Emerging Patterns of Substance Use and Buprenorphine Nonadherence

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Abstract

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Opioid overdose deaths are the leading cause of accidental death in the United States, most of which consist of opioids such as fentanyl. In the midst of this crisis, we are also experiencing a related increase in people with opioid use disorder (OUD), of which many are interested in seeking treatment. Paralleling these public health issues, use of illicit substances such as cocaine, fentanyl, heroin, methamphetamine and xylazine have also seen significant rises in use and co-use, while overdoses involving more than one substance have also increased. These interrelated concerns raise questions across many different areas of public health and clinical practice. Thinking about primary prevention, one question we may ask is how we can improve monitoring of substance use and co-use in order to be aware of emerging novel substances. This information would allow us to better engage with people who use drugs (PWUD) by providing them with useful educational information and harm reduction resources tailored to the substances in their local drug supply. Beyond primary prevention, we can ask how to better understand and aid PWUD who are interested in using harm reduction and in seeking treatment for substance use disorders. To begin to answer some of these questions, we leveraged three different datasets among populations of PWUD.

We first conducted an exploratory secondary analysis of data using the Project Needle Exchange Utilization Survey (NEXUS) to look at the prevalence of cocaine, fentanyl, heroin, methamphetamine and xylazine at six different syringe service programs using a novel dried blood spot (DBS) assay. We found that methamphetamine use was more prevalent in the Western U.S. whereas cocaine use was higher in the Eastern U.S. Xylazine and fentanyl were predominantly found on the East Coast. Using DBS assays may be an effective method for public health monitoring of substance use that can be used to tailor interventions and educational materials regarding substances that are commonly used locally.

Secondly, we leveraged data from a two-site pilot randomized trial of a behavioral mHealth intervention called the Trial of Adherence Application for Buprenorphine Treatment (TAAB) to evaluate the association between methamphetamine use and buprenorphine adherence among people receiving buprenorphine as treatment for OUD. Among this study population, we found a significant positive association between methamphetamine use and buprenorphine non-adherence (OR: 2.56; 95% CI: 1.37-4.76). Future research and treatment program design should consider potential differences in treatment experiences of people who use methamphetamine intermittently versus those who use frequently and regularly. As adherence and retention are already challenging, it is important to ensure that we understand the profiles of drug use that are associated with increased barriers to positive treatment outcomes. Only by fully understanding this can we begin to ensure the development of individualized treatment solutions for every patient and their needs.

Finally, we used data from the Rural Opioid Initiative (ROI) to described unadjusted differences in the prevalence of demographic and behavioral characteristics comparing those who reported sublingual buprenorphine injection to those who did not in the past 30 days. We also analyzed qualitative one-on-one interview data to further elucidate the context of this behavior. Buprenorphine injection was relatively common, and PWUD who injected buprenorphine more commonly reported sex- and drug-related risk behaviors for HCV and other bloodborne viruses. The finding that buprenorphine injection is a common occurrence in rural U.S. settings reinforces the need to integrate harm reduction activities into addiction treatment programs.

While these findings address different questions in the general field of substance use, increasing harm reduction and decreasing overdose are the motivation behind all of them. The high burden of both OUD and overdose deaths necessitates an immediate investment in research to better understand demographic, behavioral, and regional trends in substance use, as well as their impacts on treatment outcomes, to design well-informed and efficient prevention strategies. We also discuss here potential future research efforts that will hopefully continue to progress this body of work to improve health outcomes for people who use drugs and people with OUD.

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Dedication

To my Mom and Dad, Tami and Joe, and their parents, Mary Kathryn Carney and Matt and Phyllis Zinsli. I learned to see the world through your eyes, and the most obvious thing I saw there was compassion. Thank you for all your undying love and support, and for all of the sacrifices you made so I could make it this far and use my education to help others. I know this wasn't just my dream, but yours too. I love you.

Chapter 1: Introduction

Patterns in use of illicit substances such as fentanyl, heroin, methamphetamine, cocaine and xylazine are constantly changing and differ across regions of the United States (U.S.)[1–3]. Generally, however, these substances have seen significant rises in use and co-use[4–12]. Notably, drug overdoses have surpassed motor vehicle accidents as the current leading cause of accidental death in the United States[13–15], most of which consist of opioids such as fentanyl. Overdose deaths related to synthetic opioids, as well as seizures of fentanyl-positive drugs, and opioid use disorder (OUD) have continued to increase in recent years, leading to a significant public health concern[2,16,17]. The devastating burden of both OUD and overdose deaths necessitates an immediate investment in research to better understand demographic, behavioral, and regional trends in substance use to design well-informed and efficient prevention strategies. Understanding which regions have the highest burden of use of substances such as fentanyl will allow for designing more targeted intervention strategies. Additionally, as treatments for OUD like buprenorphine become increasingly utilized, it is critical to identify ways to improve treatment adherence and retention, especially with the rising concern that concurrent use of methamphetamine can limit buprenorphine treatment outcomes[18].

Drug Testing as Public Health Prevention

Syringe service programs (SSPs) offer harm reduction services, such as access to sterile syringes and naloxone kits, to PWUD[19]. As SSPs are a central location for so many services for PWUD already, they are also an optimal choice for PWUD study

recruitment and for targeted overdose prevention interventions. One qualitative study of PWUD in Oregon found that people reported being ready and willing to implement harm reduction strategies if available[20]. Effective harm reduction, however, first requires an awareness of current substance use trends through surveillance activities. Dried blood spots (DBS), a relatively novel method for testing blood for the presence of illicit substances, are minimally invasive, do not require phlebotomy, and can be shipped and stored at ambient temperatures[21]. This method may be an effective replacement for self-report or urine drug testing (UDT) and may allow for more accurate public health surveillance and rapid updating of outreach and harm reduction materials.

Buprenorphine Treatment and Substance Use

Buprenorphine administration is used for the treatment of opioid withdrawal symptoms and opioid use disorder (i.e. addiction)[22]. There are growing concerns about whether co-use of methamphetamine and opioids, including fentanyl, may limit buprenorphine treatment retention and adherence[18,23]. Some studies have found methamphetamine/amphetamine use or use disorder to be negatively associated with receiving methadone and buprenorphine, and that there were generally negative associations with both retention and opioid abstinence[18]. While this literature suggests that methamphetamine use may limit buprenorphine adherence, a small number of studies have also shown that buprenorphine may reduce methamphetamine cravings. Prior to the human studies on this topic, rat models and studies on other similar substances lead to this hypothesis[24–27]. Understanding the relationship between methamphetamine use and buprenorphine treatment adherence, especially with

fentanyl—a potential contaminant of methamphetamine in the current drug supply--emerging as the main driver of overdose in the current opioid crisis, is critical as co-use is common among individuals receiving treatment for OUD.

