between, we get some money from the state, we get some money from foundations, and then we get some money from private donations. It's our three-legged stool of funding…the private money is really how we fund the purchase of needles and syringes." [SSP 17]

Two newly operational programs stated their activities were funded largely through their personal funds or individual donations.

> "Up until this year, our program has been strictly funded through either our personal pockets or through donations of family and friends. My budget last year was $1,500 and that's serving hundreds of folks but that's because my syringes were donated. My naloxone, I don't have to pay for it, it's donated to us." [SSP 16]

> "A lot of this has been like tens of thousands of dollars from my personal savings account. Our first few batches of supplies were given to us by another SSP." [SSP 19]

A small minority of programs expressed optimism about funding; stating their funding had improved or stabilized in recent years. There were no defining features as to the type of SSP that reported improved funding as this small group included SSPs in urban and rural areas as well as programs that were and were not part of health departments. Programs reported that these new funds were enabling programs to expand current operations.

> "We have had philanthropic grants. Until this year, that was our biggest funding source. This year, we've received governmental funding from the state and from the federal government for the first time. [This new funding] allows us to expand. We will be able to go mobile because of this. We'll be able to lease or purchase mobile vehicles and then we can hire the additional staff." [SSP 3]

The vast majority of programs stated their funding was barely covering current operations, and universally, SSPs, including those that said their funding had improved or was able to cover current operations, acknowledged funding was not sufficient to cover the spectrum of services they believed were needed to fully address the needs of people who inject drugs. Cumulatively, these funding challenges resulted in limitations on program operations, including not being able to reach at-risk populations, fund staff positions, conduct mobile operations, and provide needed injection supplies.

> "Our funding is sufficient for what we do today. I do think that there is a need and we should be expanding and providing more services in more locations. If we had more funding, we would be able to do that. We don't currently. With what we have we're doing okay, but we need to do more." [SSP 8]

> "In the past, we would give folks as many [syringes] as they needed to cover them for two to three weeks, but again, because of funding, we've had to cut back. We give individuals about 60 a month, which is not nearly enough, but that's all we have right now." [SSP 16]

2.2. The Federal funding ban is preventing SSP implementation and growth

Across all programs, the most significant funding challenge expressed was related to purchasing syringes and needles. Underlying this challenge was the long-standing ban on using Federal funds (and in some cases state and local funds) to purchase syringes and needles. Programs felt this was a fundamental factor limiting their ability to implement

new programs and sustain and grow existing programs, to reach at-risk populations, and to deliver comprehensive services to people who inject drugs.

> "We can't buy needles with that [federal] funding, which makes absolutely no sense to me whatsoever. You would fund a syringe exchange program but you can't buy syringes…I think that becomes a policy issue because if it's a program that works, if it's effective in reducing the public health crisis of hepatitis C that we live with in this state, then why would you not want to fund it?" [SSP 9]

> "You've got to be able to buy the needles with [the funds] too because there's a lot of communities that I'm aware of that would like to consider starting a needle exchange…Some of these communities are just as poor as we are. They don't have the ability [to implement an SSP] because they don't have access to funding [for syringes and needles]." [SSP 5]

Due to the funding ban, programs were forced to rely on other funding sources to purchase syringes and needles; commonly citing that these funds were often insufficient and unreliable. This has forced some programs to limit the number of syringes and needles they can provide to participants, undercutting the primary intent of SSPs.

> "[The ban] is our biggest challenge, we are totally dependent on donations and should we lose those donations, I don't know what we would do. We cannot afford – we don't have any money to afford to buy these syringes…It has caused

us to limit them to 30 [syringes] a week. There have been times when we've run out [of syringes] and didn't have any money." [SSP 6]

Even programs that had experienced improved funding from local, state, or federal grants in recent years, expressed frustration that these new funding streams could not be used for syringes or needles.

"None of [the new funding] can be used to supply the syringes. We are still operating below the [optimal] practice model of demand and supply. I can't give them what they need, we can't afford to do that." [SSP 3]

Programs felt a shift by the federal government to more openly support SSPs and develop dedicated funding for them could have a significant impact on the implementation and expansion of SSPs.

"I think the federal government has to get behind this and make it easier for states to implement the syringe programs…You know these things work. It's not a new concept so let's implement them." [SSP 15]

"I wish that the federal government would do a little more with regards to funding because all of these things are not going to happen without appropriate funding. We provide a lot of lip service and a lot of community conversations around these issues. A lot of people are talking about it, but when the rubber hits the road,

you've got to actually put a program together. That takes money. Money doesn't solve everything but you certainly can't do these programs without the appropriate amount of funding." [SSP 9]

2.3. Perceptions of funding opportunities vary across programs

There were diverging perspectives on the expectations and requirements for non-governmental funders depending on whether the SSP was a new or established program. Established programs recounted challenges in obtaining funding because funders wanted to fund new, innovative programs, not sustain established programs and operations.

"The money comes with strings attached, that you'll do this and you'll do that. Grantors want to see certain things. They don't want to fund sustainment. They want to fund new, exciting developments, which really taxes the abilities of our organization." [SSP 10]

New programs felt they were at a disadvantage because they had not established themselves for a certain period of time.

"We have no money. Even as we're trying to get more money and we've gotten more and more legit, a lot of the funders seem to have gotten a lot more advanced over the years. They don't want to fund programs unless they've been operating for three years or more. That's almost impossible then to start a new program." [SSP 19]

A unique challenge expressed by some programs that were part of health departments was the perception that being in the health department guaranteed funding for program operations and supplies. Programs felt this contributed to being less competitive for non-governmental funding opportunities.

> "When we're looking at grants and such, especially now that we do have increased support from the city, we don't look as good on paper anymore. We never really did because we fall under the health department umbrella. Even before when we weren't really getting any city funding, it was always a really hard sell to say 'yes I know we are within the city public health division, but I really do need money, like we really don't have any money'. That has always been a barrier for us." [SSP 11]

> "We are totally dependent on donations [for syringes and needles]. We cannot afford – we don't have any money to afford to buy these syringes. All of us, we don't pay anyone to work in there [the SSP], we're all paid by other grants." [SSP 6]

Limitations on funding opportunities were amplified for SSPs operating in states where SSPs are illegal. These programs expressed frustration that many funding opportunities were beyond their reach given the legal status of SSPs in their state. For example, one program stated that even when potential funding opportunities were

available, such as those resulting from the partial lifting of Federal funding ban, the program couldn't apply for those funds because syringes were still illegal in their state.

> "Because syringes are paraphernalia, we're really just barred from a lot of funding streams that would actually go towards running our needle exchange, or funding the staff…We can get money for all sorts of things, but not the actual running of the needle exchange because it's considered paraphernalia." [SSP 17]

2.4. Stigma perpetuates SSP funding challenges

Similar to legal and policy barriers, there was strong consensus among SSPs that stigma and the historically controversial nature of SSPs was a substantial contributor to the current funding situation. Compounding this is the recent increase in number of SSPs across the U.S. that has led to greater competition for the already limited funding opportunities for SSPs.

> "One of the biggest barriers to funding is still stigma and that people don't want to fund these kinds of programs when they don't understand, and they think that it's encouraging, condoning drug use. I think, for us, one of the barriers is – because there are so few funders for syringe access, that it just is incredibly competitive." [SSP 4]

3.0. Changing drug use trends and illicit drug supply

3.1. The expanding number of people injecting drugs and seeking services at SSPs

Both new and established programs across census regions reported an increase in the number of people accessing their programs in recent years. For some programs, the increase was characterized as rapid or exponential growth.

> "Our growth hasn't been linear at all. It's pretty logarithmic. We see a radical increase in the number of people we interact with per week over time. For a couple of months, it seems like we'll stabilize for a little bit. October, November, part of September, we were giving out maybe like 2,000 syringes a month, maybe 3,000. Now, a lot of times we'll do at least that many every week or every couple of days. The demand has been increasing really rapidly." [SSP 19]

Other programs depicted slower and more predictable growth in the number of SSP participants coming to their program.

> "Very first week, first week of May, I think we had two people. We had four people the second week. I believe we had eight, eight, and eight for the next three weeks. Then it started to grow a little bit. I think we spent about three months between 15 and 30 people. In the last four months, we've averaged between 40 and 60." [SSP 9]

Across programs there were no distinguishing features (e.g., new versus established, geographic placement, affiliated with the health department) of the SSPs that saw rapid increases in growth compared to those that experienced slow and steady

increases. Responses were mixed on whether the increase in people seeking services from SSPs was due to increasing numbers of people injecting drugs or driven by increased trust and awareness of programs leading to a larger proportion of people who inject drugs seeking services.

> "I know our client base is increasing, but I don't know whether that's because more people are finding out about the exchange. I think overall more people are injecting." [SSP 20]

> Patients are gaining trust and our program has been established for over two years…I think that there is more of them using. Or there's more of them finding out about our services, but, probably a little bit of both." [SSP 22]

A number of SSPs, in both rural and urban areas in the South, Midwest, and Northeast – areas with historically higher prevalence of prescription opioid misuse compared to the West – specifically identified the clamp down on prescription opioids and the resultant switch to heroin use among people previously misusing prescription opioids as contributing to the rise in number of people injecting drugs.

> "The program grew because we have more people that are injection drug users. It really kind of had to deal with losing the supply of pills and then heroin came. It's sort of naturally caused more people to start injecting." [SSP 6]

Other programs in the West and western part of the Midwest reported that changes in the underlying population in their communities was contributing to the increase in people injecting.

> "We're seeing a population move in that is new to our state, has started moving in with the oil boom. We got some big box stores that have come in and brought people, so our population is definitely changing, and as that population changes we're just having trouble…we're seeing more drugs coming in. Methamphetamine has been around a while, but the opioids are definitely picking up here." [SSP 7]

In addition to increases in the number of people injecting, some programs, both established and new as well as those in rural and urban areas, reported demographic shifts in recent years, including an increase in women accessing SSPs. Programs characterized this shift as a result of not only an increase in injection among women, but also an increase in trust between the programs and women.

> "When we first started, we had more males and we're seeing more females as time goes on. That's because I think females have a lot more at stake and there's more of a trust issue associated with that because of children." [SSP 21]

> "We have seen a big increase in our female, number of female participants…I think one, because we were able to get in with a sex worker community; that allows the word to spread because we don't advertise…The other thing I think is

because we [those running the program] are female. I think females are comfortable with us…I think the fact that we are female makes them feel safe, thus they can approach us." [SSP 16]

Changes in the age composition of participants were also noted by several programs, with some reporting a shift to younger individuals accessing the program and others reporting an increase in older individuals. Reflections on the drivers of these changes were mixed and no consistent pattern emerged across different types of SSPs. Some programs felt the changes were due to underlying shifts in the availability of prescription opioids and subsequent changes in drug use patterns.

"We've seen a shift to seeing more older people coming in. People who were prescribed pain medications and then lost either their health insurance or their pain clinic or both and turned to illicit opiates instead for pain management." [SSP 11]

"The availability of opioids [is contributing to the rise in the younger demographic]. When I was younger, you really couldn't buy heroin here, even if you wanted to. But what happened is OxyContin, specifically, became really available. A lot of people who otherwise wouldn't have been introduced to large amounts of opioids, all of a sudden found themselves with access. It created a demand in the community. As they started cracking down and less people were being prescribed opioids, we started traveling to the city to get heroin…A place

like this that usually wouldn't have heroin available, now had this demand and there was actually enough demand that people would bring heroin here to sell it and now it's really prevalent here." [SSP 10]

Other programs felt the change in age, specifically the shift to an older demographic, signaled potential progress in the stabilization of the number of young people injecting drugs.

"I would say, thankfully, they've [SSP participants] gotten a little older, which is great and that's a good sign in general. Not by a lot but our median age has gone up a couple of years which I think is a hopeful trend." [SSP 8]

Although programs reported the vast majority of people seeking services from SSPs were from their local geographic area, a number of programs, both new and established, reported that some participants were traveling significant distances to obtain syringes, needles, and other services. This was most common among SSPs that were operating in states with one or only a few SSPs.

"We actually have a significant number of people traveling from other parts of the state because there are no other services. We do see people traveling 50 plus miles pretty regularly." [SSP 4]

"We [as the first program in the state] are going to have people coming as far as a hundred miles. I have had calls from people in towns 100 and 150 miles away.

We're centrally located so we are going to see people from all over the state." [SSP 7]

Among these programs, this was seen both as a positive in that there was interest in seeking services but also as a negative because it reflected the reality that there is much greater demand for SSPs than there are SSPs, underscoring the disconnect between where SSPs are located and where the populations that could benefit from them live.