Buprenorphine Injection

Oral or sublingual buprenorphine as treatment for OUD, also known by the most common brand name “Suboxone” (co-formulated buprenorphine + naloxone), is believed to have a lower abuse potential due to the inclusion of naloxone which is minimally absorbed in an oral/sublingual route, yet if injected it will result in the highly aversive experience of precipitated withdrawal[28]. Despite this, people injecting oral or sublingual buprenorphine monoproduct (“Subutex”) is well-documented, and there are increasing reports of people injecting the co-formulation with naloxone[28,29]. Combining personal insights and perspectives from people reporting buprenorphine injection with an understanding of the characteristics of PWUD that are associated with this behavior will improve our understanding of what groups are more likely to report this behavior and allow for us to engage with these populations to design better treatment solutions.

Dissertation Contribution

This dissertation works to fill in gaps in the literature in the areas of substance use prevalence in the United States, novel drug monitoring methods, and buprenorphine use and challenges to adherence. While these analyses represent a wide variety of topics within the broader topic area of substance use, they all ultimately work to improve

the health of people who use drugs and reduce injection-related harms, OUD and overdose, all of which are serious growing public health concerns.

Chapter 2: Substance Use Monitoring among People Who Use Drugs Using a Novel Assay to Test Dried Blood Spot Specimens

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ABSTRACT

Background & Aims: The development of rapid and efficient monitoring systems of drug use to understand demographic, behavioral, and regional trends in substance use is necessary to design effective prevention and harm reduction strategies for people who use drugs (PWUD). Dried blood spots (DBS) can be used as a non-conventional drug testing approach that meets FDA accuracy and precision guidelines.

Design, Setting and Participants: From July 2021 to July 2022, 1,559 persons who use drugs (PWUD) were enrolled at six U.S. syringe service programs (SSP). SSPs in Sacramento, California, Ellensburg, Washington, and Missoula, Montana were classified as “Western” and SSPs in Madison, Wisconsin, New Haven, Connecticut, and Wilmington, North Carolina were classified as “Eastern.”

Measures: Participants completed a survey on demographic and behavioral characteristics and provided DBS specimens. A novel toxicology assay coupling liquid

chromatography and tandem mass spectrometry was developed and used to identify the presence/absence of fentanyl, methamphetamine, xylazine, cocaine, and heroin, along with their metabolites. In this cross-sectional analysis, we describe the prevalence of each substance detected by SSPs.

Results: Among 1,380 PWUD with viable DBS, methamphetamine was more prevalent in the Western versus Eastern state SSPs (95% vs. 33%). The Eastern state SSPs saw higher prevalences of cocaine, fentanyl, heroin and xylazine than the Western state SSPs (86% vs. 25%; 41% vs. 12%; 20% vs. 17%; 20% vs. 6%, respectively). Testing positive for more than one substance was common (50%).

Conclusions: Results from this analysis of DBS specimens collected from PWUD at six U.S. SSPs highlights the effectiveness of this toxicology matrix for drug monitoring, as well as confirms substantial existing regional differences in substance use. Further research is needed on the logistical implications of the collection of DBS at SSPs.

BACKGROUND

Overdose deaths related to synthetic opioids, seizures of fentanyl, and diagnoses of opioid use disorder (OUD) have increased in recent years and are of significant public health concern[2,16,17]. Drug overdoses surpassed motor vehicle accidents as the current leading cause of accidental death in the United States (U.S.) beginning in 2011[13–15], most of which consist of opioids such as fentanyl. While fentanyl is highly associated with overdose, these deaths also often involve additional substances. Almost 80% of deaths involving a synthetic opioid in 2016 involved alcohol or another drug such as heroin, cocaine, prescription opioids, benzodiazepines, psychostimulants, and

antidepressants[30,31]. Xylazine, a tranquilizer not approved for human use, has also been increasingly linked with opioid overdoses in every region of the U.S.[31–33].

Other than fatal overdose data, the most comparable, accessible data on drug use patterns come from self-reported measures. However, self-report may be subject to measurement error if someone does not recall or is not aware of the substance(s) they used. Measurement error can also occur if a person is not honest, which may arise due to social desirability bias (a tendency for people to self-report answers that the respondent believes makes them seem more favorable) [34–36]. Specifically regarding fentanyl monitoring, research on self-report has shown that people who use drugs (PWUD) are not always able to accurately report if fentanyl is in their drug supply[37,38]. Prior research has found evidence of illicit drug impurities through the inclusion of substances such as fentanyl or xylazine[33,39]. The devastating burden of OUD and overdose deaths necessitates an immediate investment in research to understand trends in substance use that allows for the development of well-informed and efficient prevention and harm reduction strategies.

We aimed to describe patterns of fentanyl, methamphetamine, xylazine, cocaine and heroin at six U.S. syringe services programs (SSPs) and quantify specific combinations of drugs. Understanding which U.S. regions have the highest burden of use of substances such as fentanyl will allow for designing of more targeted intervention strategies to prevent overdose among PWUD. Additionally, incorporating dried blood spot (DBS) testing methods into surveillance systems or programs may allow for more

rapid substance use monitoring can help get ahead of emerging threats to public health among PWUD.

METHODS

Analysis design: This analysis was an exploratory secondary analysis of data from Project Needle Exchange Utilization Survey (NEXUS), a collaborative effort between the Centers for Disease Control and Prevention (CDC) and the University of Washington (UW) aiming to create a national program for the monitoring of HIV prevalence, drug use, and related behaviors. Survey methodology has been previously published[40]. Project NEXUS was a multisite, cross-sectional surveillance survey of PWUD conducted in SSPs in the U.S. from June 2021 to July 2022. This project was conducted at six SSPs located in Ellensburg, WA, Wilmington, NC, New Haven, CT, Madison, WI, Sacramento, CA and Missoula, MT. SSPs were sampled in two-stages. The first stage involved selection based on the setting (urban, suburban, rural), the U.S. Census region (East, South, Midwest, and West), the length of operation (<5 years, 5 years or longer) the syringe distribution model (needs-based vs. all others), and health department affiliation. All survey and testing procedures were anonymous; no identifiers were collected. SSPs in CA, WA, and MT were classified as “Western” U.S. SSPs and SSPs in WI, CT, and NC were classified as “Eastern” U.S. SSPs.