3.2. The emergence of illicit fentanyl has amplified the challenges faced by SSPs

Since 2013, the proliferation of highly potent illicitly-made synthetic opioids such as fentanyl has significantly fueled the rise in opioid overdose deaths (Jones, Einstein, & Compton, 2018). Programs expressed substantial concern about how this rapid change in the illicit drug supply has impacted their participants and programs.

"We thought we had seen the top of the curve in overdose deaths. Then fentanyl hit and it exploded to a point that was unfathomable." [SSP 3]

"I think fentanyl has really changed everything, just the way people are overdosing and the way people are using. I think behaviors are different. I think the daily hustle looks different. I think the way overdose reversals are happening is different." [SSP 11]

A number of programs described how the emergence of illicit fentanyl changed the way SSPs and participants interact, including discussing steps such as using tester shots and not injecting alone, and how participants are changing their behavior to reduce their overdose risk in the context of increasing fentanyl availability.

> "Definitely [people are taking additional steps to mitigate their risks]. We are seeing tester shots, not using alone, watching each other, using less at first to test it if it's an unknown bag or an unknown source." [SSP 2]

> "In late 2016, people didn't know what they had. They were scared. They didn't know what color it was going to be, they didn't know what was in it, they didn't know how potent it was…Then they became more familiar and they knew how to reduce their risks. When there was a change in dealer, a change in color, or any change in the product, they would take measures to reduce their risk." [SSP 3]

However, other programs expressed concern and some frustration that participants were not engaging in risk reduction behaviors even when steps to reduce risk were discussed by staff with program participants.

> "I don't really feel like [people are taking extra steps to protect themselves in the wake of fentanyl]. I feel like the people that use alone still use alone. Nobody ever wants to do test shots. They say that it doesn't matter anyway, you can buy the

same two bundles from the same dealer and one would have fentanyl and the other will have Wellbutrin [bupropion] in it, so doing a test shot doesn't matter." [SSP 20]

"When I ask people if they do test shots, the general comment is, 'No, I'm going to slam it. If I've got it, I'm going to slam it.' I think the general thought is, 'If I do a test shot, and if I go out, then somebody's going to get the rest of my shit.'" [SSP 16]

Recently, the use of fentanyl test strips has been proposed by drug policy researchers as an important overdose risk reduction intervention (Krieger et al., 2018); however, programs were mixed on whether they were pursuing this strategy.

"We give out test strips, they either will test for their friends, or if they all know they've got the same batch, they'll share the results from that test. Many of our people have actually said that they've gone back to their dealer and said "I don't want this, get me some heroin." [SSP 14]

"We don't use test strips. We reviewed the fentanyl test strip concept and found that would be probably of little value here since it can be assumed that we have fentanyl in every product…Testing for fentanyl doesn't change behavior in that setting. We do recommend smaller doses and test dosing and slower injection." [SSP 3]

3.3. A resurgence of methamphetamine is further challenging SSPs

Sixteen of the 23 programs interviewed, including programs in each census region and programs in both rural and urban areas, reported an increase in methamphetamine injection in the past two to three years. The general sentiment was this increase was connected to the opioid crisis. In some cases, SSPs reported they had seen an increase in individuals injecting opioids and methamphetamine together.

> "We are seeing way more meth[amphetamine] injections than we were seeing even two or three years ago…about 80% of people who reported being primarily opiate users reported having injected methamphetamines in the last three months. That's 50% more than it was; 30% had reported that [two years prior]." [SSP 8]

Other programs stated that some of their SSP participants were switching to methamphetamine from opioids due to concerns about the unpredictability of fentanyl and other synthetic opioids. This sentiment was more commonly expressed by programs operating in the Eastern part of the U.S. where illicit fentanyl and other synthetic opioids have been more prevalent.

> "Yes, that's [methamphetamine use] changing. It used to be where they didn't use opioids and methamphetamine together. I think they're mixing them and even some of them are transitioning over to methamphetamine because of the danger of heroin overdose. Of course, now we're finding out that they're putting fentanyl in methamphetamine." [SSP 21]

Programs expressed significant concern about the impacts of increasing methamphetamine use, both from a policy perspective and from an intervention perspective. Programs felt this emerging trend could significantly impact SSP efforts and add fuel to the already worsening opioid crisis.

> "Overall I would say that the increase in methamphetamine use has created a lot more 'not in my backyard' than we've seen historically. We've had a lot more problems with people being upset about discarded syringes and things like that…Here we're seeing a huge shift away from just opiates to opiates and methamphetamines. There are good interventions around opiate addiction; we've got great medication-assisted treatment options. We've got nothing for meth." [SSP 8]

4.0. Strategies SSPs are pursuing to overcome barriers and challenges

4.1. Advocacy and engagement in the policy process to remove legal and policy barriers

Programs stressed the importance of advocating for SSPs and engaging in the policy process as a key strategy to advance the implementation and expansion of SSPs. Programs operating in states where SSPs are illegal described the power of engaging and educating policymakers about their experiences running a SSP.

> "The thing that I think has been most valuable is that we are running an underground exchange while advocating for a change in the law because it gives us a lot of real-world experience to speak from. Legislators have a lot of curiosity

about how these programs fundamentally work. Being able to speak to some of their questions from life's experience is really valuable" [SSP 19]

Other programs operating in states where local approval of SSPs was required described the importance of engaging partners and curating champions as key components to a successful strategy. In some cases, this approach involved influencing local elected leaders.

"I find identifying people that have a good relationship with that person [the political leader in a community who opposes the SSP] and working with them to help navigate and figuring out how to move things forward. I guess you could call those gatekeepers. A lot of times it's not necessarily having a relationship with an ally to gain access to the elected person, but rather to try to get others to advocate for syringe access and all of that stuff. That's really been what's moved our work forward." [SSP 2]

For other programs, the strategy entailed engaging other community leaders such as law enforcement that can influence community acceptance of a SSP.

"Our local law enforcement has been very pro what we're doing. In fact, before the new police chief was sworn in…I just walked up to him the day he got sworn in and I was like, 'Chief, this is who I am, this is what we do. This [SSP] is going to be legal in less than a week. I need your guys just to leave me alone until then.'

> He just kind of looked at me in shock…Then, he was like, 'You do it.' It really kind of blew me away. Ever since then, he has been one of our biggest champions." [SSP 16]

Multiple SSPs, across all programs types, described how the implementation of naloxone distribution and overdose education in their program opened doors for new relationships and opportunities to create new support for syringe services, even among stakeholders that historically had opposed SSPs. This was seen as an important opportunity to advance SSP advocacy and policy efforts.

> "When we go and do a presentation or training [on naloxone] we're able to slip in the philosophy of harm reduction…why we believe it's important to take care of people who use drugs…we've had some really positive experiences with people that I never would have expected would get on board with our work." [SSP 11]

Underlying their advocacy and policy engagement efforts was a strong sense of duty, doing the right thing for people who inject drugs, and feeling resolute that the science and evidence were on their side. A key point of these efforts was combating the pervasive stigma that was seen as a fundamental barrier to expanding the reach and impact of SSPs.

> "Everything we do, all the people we serve, they are stigmatized groups in some way. I think that, so often, people that are in this world don't understand. When

we're talking to potential funders or community members, I think there's still so much misinformation out there. I really view one of our roles is really doing our best to educate folks and educate our policy makers, educate people in the community." [SSP 4]

"We know that drug users are actually more likely to enter into treatment when they're involved in a syringe exchange program than if they weren't involved in one. We know that it stops the transmission of diseases, we know that it saves literally millions of dollars in taxpayer money for HCV and HIV. You are able to build that bridge, I think that's my favorite part of the syringe exchanges, aside from the stopping of transmission, but you are able to come in contact with people who are otherwise marginalized. It puts you in contact with drug users and gives you an opportunity every time to work on their wellbeing, whether they need treatment or health services or housing or jobs and those are people that you otherwise would not come in contact with and that's huge, that's so big. I think we have all the facts. It's just a matter of showing people and not beating them over the head with it necessarily but just educating people like, look, this actually can improve people's lives and save us money too." [SSP 18]

4.2. Capitalizing on all potential funding sources

Recognizing the necessity to braid multiple funding streams together to sustain and grow SSPs, programs described a number of strategies they were pursuing to improve and sustain their funding. The partial lifting of the Federal funding ban that now

allows funds to be used for certain SSP services was cited as an important new funding stream, even after accounting for near universal frustration about not being able to purchase syringes or needles with these funds. This was a pragmatic reflection that in an unstable and competitive funding environment, every potential funding source is valuable. Further, programs stated this new funding stream could be used to offset other funds that were not subject to the same restrictions that could then be shifted to purchase syringes and needles.

> "Prior to that appropriations law, as a government entity, we would not have been able to utilize any money for SSPs. It currently does not allow purchase of syringes and needles, but it pretty much covers everything else…When we receive our allocation from the state, it'll go towards others supplies and salaries to run the program." [SSP 9]

> "The state actually got a bit of money because of the two counties they identified to be at risk for an HIV outbreak similar to Scott County. We actually got some federal money. We haven't seen it yet, but that will be kicking in in the next funding cycle, which is a big deal." [SSP 4]

Capitalizing on opportunities to engage with Medicaid to obtain reimbursement for certain services for the program or to get program participants covered by Medicaid was cited by several programs as an important strategy, this was particularly true for SSPs operating in states that expanded Medicaid under the Affordable Care Act (ACA).

> "The ACA has been incredibly helpful in helping folks be able to access both our medical clinic and treatment options. We went from having our medical clinic with 90% uninsured patients to 80% insured." [SSP 8]

Additional strategies to improve SSP funding included engaging in traditional and crowd-sourced fundraising, cultivating new donors and non-governmental funding partners, improving data collection and hiring grant writers to strengthen grant applications in an increasingly competitive funding environment, and expanding relationships with state and local government agencies to access new funding opportunities.

> "We've raised a ton of money recently through individual donors. Between September and December 2017, we raised $11,000 through individual donations and selling merchandise in an online shop…We've actually gotten a ton of money through Facebook's giving platform, which has been really awesome." [SSP 19]

> "One of the big ones is being really good about keeping our data systems updated constantly so we really can show our numbers and that things are actually working and that we are actually growing, that we need more money now than ever. I think that helps with securing more funding in our state." [SSP 4]

> "The state department of health has been phenomenal. As time goes on, they are more and more coming up with it, they've got extra funding. They'll create a grant or they'll have some funding available. Through that, we have been able to purchase a lot of supplies that we wouldn't be able to normally provide." [SSP 5]

4.3. Expanding the reach of SSPs

Despite the barriers described by SSPs during study interviews that were viewed as limiting the ability of SSPs to reach at-risk population, programs depicted multiple approaches they are deploying to expand their reach.

Seven of the 23 programs currently provide mobile exchange services and an additional four programs indicated they were planning to start mobile exchange services in the coming year. Programs described mobile services as a key part of their ability to access populations that for a variety of reasons were not able to get to the SSP's fixed site.

> "We bought a mobile health unit and we started taking it to different neighborhoods. That increased access, especially among different demographics that weren't accessing our services downtown." [SSP 10]

In addition, more than half of interviewed SSPs stated they engaged in some form of secondary syringe exchange – where participants distribute sterile syringes and injection equipment to peers within their social and drug-using networks – as a strategy to reach at-risk populations.

> "We recognize we should be in more places than we are, but we are just really limited by the city, and by neighborhoods who don't want to have needle exchanges in them…One way that we try to address that is through secondary exchange…If somebody comes from an area that we know doesn't have pharmacies that sell syringes, or it took them 40 minutes to get here, we'll make sure they get hundreds of syringes to distribute out among their drug user group." [SSP 17]

However, a minority of programs, including new and established programs, were not able to engage in secondary exchange because either their authorizing statute, regulation, or policy restricted them to one-for-one exchange with limits on the number of syringes that could be given out or the program had limits on the number of syringes per person that were dispensed (e.g., 30 per week) due to funding constraints.

> "I would say [secondary exchange] is limited because we're a one-for-one program and against best practices we have caps on the number of syringes we give out, which is a nightmare. Other sites do more secondary exchange than we do because of that." [SSP 8]

In addition to mobile and secondary exchange, programs described using traditional and social media to increase awareness of the program, combat stigma, and encourage individuals to seek services. Programs routinely discussed engaging with local television and print media (both proactively and reactively), and maintaining program

websites, Facebook pages, and engaging in other social media platforms. One particularly innovative approach described by a new program operating in a state where SSPs are illegal involved the use of Instagram.