Recruitment and eligibility: Participants were recruited by SSP staff, peer referral, and word of mouth. Incentivized peer referrals (i.e. snowball sampling), helped expand survey reach to PWUD who did not use the SSP. Eligible participants had to be 18

years of age or older, able to complete the survey in English, had to have injected or used injection drugs via a non-injection route in the past 6 months, and had not previously participated in the survey.

Data Collection: During the consent process, participants were given the option of consenting to have any leftover DBS saved for future testing. Participants not consenting to future DBS use or without sufficient leftover DBS specimens were excluded from this analysis. After providing consent, participants completed a detailed behavioral interview and testing for HIV and hepatitis C virus (HCV). If the participant provided consent to collect and store specimens for future research use, five drops of fingerstick whole blood (approximately 50 µL per drop) were collected on Whatman 903 protein saver DBS cards (GE healthcare Bio-sciences, Pittsburgh, PA). The DBS cards were first sent to a commercial laboratory for HCV RNA testing, which used up to 4 of the 5 spots in the card. The leftover DBS cards with at least one spot were stored frozen at -80°C and later transported in bulk on dry ice with desiccant packets to another commercial laboratory for drug testing.

Survey measures:. The survey collected data on residence (past six months), health care access and utilization (past six months), socioeconomic status, having a disability, sexual behaviors (past six months), injection drug use (frequency, equipment sharing, injecting partners) and non-injection drug use (past six months), drug overdose history (past six months), naloxone access (past six months), justice system and law enforcement experience (past six months), drug treatment history (past six months),

HIV testing experiences (ever), health conditions, and SSP access (past six months). Participants were asked about their injection drug use and non-injection drug use of different substances in the past six months (yes/no).

Drug testing analyses: The protocol for testing DBS specimens was developed and validated by the Center for Forensic Science Research and Education (CSFRE). The analytical method coupled liquid chromatography (LC) and tandem quadrupole mass spectrometry (MS) to identify the presence or absence of fentanyl, methamphetamine, xylazine, cocaine, benzoylecgonine (cocaine metabolite), morphine (heroin metabolite), and 6-monoacetylmorphine (heroin metabolite) above established cut-off concentration values (ng/mL). The instrument used was a Water Acquity UPLC® coupled to a Water Xevo TQ-S Micro MS. The column was an Agilent Infinity Lab Poroshell C-18 (2.7 µm, 3.0 x 100 mm) which was heated to a temperature of 60°C. The mobile phases consisted of mobile phase A: 5mM ammonium formate in deionized water (pH 3) and mobile phase B: 0.1% formic acid in methanol (MeOH). The injection volume was 10 µL.

A 13-mm diameter hole was punched from each spot and placed in a 2 mL Eppendorf tube and 1 mL of 50:50 methanol:acetonitrile was added along with 50 µL of internal standard (0.1 ng/µL; methamphetamine D5, morphine D6, benzoylecgonine D3, cocaine D3, 6-monoacetylmorphine D6, and fentanyl D5). The samples were then centrifuged at 10,000 RPM for 5 minutes. The supernatant was transferred to a glass tube and evaporated to dryness using a TurboVap set to 35 °C. Lastly, the samples were reconstituted with 100 µL of 90:10 5mM ammonium formate in deionized water (pH 3):

0.1% formic acid in MeOH, and then transferred to autosampler vials. Three calibrators were run with each set of samples. These calibrators were made from blood spiked at 1, 10, and 50 ng/mL using a 1 ng/μL stock solution (fentanyl, methamphetamine, xylazine, cocaine, benzoylecgonine, morphine, 6-monoacetylmorphine). A pipette was used to spot 75 μL of each spiked blood on correspondingly labeled Whatman 903 protein saver cards. The cards were left to dry overnight and were stored in -4°C conditions after drying. These calibrators were prepared the same as the samples for each run. Additionally, there was also a matrix blank with internal standard (ISTD) and one without that were included in each run. The matrix blank with the ISTD consisted of a blank punch that was prepared the same as the samples while the matrix blank with no ISTD was a blank punch that received no ISTD during the sample preparation steps.

This testing method met FDA accuracy and precision guidelines, samples were relatively simple to collect and analyze, and the construction of the overall assay allowed for the rapid incorporation of new substances and/or analogues as they arise without revalidation of the entire method.

Table 2.1 shows the cutoff concentrations that were obtained for the assay for each of the six substances. In developing cut-off concentrations, identifying the lowest detectable amount of a substance was prioritized. Cocaine and benzoylecgonine were combined as a single measure as they both measure cocaine use, while morphine and 6-monoacetylmorphine were combined as the single measure of heroin use. For the purposes of this analysis, the results were qualitative; meaning we were only able to

assess whether any amount of the substance was present (positive/negative) at or above the cutoff concentration.

Ethical review: Project NEXUS was determined by the CDC and UW Human Subjects Division to be public health surveillance and did not require IRB approval.

Statistical analyses: We described unadjusted estimates of demographic characteristics and the prevalence of people testing positive for each substance by SSP. We next determined the percentage of participants testing positive for two different substances to identify frequent combinations of co-use. As this analysis was purely exploratory in nature and did not involve adjustment for confounders, no statistical testing was performed. The survey did not ask about very recent use (e.g., within the past 24-48 hours) which would have been preferred for calculating validity. However, the survey did ask about an alternative measure of self-reported use in the past 6 months. Using this survey question, we compared self-reported drug use (past 6 months vs. no use in the past 6 months) to the DBS results (“gold standard”) using common validity measures: sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). For example, sensitivity was the proportion of those that self-reported use in the past 6 months among those that tested positive via the DBS assay. As the survey did not ask about xylazine use, we were not able to calculate validity measures for xylazine. Participants missing demographic or behavioral characteristics were not included in percentage calculations for those characteristics.