> "We had an Instagram ad that we ran over the Christmas holidays, we got a decent number of calls on our hotline from really young people like 16-18 years old. That was really interesting because the normal demographic of people who engage with our content on Instagram, it is usually women between 25 and 34. After that Instagram ad campaign, it was all 15 to 23 year old males…They would never show up at one of our sites. They didn't want deliveries. They all wanted to receive supplies in the mail. They were probably the most fearful of making contact than anyone else." [SSP 19]

Marketing the availability of SSP services to pharmacies, substance abuse treatment facilities, recovery community organizations, healthcare providers, emergency departments, and other healthcare and social services settings likely to interact with people who inject drugs was a commonly employed strategy, especially by programs operating under a supportive legal framework. Programs that were operating underground or under a fragile legal agreement with local jurisdictions or law enforcement were much more limited in their marketing efforts.

Finally, programs stressed the importance of engaging with people who inject drugs as a critical step in reaching at-risk populations and developing programming to meet the needs of this population.

> "Let their voices be the guiding factors in what you do, what you provide, how you provide services, when you provide services, where you provide services. Really trusting that they are way more of an expert than anyone else will be. Period." [SSP 8]

DISCUSSION

There is a dearth of recent research exploring how SSPs are responding to the rapidly changing policy environment in the midst of the growing opioid crisis in the U.S. This qualitative study of a geographically diverse sample of SSPs provides key insights into the legal and policy barriers, funding challenges, and contextual factors currently impacting SSPs. Despite progress in expanding the number of SSPs in recent years, interviewed programs identified multiple legal, policy, funding, and community barriers that are limiting the scope, scale, and reach of SSPs. However, programs also described strategies they are deploying to address these barriers, taking in to account how specific barriers were playing out in the state or local context of the program.

Programs depicted multiple layers of legal and policy barriers that constrain their current operations. A number of programs were operating in an ambiguous legal environment that created a sense of uncertainty about the sustainability of the program and limited their ability to expand. A small minority of programs were operating underground or without any legal protection at the state or local level. It was common for programs, even those with state laws allowing SSPs, to describe a complex process for receiving local approval or attaining community buy-in to implement new SSPs or expand existing ones. Even after accounting for the variation in how these barriers were

operationalized for different programs, these barriers resulted in missed opportunities to implement or expand SSPs in communities where there was a clear need for services. This was particularly true for those programs that had no explicit legal authorization to establish SSPs. In contrast, a small minority of programs described how SSPs quickly expanded after state laws were revised to support SSPs. Thus, revising state laws, regulations, and local ordinances to explicitly authorize the establishment of SSPs is paramount to their long-term growth and sustainability.

In addition to enacting supportive SSP laws, how those laws are operationalized at the state should be reviewed so that the process for approval and implementation of SSPs is streamlined and equitable for different types of organizations (e.g., local public health department compared to a community-based organization). For some states, this would entail removing the requirement that local political officials have to approve SSPs, and for other states, this would entail a lower threshold of requirements that must be met in order to establish an SSP, e.g., having a medical director and biohazard facility on site in order to get approval from the state to establish an SSP.

Other policies such as how many syringes could be distributed to an individual at one time as well as the existence of drug paraphernalia laws that only provided protection for sterile injection equipment but not used injection equipment were viewed as undercutting the public health mission and impact of SSPs. This was true even for some programs operating in states with laws authorizing SSPs. Enacting or revising laws and policies that authorize broad syringe and needle possession and exempt both sterile injection equipment distributed from and used injection equipment returned to SSPs from drug paraphernalia laws as well as removing limits on the number of syringes that can be

given to an individual at one time should be pursued in tandem with laws authorizing SSPs.

Similar to the effect legal and policy barriers are having on SSPs, the funding challenges SSPs described are restricting their ability to meet the needs of people who inject drugs and reach at-risk populations. Emblematic of these funding challenges are the limited number of locations, days, and hours SSPs in this study were operating – with nearly 45% open a single day per week and 41% open 3 hours or less on the days the programs were open. As acknowledged by many program administrators, these limited windows of opportunity to engage with people who inject drugs are incongruent with the patterns and demands of individuals using drugs and inconsistent with best practice recommendations for SSPs (Harm Reduction Coalition, 2010).

Coupled with limited funding to purchase syringes that necessitated some programs to place arbitrary limits on the quantity of syringes distributed, it is clear that the current funding challenges SSPs are dealing with are inhibiting them from reaching their maximum public health impact. This was particularly true for the vast majority of programs that were not connected to a local public health department. They simply had fewer options for funding and did not have the luxury of being able to tap in to staff or other programmatic funding streams to support their operations in the same manner as many of the programs that were housed in local health departments.

Although the recent change in Federal appropriations law allowing use of funds for certain SSP services was viewed as a positive and important policy change, the continued ban on using funds to purchase syringes and needles was a universally identified barrier to opening new SSPs and limiting the ability of existing programs to

operate at an optimal level, to reach at-risk populations, and to adapt as the opioid crisis evolves. The Federal funding ban also reinforces stigma because it implies there is not full support for these programs and the services they provide. Compounding the funding challenges for SSPs is the fact that there are no Federal funding programs dedicated to SSPs. The Federal funding that is available to support certain SSP services is targeted broadly for substance use or infectious disease prevention and treatment; thus, SSPs are competing with numerous other potential recipients for these funds. It is highly unlikely that SSPs will achieve sufficient numbers and scale to reach at-risk populations and provide comprehensive services for people who inject drugs until a full repeal of the funding ban is implemented and dedicated funding programs are developed. Taking these steps will provide much needed stability to current programs and would likely induce, both politically, socially, and financially, additional jurisdictions to open and expand SSPs. Moreover, the legal status of programs is intertwined with their ability to access funding, with several programs noting that even when funding opportunities were available, they were not able to pursue them because syringes and needles were considered illegal in their state. Therefore, to fully maximum the role of SSPs, efforts to address funding gaps must occur in concert with the enactment of laws and policies that fully authorize SSPs.

The increase in methamphetamine injection reported by the majority of SSPs in this study is concerning. These findings corroborate emerging evidence of increased methamphetamine injection, in particular in combination with heroin, in certain jurisdictions in the U.S. (Glick et al., 2018; Al-Tayyib et al., 2017). Study respondents indicated that not only were they seeing an increase in combined injection of opioids and

methamphetamine, but that some individuals were switching from opioid injection to methamphetamine injection due to concerns about increased risk for overdose from fentanyl and the contaminated heroin supply. These key insights can be used to inform targeted initiatives to reduce harm among individuals who are using opioids and methamphetamine. In addition, although individuals may believe switching to methamphetamine can protect them from fentanyl and the changing illicit opioid supply, emerging data indicate that the supply of methamphetamine in the U.S. has been contaminated with fentanyl and other synthetic opioids (DEA, 2017). Thus, SSPs can take additional steps to mitigate overdose risk by educating people injecting drugs about the risks of exposure to opioids when using other illicit drugs as well as equipping these individuals with naloxone to reverse an opioid overdose if their methamphetamine or other illicit drug supply unknowingly contains opioids.

Finally, stigma at all levels in the community was identified as a primary factor that enabled many of the barriers SSPs face to persist. As part of their advocacy and policy engagement strategies, SSPs were pursuing multiple approaches to combat stigma, including educating policymakers about the evidence behind SSPs and the benefits they can provide to a community, educating stakeholders about addiction as a chronic medical condition and why it is important to address the health of people who inject drugs, and leveraging the media and key opinion leaders to disseminate scientifically-based information on SSPs and increase awareness of these programs. Although these strategies can be influential, taking actions at the Federal level such as removing the Federal funding ban, creating dedicated funding opportunities for SSPs, and implementing anti-stigma campaigns for addiction and harm reduction have the potential to substantially

change social norms and facilitate the implementation of policies at all levels of government to expand SSPs and other services for people who inject drugs.

STUDY LIMITATIONS

This study is subject to several limitations. First, although steps were taken to capture the experiences of a geographically diverse sample of SSPs, the findings represent the experiences of a purposive sample of SSP program administrators and may not be representative of all SSPs or generalizable to SSPs that did not participate in the study. Purposive sampling and the criteria used to define the sampling frame is subject to researcher bias. Second, important barriers and facilitators may not have been captured by the interview guide or through the semi-structured interviews. Thus, relevant factors that are impeding as well as enabling SSP implementation and operation may not have been identified in this study. Third, because a single investigator reviewed and coded the responses, it is possible that the findings are influenced by researcher bias and may not solely reflect the experiences of study participants. Fourth, the phenomenon of reactivity, where the researcher or research participants adjust behavior or responses while participating in research, is a known limitation of qualitative research. Steps taken to mitigate these limitations and strengthen the rigor of the analysis included: 1) using maximum variation purposive sampling that included a sample of approximately 9% of all known SSPs in the U.S. and was based on *a priori* criteria to capture both new and old programs, programs in rural and urban areas, and programs in all four U.S. census regions; 2) use of a second coder to review transcripts and to validate and refine codes and themes; 3) explicitly exploring deviant cases and concepts identified during the interviews with interview participants; 4) writing notes during interviews and memos

after interviews to reflect on the evolving meaning of the study interviews and coding analysis and to identify potential researcher bias and influence during the study and thematic analysis; and member checking with interview participants to examine interpretations of the data and to clarify concepts during interviews.

CONCLUSION

The opioid crisis in the U.S. continues to expand and evolve. In recent years, significant progress has been made in expanding SSPs in the U.S. However, programs continue to encounter multiple barriers that are limiting the number, scope, and reach of SSPs. To counter these barriers, SSPs are employing multiple strategies to engage policymakers and communities, strengthen their funding base, and reach at-risk populations. Coupling these strategies with policy changes that address the underlying legal and financial barriers and advancing efforts to combat stigma around drug use and addiction stand to substantially expand the role of SSPs as part of the public health response to the opioid crisis in the U.S.

Chapter 5: Conclusion

This dissertation includes three stand-alone, but complementary studies that examine prescription opioid injection misuse in the United States and the role Syringe Services Programs can play in response to the opioid crisis. This chapter contains a summary of the key findings for each study, a discussion of policy, programmatic, and clinical practice implications of the research, and identifies key opportunities for future research.

Summary of Study One

Study one, based on a systematic review of the published literature from 2000 to 2017, provided a synthesis of the available data on the prevalence of prescription opioid injection misuse, the sociodemographic and geographic characteristics of people who inject prescription opioids, and the health outcomes associated with prescription opioid injection misuse in the U.S. The study also identifies areas for future research based on gaps identified during the systematic review.

The study aimed to address four key research questions: 1) What is the prevalence of prescription opioid injection in the U.S.?; 2) What is known about the demographic, socioeconomic, and geographic characteristics and risk factors for prescription opioid injection in the U.S.?; 3) What is known about co-occurring substance use, mental health, and health-related outcomes among people who inject prescription opioids in the U.S.?; and 4) What other characteristics have been associated with prescription opioid injection in the U.S.?

Out of an initial search of 4,183 unique studies published between 2000 and 2017, a total of 58 peer-reviewed articles were included in the systematic review. Based on

these studies, the prevalence of prescription opioid injection increased significantly in the past decade, with an overall estimated prevalence of lifetime prescription opioid injection among people 12 years and older in the U.S. of approximately 0.3%, and a prevalence among people with opioid use disorder estimated at 16%-25%.

Other key findings include the following demographic, socioeconomic, and clinical characteristics that were consistently associated with prescription opioid injection: 1) demographic characteristics: male sex, non-Hispanic white race, age 18 to 44 years, and living in a rural area; 2) socioeconomic factors: lower educational attainment, being homeless, being unemployed, having a low annual household income, being uninsured, and receiving Medicaid and 3) clinical characteristics: initiating prescription opioid misuse at an earlier age, having a prescription opioid use disorder, using heroin or having a heroin use disorder, using cocaine or having a cocaine use disorder, prior receipt of substance use treatment, experiencing a nonfatal overdose, having chronic pain, and having a history of psychiatric illness or high severity of psychiatric problems. Finally, the study identified a significant increase in risk for risky injection practices such as syringe sharing and reuse and subsequent transmission of infectious disease such as HCV and HIV among people who inject prescription opioids compared to people who inject other drugs.

Despite the substantial published literature on prescription opioid misuse, use disorder, and overdose over the past 18 years, only a small proportion provided information on the four key research questions of the systematic review. Thus, there is a need for additional research on the prevalence and characteristics of people who inject prescription opioids and other drugs.

Summary of Study Two

The second study, using data from the 2003 to 2014 National Surveys on Drug Use and Health, provided the first nationally representative analysis of prescription opioid injection in the U.S. This study provided estimates on the magnitude of prescription opioid injection and identified key correlates of prescription opioid injection, including quantifying the extent of unsafe injection practices and syringe sources for people who inject prescription opioids and other drugs.