RESULTS

Demographic characteristics by SSP

Among 1,695 people screened for the NEXUS survey, 1,559 PWID were eligible and completed an interview. Over 80% of these participants (n = 1,381) provided and had at least one spot in the DBS card and consented to their DBS being used for future research. Proportionally more participants who did not have DBS test results were in the younger (18-39) and older (60+) age categories as compared to those who did have DBS test results (p-value=0.007). There were no other significant differences by gender, race/ethnicity, education and housing status between the two groups. Among all SSPs, more than half of the participants were men (62%) between the ages of 30-49 years (58%), reported being non-Hispanic White or non-Hispanic Black race (51%, 19%, respectively), had completed high school or a GED (41%), and reported experiencing unstable housing in the past 6 months (68%). Sacramento, CA, Madison, WI, and New Haven, CT displayed a higher proportion of participants that were older in age than in Ellensburg, WA, Missoula, MT and Wilmington, NC (**Table 2.1**). The Ellensburg, WA, Missoula, MT, and Wilmington, NC SSPs enrolled proportionally more people reporting non-Hispanic White race (72%, 56%, 70%, respectively), whereas the other SSPs had proportionally more participants of other races/ethnicities. **Supplementary Tables 2.1 and 2.2** display demographic characteristics described by substance positivity.

Substance use detected via DBS testing by SSP

The Western SSPs saw the highest proportion of participants testing positive for methamphetamine (95%, **Table 2.3**). A high proportion of participants tested positive for

cocaine, fentanyl, heroin and xylazine in the Eastern SSPs (cocaine: 86%; fentanyl: 41%; heroin: 20%; xylazine: 20%, respectively). The Sacramento, CA SSP saw the highest prevalence of cocaine detected (43%) among Western SSP, and Wilmington, NC saw the highest prevalence of methamphetamine detected (64%) among Eastern SSP. New Haven, CT had the highest prevalence of both fentanyl (52%) and xylazine (32%) among all SSPs.

Co-positivity patterns

Testing positive for more than one substance was common (50% of population). Among the Western SSPs, nearly all individuals who tested positive for fentanyl, xylazine, cocaine or heroin also tested positive for methamphetamine (fentanyl: 100%, xylazine: 100%, cocaine: 99%, heroin: 100%, **Table 2.4, 2.5**). Individuals testing positive for fentanyl, methamphetamine, xylazine and heroin at the Eastern SSPs commonly tested positive for cocaine (fentanyl: 96%, methamphetamine: 83%, xylazine: 99%, heroin: 99%). Among Eastern SSPs, cocaine and fentanyl were commonly detected among those who tested positive for heroin (both >96%) and xylazine (cocaine: 99%, fentanyl: 83%). Of important note, DBS testing cannot determine co-ingestion or concurrent use (e.g., speedballs of fentanyl and cocaine) vs. sequential use (i.e., drugs ingested at differing points but close in time).

Validity measures comparing DBS results and self-report

The sensitivity of the 6-month self-report measure when compared to DBS positivity ranged from 85%-92% (**Table 2.6**). The specificity of the 6-month self-report measure

ranged from 38%-60%. Over 89% of participants who tested positive for fentanyl did report that they believed to have used fentanyl in the past 6 months. Similarly, among those self-reporting no fentanyl use in the past 6 months, over 92% tested negative. While the sensitivity for heroin was high (92%), the positive predictive value for heroin was low (26%%). Among those who self-reported no fentanyl use but self-reported heroin use in the past 6 months and tested negative for heroin, 6.9% (11/159) tested positive for fentanyl.

DISCUSSION

These results reinforced previous knowledge of pronounced differences in regional trends in substance use in the U.S. Methamphetamine use was more prevalent in the Western U.S. whereas cocaine use was higher in the Eastern U.S[41–43]. At the time these data were collected, xylazine was not prevalent on the West Coast and was predominantly found at the East Coast New Haven, CT SSP[33,44]. Fentanyl was detected at every SSP and was most prevalent at the New Haven, CT SSP. The observed high prevalence of xylazine and fentanyl at the same SSP was expected given that xylazine is nearly always co-identified alongside fentanyl in the drug supply[33].

The differing trends in drugs detected by region were consistent with prior research. Studies have shown that methamphetamine use is more prevalent in the Western region of the U.S. based on self-report measures and drug seizure data[41,42]. Overdoses involving cocaine in 2021 were higher in the Northeastern U.S. compared to the West[43], which tracks with our finding of cocaine use being more common in the Eastern U.S. in

the Eastern and Southern U.S., xylazine prevalence has been increasing, overwhelmingly in combination with fentanyl, , which aligns with our results[33,44]. The migration of xylazine from the Northeastern U.S. to the South and then across to the West follows a similar path to the spread of fentanyl[33]. The high proportion of people testing positive for greater than one substance has also been echoed in the literature in recent years[30,31]. Xylazine and fentanyl have been declared emergency threats due to their high risk of overdose. It is essential to keep monitoring these substances in order to know where prevention efforts should be prioritized[2,16,17,44].

We were not able to compare the DBS to a self-report measure matching the window of detection for the targeted substances. However, the sensitivity values for the substances were relatively high, indicating that people who used in the past 6 months likely used in the past 1-2 days. Unintentional fentanyl exposure is a significant concern with respect to overdose risk. Our findings showed that the vast majority of participants who tested positive for fentanyl reported that they believed to have used fentanyl in the past 6 months, and the majority of those self-reporting no fentanyl use in the past 6 months tested negative. Despite this, the data confirms that some people are not aware that they are using fentanyl and at increased risk of overdose. The low positive predictive value for heroin indicates a low proportion of people testing positive for heroin among those reporting past 6-month use. This agreement difference is not as large for the other substances. One hypothesis for this difference is that people surveyed believed they were using heroin when they were in fact using an alternative substance. We found that 7% of people who self-reported heroin use, self-reported no fentanyl use,

and tested negative for heroin tested positive for fentanyl. If this discrepancy is a true disparity in PWUD's awareness of their drug use, this may be a reflection of the previously observed replacement of heroin with other substances such as fentanyl [45,46]. Lack of awareness of what is in the drug supply can increase overdose risk when substances such as fentanyl or xylazine are mixed in without PWUD's knowledge. Additionally, people may be using the term "heroin" as a catch-all term for opioid powder or dope. These concerns warrant intervention efforts to increase participants awareness of the potential exposure to fentanyl and access to things such as fentanyl testing strips.

There are limitations to our analysis. First, the six SSP sites may not be representative of all SSPs in the U.S.. Second, the prevalence of substance use within each SSP population reflects that at the time of DBS collection (2021-2022) and may not reflect the current landscape of substance use as drug markets have been shown to change overtime. Third, we are not able to verify the accuracy of these DBS results with the true contents of the drug products used within the detection window prior to DBS specimen collection. Fourth, it is possible that the assay detected trace amounts of drugs (e.g., cocaine) present from the environment (e.g., unclean fingers) that would not appear with sampling by alternative collection procedures (e.g., venous blood draw). However, assuming these drugs were consumed by the individual if they were handled, the information may still provide useful insights. Fifth, while we included supplementary tables of some demographic information by substance positivity, our analysis did not focus on these differences. It is important as we increase the monitoring of substance use trends, that we include analyses of demographics such as race/ethnicity and

gender (factors shown to be associated with substance use due to societal-level factors such as structural racism[47–53]) to ensure that groups exposed to substances associated with overdose are receiving proper prioritization of resources. Sixth, there was potentially measurement error via the DBS assay as the drugs do not remain in the bloodstream for the same window of time asked about in the survey. Typical detection times [54] as well as frequency of use could differ between these five substances. While these are important limitations to be aware of, a strength is that this assay met FDA accuracy and precision guidelines[55]. Additional strengths of this analysis are that it included a large sample of PWUD from SSPs in different regions of the U.S. and is the first analysis to use DBS to test for substance use at multiple SSPs.

Drug use monitoring is an important public health tool, as it allows for real-time surveillance of drug trends and changes in drug use patterns. While there are many different methods for drug surveillance in the U.S., many are not quick enough to function as real-time surveillance to allow for rapid public health responses [56–58]. With the increasing rates of overdose in the U.S. [2,16,17] and the lack of real-time drug use surveillance methods [56–58], delays in detecting novel drug use trends is detrimental to effective prevention efforts. Traditional blood draw is invasive, has complex handling and storage requirements and a higher risk of blood borne infection transmission[59]. Urine drug testing (UDT) is common, especially in clinical settings, and simple to collect, but isn't considered the gold standard because different urinalysis methods have yielded different results and evasion (providing a sample from someone else) is easier than with directly-observed blood testing[59–61]. DBS sampling, a relatively novel method

for testing blood for the presence of drugs, is minimally invasive, does not require phlebotomy, and can be shipped and stored at ambient temperatures [21]. Cost solutions have allowed DBS to become a relatively affordable drug testing method due to cheaper storage and transport, especially compared to traditional blood specimens[62–64].

Due to the characteristics of DBS testing, this method may be a good alternative to current measurement methods in practice or as a complementary data collection instrument to existing monitoring systems or public health programs. As SSPs are a central location for PWUD to seek services, they are also an optimal choice for study recruitment and targeted overdose prevention interventions and harm reduction tactics. One qualitative analysis of PWUD in Oregon found that people reported being ready and willing to implement harm reduction strategies, such as fentanyl testing strips, reducing amount of drugs used, and switching from injection to smoking. [20]. Effective harm reduction including drug checking and community education and outreach, however, first requires an awareness of current substance use trends. Further research is needed to evaluate whether drug testing via DBS may be an effective and feasible replacement for self-report or urine drug testing, for public health monitoring purposes. If so, the use of DBS may allow for more accurate public health surveillance and rapid updating of outreach and harm reduction materials that can ultimately improve lives and prevent deaths due to overdose.

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Tables and Figures

Table 2.1: Cutoff Concentrations of Five Substances

Substance	Target During Testing	Cutoff Concentration (ng/mL)
Fentanyl	**Fentanyl**	1 ng/mL
Methamphetamine	**Methamphetamine**	10 ng/mL
Heroin	**Morphine**	50 ng/mL
	6-Monoacetylmorphine	10 ng/mL
Cocaine	**Cocaine**	1 ng/mL
	Benzoylecgonine	1 ng/mL
Xylazine	**Xylazine**	50 ng/mL

Table 2.2: Project NEXUS Demographic Characteristics at 6 U.S. Syringe Service Programs (June 2021-July 2022)

	Ellensburg, WA N=63 n, col %	Sacramento, CA N=256 n, col %	Missoula, MT N=264 n, col %	Madison, WI N=251 n, col %	Wilmington, NC N=247 n, col %	New Haven, CT N=300 n, col %	Total N=1,381 n, col %
Age							
18-29	13 (21%)	17 (7%)	43 (16%)	18 (7%)	39 (16%)	15 (5%)	145 (11%)
30-39	24 (38%)	55 (22%)	105 (40%)	59 (24%)	76 (31%)	69 (23%)	388 (28%)
40-40	17 (27%)	72 (28%)	60 (23%)	79 (31%)	80 (32%)	100 (33%)	408 (30%)
50-59	7 (11%)	83 (32%)	41 (15%)	73 (29%)	42 (17%)	85 (29%)	331 (24%)
60+	2 (3%)	29 (11%)	15 (6%)	22 (9%)	10 (4%)	31 (10%)	109 (8%)
Race/Ethnicity							
NH American Indian / Alaska Native	2 (3%)	11 (4%)	62 (23%)	5 (2%)	7 (3%)	2 (<1%)	89 (7%)
NH Asian	0 (0%)	3 (1%)	0 (0%)	2 (<1%)	0 (0%)	1 (<1%)	6 (<1%)
NH Black	4 (6%)	48 (19%)	4 (1%)	99 (40%)	31 (12%)	78 (26%)	264 (19%)
NH NHOPI	0 (0%)	3 (1%)	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	5 (<1%)
NH White	45 (72%)	95 (38%)	147 (56%)	99 (40%)	172 (70%)	135 (45%)	693 (51%)
NH Multiracial	5 (8%)	22 (9%)	29 (11%)	23 (9%)	26 (10%)	11 (4%)	116 (9%)
Hispanic	7 (11%)	71 (28%)	20 (8%)	19 (8%)	9 (4%)	71 (24%)	197 (14%)
Gender							

Man	41 (65%)	128 (50%)	148 (56%)	180 (72%)	145 (59%)	211 (70%)	853 (62%)
Woman	20 (32%)	128 (50%)	112 (42%)	60 (24%)	100 (40%)	85 (28%)	505 (37%)
Transgender/Nonbinary/ Genderqueer/Other	2 (3%)	0 (0%)	4 (2%)	11 (4%)	2 (<1%)	4 (2%)	23 (2%)
Education							
Less than High School	21 (33%)	75 (29%)	63 (24%)	40 (16%)	69 (28%)	75 (25%)	343 (25%)
High School/GEDD	23 (36%)	97 (38%)	104 (39%)	104 (42%)	89 (36%)	152 (50%)	569 (41%)
Some college/AA/Technical	18 (29%)	78 (30%)	79 (30%)	88 (35%)	73 (30%)	65 (22%)	401 (29%)
Bachelor's	1 (2%)	4 (2%)	10 (4%)	13 (5%)	13 (5%)	7 (2%)	48 (4%)
Post graduate studies	0 (0%)	2 (<1%)	7 (3%)	5 (2%)	3 (1%)	1 (<1%)	18 (1%)
Houseless, past 6 months							
Yes	42 (67%)	177 (69%)	200 (76%)	179 (71%)	155 (63%)	188 (63%)	941 (68%)
No	21 (33%)	79 (31%)	63 (24%)	72 (29%)	92 (37%)	112 (37%)	439 (32%)