The study found significant increases in prescription opioid injection misuse between 2003 and 2014. Rates increased 65% among people 12 years or older, and the magnitude of the increase was greater when prescription opioid injection was examined among people who misuse prescription opioids – increasing 72% among people who have ever misused prescription opioids and 200% among people who had initiated prescription opioid misuse in the past five years. By 2012–2014, 710,100 people had reported ever injecting prescription opioids, an increase of more than 300,000 people since 2003–2005.

The increases in prescription opioid injection occurred across a broad range of demographic and substance using groups, with particularly large increases among women, non-Hispanic whites, and people aged 18–25 years. Importantly, these increases were consistent with increases in other indicators of opioid-related harms during the study period (Ronan & Herzig, 2016; Han et al., 2015; Zibbell et al., 2015; Compton et al., 2016; Suryaprasad et al., 2014; Zibbell et al., 2018). The study also found high rates of syringe reuse and sharing with nearly 60% of people who had ever injected prescription opioids reporting reuse of their own needle the last time they injected, and

roughly 1 in 5 reporting reuse of someone else's needle as well as allowing someone else to reuse their needle. In addition, only 2.3% reported getting their most recent syringe or needle from an SSP compared to nearly 6% for people who injected other drugs but not prescription opioids. The findings of this study underscore the importance of broader implementation of opioid prevention initiatives, expanding access to medication-assisted treatment for underlying opioid use disorders, and the scaling-up of the provision of sterile injection equipment through SSPs.

Summary of Study Three

The third study used applied qualitative methods to explore how SSPs are responding to the evolving opioid epidemic and rapidly changing policy environment. In addition, the study identified barriers SSPs are facing that inhibit their accessibility and utility, as well as facilitators, innovative collaborations, and successful strategies SSPs are pursuing to meet the needs of the expanding population of people injecting opioids and other drugs and address the evolving opioid crisis.

The study found that despite progress in expanding the number of SSPs in recent years, some participating programs are facing multiple legal, policy, funding, and community barriers that are limiting the scope, scale, and reach of their SSPs. However, programs also described strategies they are deploying to address these barriers, taking in to account how specific barriers were playing out in the state or local context of the program.

Key themes related to legal and policy barriers included: 1) SSPs are operating in a fragile legal environment; 2) community resistance is a non-legal barrier facing SSPs; and 3) pervasive stigma fuels legal and policy barriers. Key themes related to funding

challenges included: 1) SSPs are currently operating with a patchwork of funding; 2) the Federal funding ban is preventing SSP implementation and growth; 3) perceptions of funding opportunities vary across programs; and 4) stigma perpetuates SSP funding challenges. The changing illicit drug supply and drug use trends were also identified as an important domain in the study, with key themes in this domain including: 1) the expanding number of people injecting drugs and seeking services at SSPs; 2) the emergence of illicit fentanyl has amplified the challenges faced by SSPs; and 3) a resurgence of methamphetamine is further challenging SSPs. Finally, SSPs identified multiple strategies they were pursuing to overcome these barriers and challenges. Key themes in this domain included: 1) Advocacy and engagement in the policy process to remove legal and policy barriers; 2) capitalizing on all potential funding sources; and 3) innovative approaches to expanding the reach of SSPs.

Policy, Programmatic, and Clinical Practice Implications of the Research

Collectively, the findings from the three studies carry important implications for prevention, treatment, and harm reduction policy, programmatic interventions, and clinical practice.

In the area of prevention, the findings from studies one and two that earlier age of initiation of prescription opioid misuse and increasing years of misuse are associated with increased risk of prescription opioid injection emphasize the importance of prevention among youth. Further, the strong association between prescription opioid injection and both prescription opioid use disorder and heroin use disorder identified in studies one and two support prior research documenting the intertwined nature of prescription opioid misuse and heroin use and stress the importance of prescription opioid misuse prevention

as a key strategy to prevent future heroin use, heroin use disorder, and overdose. Multiple studies have found that prescription opioid misuse typically preceded heroin initiation among current heroin users in the U.S. (Carlson et al., 2016; Cicero et al., 2014; Jones, 2013). Carlson et al., 2016, in a prospective study found that people who misused prescription opioids by non-oral routes, including injection, were significantly more likely to initiate heroin use over a three year period compared to those who reported oral misuse.

Policies and programmatic interventions in the prevention space include community and school-based prevention programs to increase protective factors and reduce risk factors as well as clinical practice initiatives to curb inappropriate opioid prescribing in order to reduce the direct exposure of opioids through prescribing to youth and indirectly through environmental availability of opioids that can be diverted for misuse. Preventive interventions have demonstrated long-term effectiveness in reducing opioid misuse among youth with protective effects into early adulthood in multiple randomized controlled trials (Spoth et al., 2013).

The significantly elevated risk of prescription opioid injection among people with a prescription opioid use disorder and among those using heroin or with a heroin use disorder coupled with the increased risk for overdose associated with prescription opioid injection identified in study one and in study two highlight the pressing need to rapidly expand access to medication-assisted treatment (MAT) for opioid use disorder. MAT, with methadone or buprenorphine in particular, reduces opioid use, opioid-related mortality, and the transmission of infectious diseases such as HIV and HCV (Mattick et al., 2009; Mattick et al., 2014; Lee et al., 2016; Tsui et al., 2014; Krupitsky et al., 2011;

Schwartz et al., 2013). Expanding access is particularly important in areas of the country that have historically had limited access to MAT such as in the South and in rural areas (Jones et al., 2015; Jones et al., 2017) – areas identified in studies one and two as having a higher burden of prescription opioid injection misuse.

SSP and Harm Reduction Policy

The high prevalence of risky injection practices among people who inject prescription opioids identified in studies one and two provide insight into the underlying mechanisms contributing to elevated infectious disease transmission risk among people who inject prescription opioids. These findings, coupled with data indicating people who inject prescription opioids are less likely to get syringes from SSPs and often lack awareness of these programs and the services they offer (Mateu-Gelabert, 2015; Jones, 2018), lend empirical support for initiatives to educate this at-risk population about safer injection techniques and harm reduction service availability, as well as efforts to expand the availability of comprehensive SSPs. Scaling these interventions is acutely needed in rural areas of the U.S. and in the South and Midwest where access to these interventions is particularly limited and prescription opioid misuse, including prescription opioid injection, as identified in studies one and two, is disproportionately high (Jones, 2018; Jones et al., 2017; Des Jarlais et al., 2015; Van Handel et al., 2016).