Missing: Race/ethnicity: n=11, Education: n=2, Houseless: n=1
NH= Non-Hispanic, NHOPI= Native Hawaiian / Pacific Islander, GED= General Education Development Degree, AA = Associates of Arts Degree

Table 2.3: Project NEXUS Substance Use Prevalence at 6 U.S. Syringe Service Programs (DBS Test Result, June 2021-July 2022)

	WESTERN U.S.				EASTERN U.S.			
	All SSPs	**Ellensburg, WA**	**Sacramento, CA**	**Missoula, MT**	**All SSPs**	**Madison, WI**	**Wilmington, NC**	**New Haven, CT**
Cocaine (N=833)	143 (24.5%)	11 (17.5%)	110 (43%)	22 (8.3%)	690 (86.5%)	227 (90.4%)	184 (74.5%)	279 (93%)
Fentanyl (N=394)	69 (11.8%)	13 (20.6%)	39 (15.2%)	17 (6.4%)	325 (40.7%)	94 (37.5%)	76 (30.8%)	155 (51.7%)
Heroin (N=257)	97 (16.6%)	14 (22.2%)	61 (23.8%)	22 (8.3%)	160 (20.1%)	68 (27.2%)	37 (15.0)	55 (18.3%)
Methamphetamine (N=819)	555 (95.2%)	59 (93.7%)	256 (100%)	240 (90.9%)	264 (33.1%)	77 (30.7%)	158 (64.0%)	29 (9.7%)
Xylazine (N=192)	33 (5.7%)	0 (0%)	31 (12.1%)	2 (0.8%)	159 (19.9%)	36 (14.3%)	27 (10.9%)	96 (31.9%)
None	27 (4.6%)	4 (6.3%)	0 (0%)	23 (8.7%)	53 (6.6%)	15 (6.0%)	24 (9.7%)	14 (4.7%)
Total Participants	**583**	**63**	**256**	**264**	**798**	**251**	**247**	**300**

One heroin test result could not be reported and is not included in this table.
Participants may be present in multiple rows as they may have tested positive for more than one substance.

Table 2.4: Project NEXUS Substance Co-Use Prevalence Among Participants who Used 2 or More Substances at 6 U.S. Syringe Service Programs (June 2021-July 2022, Western SSPs, N, %)

			Other Substances Detected				
Western SSPs	**Count N=556[a] n (%)**	**No Additional Substance[b] Detected n=327 n (%)**	**Cocaine n (row %)**	**Fentanyl n (row %)**	**Heroin n (row%)**	**Methamphetamine n (row %)**	**Xylazine n (row %)**
Among Cocaine +	143	1		34 (23.8%)	43 (30.1%)	142 (99.3%)	17 (11.9%)
Among Fentanyl +	69	0	34 (49.3%)		33 (47.8%)	69 (100.0%)	11 (15.9%)
Among Heroin +	97	0	43 (44.3%)	33 (34.0%)		97 (100.0%)	10 (10.3%)
Among Methamphetamine +	555	326	142 (25.6%)	69 (12.4%)	97 (17.5%)		33 (6.0%)
Among Xylazine +	33	0	17 (51.5%)	11 (33.3%)	10 (30.3%)	33 (100.0%)	

One heroin test result could not be reported and is not included in this table.
[a]Reflects the total number of participants that tested positive for that substance. This column is not mutually exclusive. 27 participants did not test positive for any substance.
[a]Additional substance only refers to the five susbtances that were tested for (cocaine, fentanyl, heroin, methamphetamine and xylazine).

Table 2.5: Project NEXUS Substance Co-Use Prevalence Among Participants who Used 2 or More Substances at 6 U.S. Syringe Service Programs (June 2021-July 2022, Eastern SSPs, N, %)

			Other Substances Detected				
Eastern SSPs	**Count N=744[a] n (%)**	**No Additional Substance[b] Detected n=282 n (%)**	**Cocaine n (row %)**	**Fentanyl n (row %)**	**Heroin n (row%)**	**Methamphetamine n (row %)**	**Xylazine n (row %)**
Among Cocaine +	690	233		311 (45.1%)	158 (22.9%)	220 (31.9%)	157 (22.8%)
Among Fentanyl +	325	8	311 (95.7%)		154 (47.5%)	102 (31.4%)	132 (40.6%)
Among Heroin +	160	1	158 (98.8%)	154 (96.3%)		62 (38.8%)	71 (44.4%)
Among Methamphetamine +	264	40	220 (83.3%)	102 (38.6%)	62 (23.5%)		50 (18.9%)
Among Xylazine +	159	0	157 (98.7%)	132 (83.0%)	71 (44.7%)	50 (31.5%)	

One heron test result could not be reported and is not included in this table.
[a]Reflects the total number of participants that tested positive for that substance. This column is not mutually exclusive. 53 participants did not test positive for any substance.
[b] Additional substance only refers to the five susbtances that were tested for (cocaine, fentanyl, heroin, methamphetamine and xylazine).

Table 2.6: Sensitivity, Specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) of Self-Report (Past 6 mo.) Compared to DBS Assay of Substance Use

Substance	Half-Life[a]	Sensitivity	Specificity	PPV	NPV
Cocaine	0.7-7.5 hours (cocaine) 4.5 hours (benzoylecgonine)	85.1	59.4	76.1	72.4
Fentanyl	3-30 hours	89.5	57.2	46.4	92.9
Heroin	6-25 minutes (6-Monoacetylmorphine) 1.3-6.7 hours (morphine)	92.2	38.1	25.5	95.5
Methamphetamine	6-15 hours	91.9	59.6	76.9	83.5

[a] Source: Baselt, R.C. (2020) Disposition of toxic drugs and chemicals in man. 12. ed., Biomedical Publ, Seal Beach, Calif.
Xylazine is excluded since use was not asked about during survey. The half-life of xylazine is 2-3 hours.
Sensitivity: The proportion of people who self-reported using the substance in the past 6 months among those whose DBS specimen tested positive for that substance.
Specificity: The proportion of people who self-reported not using the substance in the past 6 months among those whose DBS specimen tested negative for that substance.
PPV (Positive Predictive Value): The proportion of people whose DBS specimen tested positive for the substance among those who self-reported that they used the substance in the past 6 months.
NPV (Negative Predictive Value): The proportion of people whose DBS specimen tested negative for the substance among those who self-reported that they did not use the substance in the past 6 months.

Supplementary Table 2.1: Demographic Characteristics by Stimulant Use (DBS Test Result)

Characteristics	Cocaine (n=833)		Methamphetamine (n=819)	
	Positive N, col %	Negative N, col %	Positive N, col %	Negative N, col %
Age (Mean, SD)				
18-29	66 (7.9)	79 (14.4)	106 (12.9)	39 (6.9)
30-39	204 (24.5)	184 (33.5)	252 (30.8)	136 (24.2)
40-49	269 (32.3)	139 (25.4)	239 (29.2)	169 (30.1)
50-59	215 (25.8)	116 (21.2)	168 (20.5)	163 (29.0)
60+	79 (9.5)	30 (5.5)	54 (6.6)	55 (9.8)
Race/Ethnicity				
NH AI/AN	20 (2.4)	69 (12.6)	79 (9.7)	10 (1.7)
NH Asian	3 (0.4)	3 (0.6)	4 (0.5)	2 (0.4)
NH Black / African American	232 (28.2)	32 (5.9)	86 (10.6)	178 (32.0)
NH NHOPI	2 (0.2)	3 (0.6)	5 (0.6)	0 (0)
NH White	380 (46.1)	313 (57.3)	448 (55.1)	245 (44.0)
NH Multirace	71 (8.6)	45 (8.2)	78 (9.6)	38 (6.8)
Hispanic	116 (14.1)	81 (14.8)	113 (13.9)	84 (15.1)
Gender				
Man	570 (68.4)	283 (51.6)	475 (58.0)	378 (67.3)
Woman	248 (29.8)	257 (46.9)	334 (40.8)	171 (30.4)
Trans man *Trans woman* *Non-binary/GQ* *Trans/ Non-binary/GQ/Multiple/Other*	15 (1.8)	8 (1.5)	10 (1.2)	13 (2.3)
Education				
< HS	197 (23.7)	146 (26.6)	223 (27.3)	120 (21.4)
HS/GED	369 (44.4)	200 (36.6)	310 (37.9)	259 (46.1)
Some college/AA/Technical	225 (27.0)	176 (32.2)	246 (30.1)	155 (27.5)
Bachelor's	31 (3.7)	17 (3.1)	27 (3.3)	21 (3.7)
Post graduate studies	10 (1.2)	8 (1.5)	11 (1.4)	7 (1.3)

Housing Status, past 6 months				
Did not experience homelessness	280 (33.6)	159 (29.1)	252 (30.8)	187 (33.3)
Experienced homelessness	553 (66.4)	388 (70.9)	566 (69.2)	375 (66.7)

Missing: Race/ethnicity=11, Education = 2, Housing = 1

Supplementary Table 2.2: Demographic Characteristics by Opioid and Sedative Use (DBS Test Result)

	Heroin (n=257)		**Fentanyl (n=394)**		**Xylazine (n=192)**	
Characteristics	Positive N, col %	Negative N, col %	Positive N, col %	Negative N, col %	Positive N, col %	Negative N, col %
Age (Mean, SD)						
18-29	32 (12.5)	113 (10.1)	42 (10.6)	103 (10.4)	14 (7.3)	131 (11.0)
30-39	76 (29.6)	311 (27.7)	118 (30.0)	270 (27.4)	56 (29.2)	332 (27.9)
40-49	79 (30.7)	329 (29.3)	127 (32.2)	281 (28.5)	62 (32.3)	346 (29.1)
50-59	55 (21.4)	276 (24.5)	87 (22.1)	244 (24.7)	42 (21.8)	289 (24.3)
60+	15 (5.8)	94 (8.4)	20 (5.1)	89 (9.0)	18 (9.4)	91 (7.7)
Race/Ethnicity						
NH AI/AN	11 (4.3)	78 (7.0)	9 (2.3)	80 (8.2)	5 (2.6)	84 (7.2)
NH Asian	2 (0.8)	4 (0.4)	2 (0.5)	4 (0.4)	0 (0)	6 (0.5)
NH Black / African American	58 (22.8)	206 (18.5)	74 (19.0)	190 (19.4)	43 (22.6)	221 (18.7)
NH NHOPI	3 (1.2)	2 (0.2)	2 (0.5)	3 (0.3)	1 (0.5)	4 (0.3)
NH White	130 (51.0)	562 (50.5)	220 (56.4)	473 (48.3)	97 (51.1)	596 (50.5)
NH Multirace	16 (6.3)	100 (8.9)	22 (5.6)	94 (9.6)	9 (4.7)	107 (9.1)
Hispanic	35 (13.6)	162 (14.5)	61 (15.7)	136 (13.8)	35 (18.5)	162 (13.7)
Gender						
Man	166 (64.6)	686 (61.1)	264 (67.0)	589 (59.7)	130 (67.7)	723 (60.8)
Woman	85 (33.1)	420 (37.4)	122 (31.0)	383 (38.8)	59 (30.7)	446 (37.5)
Trans/Non-binary/GQ/ Multiple/Other	6 (2.3)	17 (1.5)	8 (2.0)	15 (1.5)	3 (1.6)	20 (1.7)
Education						
< HS	54 (21.1)	289 (25.8)	89 (22.6)	254 (25.8)	44 (22.9)	299 (25.2)

HS/GED	110 (43.0)	458 (40.8)	179 (45.4)	390 (39.6)	85 (44.3)	484 (40.7)
Some college/AA/Technical	83 (32.3)	318 (28.3)	107 (27.2)	294 (29.8)	51 (26.6)	350 (29.5)
Bachelor's	6 (2.3)	42 (3.7)	15 (3.8)	33 (3.4)	10 (5.2)	38 (3.2)
Post graduate studies	3 (1.2)	15 (1.3)	4 (1.0)	14 (1.4)	2 (1.0)	16 (1.4)
Housing Status, past 6 months						
Did not experience homelessness	94 (36.6)	345 (30.7)	147 (37.3)	292 (29.6)	67 (34.9)	372 (31.3)
Experienced homelessness	163 (63.4)	777 (69.3)	247 (62.7)	694 (70.4)	125 (65.1)	816 (68.7)

Missing: Race/ethnicity=11, Education = 2, Housing = 1

Chapter 3: The Association Between Methamphetamine Use and Buprenorphine Adherence

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ABSTRACT

Background: Prior studies suggest that methamphetamine use may impact buprenorphine treatment outcomes, and that buprenorphine may decrease methamphetamine cravings. This bidirectional relationship presents challenges to evaluating whether co-use of methamphetamine among patients receiving buprenorphine as treatment for opioid use disorder (OUD) has an impact on buprenorphine adherence.