As identified in study three, there are a number of legal, policy, funding, and community barriers to expanding SSPs in the U.S. Steps must be taken to revise state laws, regulations, and local ordinances to explicitly authorize SSPs. At the same time, how these laws and regulations are implemented on the ground must be reviewed and streamlined so that the threshold of requirements to establish a quality, comprehensive

SSP can be met by the widest possible group of stakeholders (e.g., local public health department, community-based harm reduction program, AIDS service organization). Further, to ensure that SSPs can maximally impact public health and that additional operational barriers are removed, laws and policies that authorize broad syringe and needle possession and exempt both sterile injection equipment distributed from and used injection equipment returned to SSPs from drug paraphernalia laws as well as removing limits on the number of syringes that can be given to an individual at one time should be implemented.

With respect to funding, study three documented the patchwork of funding and limited funding opportunities SSPs are currently facing. A critical first step in addressing these barriers is fully removing the Federal funding ban that bars the use of Federal funds to purchase syringes and needles. This was a universal barrier for programs interviewed in study three. In addition, because there are so few funding opportunities for SSPs and competition has only increased in recent years as new SSPs have opened, new funding streams that are dedicated to supporting the implementation and operation of SSPs should be created at all levels of government. Finally, new models for running SSPs, such as housing them within local health departments, may provide a more solid financial foundation and enable further expansion of SSPs.

The increased overdose risk among people who inject prescription opioids identified in study one underscores the importance of access to overdose prevention education and naloxone among people who inject prescription opioids. In recent years, significant progress to expand access to naloxone has been made due to implementation of state naloxone access laws such as pharmacy standing orders, increased community

distribution, and efforts to increase community engagement (Jones et al., 2016). However, in 2017, approximately 350,000 naloxone prescriptions were dispensed from U.S. retail pharmacies (IQVIA, 2018); significantly smaller than the 11 million reporting prescription opioid misuse and 1.7 million with a prescription opioid use disorder in 2017 (SAMHSA, 2018). Among the SSPs interviewed in study three, naloxone and overdose education was seen as a key service they provided to people who inject drugs. Thus, while there has been a significant amount of focus on getting medical providers to co-prescribe naloxone to patients at-risk for opioid overdose (Office of the Surgeon General, 2018), expanding naloxone access within SSPs provides an additional avenue to equip high-risk populations with naloxone to reverse opioid overdoses.

Finally, across all three studies, a number of socioeconomic factors such as lower educational attainment, being homeless, being unemployed, having a low annual household income, lack of transportation, being uninsured, and receiving Medicaid were consistently associated with increased risk for prescription opioid injection. These findings underscore the complex social challenges facing this population and point to the importance of addressing structural barriers and implementing policies targeting the underlying social determinants of health such as stable and affordable housing, education and employment opportunities, and insurance coverage and access to care, that are critical to improving the health and outcomes of people who inject drugs.

Key Opportunities for Future Research

A number of opportunities for future research were identified during the conduct of the three studies. Through the systematic review, it was clear that there is still much to be learned about people who inject prescription opioids. For example, the most recent

estimate of population-level prevalence of prescription opioid injection is based on data from 2014. Since that time, the opioid epidemic has evolved considerably, including a decline in the prescribing of opioid analgesics (Guy et al., 2017), continued increases in heroin use (SAMHSA, 2017), and the emergence and use of highly potent synthetic opioids such as illicitly made fentanyl and fentanyl analogs that are substantially shifting the illicit drug market in the U.S. and driving the recent increases in opioid-related overdose deaths (Jones et al., 2018; DEA, 2017). How these changes are influencing the prevalence of prescription opioid injection and correlates of prescription opioid injection has not been explored.

In addition, the systematic review did not assess questions related to the effectiveness of opioid-related prevention or treatment policies or programs on prescription opioid injection and related harms; future research should examine these important research questions. Finally, the studies included in study one as well as the data used in study two were either retrospective or cross sectional in design; future research should employ prospective study designs to provide insights into the trajectories and substance use patterns of people who have not yet initiated prescription opioid injection. The recently announced HEAL Initiative from the National Institute on Drug Abuse at the National Institutes of Health may provide a significant influx of research dollars to explore these important research questions. (National Institute on Drug Abuse, 2018).

The rich qualitative findings of study three identify numerous areas for future research related to SSPs. For example, future research could explore the impacts and outcomes of different models of SSPs such as stand-alone SSPs run by community organizations, SSPs that are part of a local health department, and those that are

integrated into medical clinic settings. Given the variation in state laws and policies, research that explores this variation to assess how these laws and policies influence SSP implementation and impact health outcomes such as incidence of HCV or HIV infections and overdose deaths should be undertaken. In addition, there is a need to better understand the optimal suite of services (e.g., syringes/needles, naloxone, infectious disease testing, substance use treatment) and linkages to services and service providers to fully realize the public health benefits of SSPs. Further, there is a need for research to identify populations of individuals who inject drugs that are in need of SSP services and to quantify the resources required to match service need with service delivery. This information could substantially improve the targeted placement of SSPs as well as help policymakers appropriately allocate resources to support and sustain SSPs.

Finally, none of the three studies specifically assessed the experiences of people who inject prescription opioids. However, study one did identify a small number of studies that specifically explored the attitudes, beliefs, preferences, and experiences of people who inject prescription opioids, and study three identified, through the experience of SSP program administrators, the importance of engaging with people who inject drugs to help guide SSP operations. Future research should prioritize the study of this population and focus on their attitudes, needs, preferences, and motivations in order to better inform the development of policies and programs that meet their needs.

Conclusion

The three studies conducted as part of this dissertation provide key insights into prescription opioid injection trends, demographic, socioeconomic, geographic, and clinical characteristics as well as health outcomes associated with prescription opioid

injection, and the experiences and barriers of SSPs and the strategies they are deploying to address these barriers in the midst of the opioid crisis and a rapidly evolving policy environment. Taken together, the new knowledge produced from this dissertation can be used to inform the development, prioritization, and implementation of policies, programs, and clinical practices that aim to reduce prescription opioid injection and its related harms and highlight areas for additional and necessary research.

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Appendix A

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