Methods: From January 2019 – May 2020, we enrolled patients who initiated buprenorphine treatment (n=78) at two sites (Seattle, WA and Boston, MA). We use inverse probability of treatment weighted (IPTW) estimation of a marginal structural model (MSM) to estimate the odds of buprenorphine adherence under the hypothetical scenario of comparing patients always testing positive for methamphetamine at every study visit versus never testing positive for methamphetamine.

Results: Among all 78 patients, the odds ratio of being non-adherent to buprenorphine was 2.56 (95% CI: 1.37-4.76) for a potential outcomes comparison between hypothetical patients always testing positive for methamphetamine versus those never testing positive for methamphetamine. Among the 22 patients who were observed to have intermittently tested positive and negative for methamphetamine, the estimated effect of methamphetamine use on non-adherence to buprenorphine was a non-significant 87% increased odds of non-adherence due to methamphetamine use (OR=1.87; 95% CI: 0.89-3.95).

Conclusions: Among this study population, we found a significant positive association between methamphetamine use and buprenorphine non-adherence. Future research

and treatment program design should potentially consider differences among patients with different methamphetamine use patterns.

BACKGROUND

Buprenorphine administration is for the treatment of opioid withdrawal symptoms and opioid use disorder (OUD, i.e. addiction) and is considered safer than methadone as it is only a partial mu opioid agonist[22]. While it is effective at treating OUD, retention and adherence to buprenorphine have remained challenging[65–68]. Prior studies have shown that the average treatment length for patients is less than 6 months, and very few are retained after 1 year[66–68]. Alongside these trends, public health surveillance data and the scientific literature has noted a rise in fentanyl and methamphetamine use as well as co-use of these substances with other opioids[23,69,70]. Ellis et al found evidence of a marked increase in methamphetamine among patients with OUD and that methamphetamine was reported as an opioid substitute to balance out opioid effects[69]. The authors suggested that efforts to limit access to opioids may even be associated with increases in methamphetamine use. Another study by Cicero et al found that among a national sample of persons entering drug treatment programs for OUD, greater than 90% reported use of at least one other drug besides opioids, and that there was an 85% increase in reported methamphetamine use from 2011 to 2018[70]. With these rising patterns of polysubstance use, there are concerns about whether co-use of methamphetamine may be increasingly limiting buprenorphine treatment retention and adherence[18,23].

A systematic review of studies on methamphetamine use and its effect on receipt and outcomes of medications for OUD (mOUD) reported that most studies found that methamphetamine/amphetamine use or use disorder was negatively associated with

receiving methadone and buprenorphine, and that there were generally negative associations with both retention and opioid abstinence[18]. While this literature suggests that methamphetamine use may limit buprenorphine adherence, a small number of studies have also shown that buprenorphine may reduce methamphetamine cravings. Prior to the human studies on this topic, rat models and studies on other similar substances lead to this hypothesis[24–27]. Specifically, buprenorphine enhances dopamine release in the brain, which may decrease cravings for cocaine and methamphetamines. Three randomized control trials among humans have now shown evidence that buprenorphine is effective in reducing cravings[24–26]. As buprenorphine and methamphetamine both involve the endogenous opioid system, buprenorphine may be an alternative for people addicted to methamphetamine.

Understanding the relationship between methamphetamine use and buprenorphine treatment adherence is critical as co-use is common among individuals receiving treatment for OUD. This is especially true as fentanyl has emerged as the main driver of overdose in the current opioid crisis. The literature discussed above supports a causal relationship where methamphetamine use reduces buprenorphine adherence, and the prior week's adherence effects the following week's methamphetamine use. Past studies have not adequately adjusted for this complex casual-feedback relationship between exposure and outcome over time. Inverse probability of treatment weighted (IPTW) estimation of a marginal structural model (MSM) has been shown to be an effective method to address this complex time-varying confounding[71–73]. We aimed to use this MSM approach to evaluate the association between methamphetamine use

and buprenorphine adherence over time using data from a longitudinal randomized trial of people receiving treatment for OUD.

METHODS

Study Design and Setting: This analysis leveraged data from a two-site pilot randomized trial of a behavioral mHealth intervention (described previously[74,75]) called the Trial of Adherence Application for Buprenorphine Treatment (TAAB). Briefly, patients were recruited from January 2019 – May 2020 from two office-based opioid treatment (OBOT) programs in Seattle, WA and Boston, MA and randomized to either treatment-as-usual (TAU) or a combination of TAU plus a mobile health adherence tool of video directly-observed therapy (DOT)[76]. To be eligible, patients needed to be 18 years or older, able to read and understand English, and within their first 28 days of starting or restarting prescribed sublingual buprenorphine treatment from either recruitment site. The parent study did not find any difference in outcomes between the control (TAU) arm and the treatment (TAU + mobile DOT app) arm[75]. Our study includes participants from both intervention and control arms of the original RCT.

Data Collection: After completing an eligibility screener via the REDCap[77] web platform, eligible patients completed consent, enrollment, randomization and the baseline questionnaire. The baseline and the final questionnaires both asked about demographic characteristics, buprenorphine treatment, buprenorphine adherence, status of current mental and physical health and substance use. Patients completed 12 in-person weekly visits where they were asked about their participation in treatment and

adherence to their prescribed buprenorphine. Participants provided a urine sample at each follow-up visit that was tested for the presence of drugs (marijuana, heroin, methamphetamine, amphetamine, benzodiazepines, barbiturates, methadone, buprenorphine glucuronide, nortriptyline, MDMA, oxycodone, phencyclidine, propoxyphene, fentanyl) and to verify recent buprenorphine use. All participants received $50 compensation for completing baseline and final visits, and $20 for each follow-up visit.

Data Measures: Data collected during the study included demographic characteristics (baseline), changes in buprenorphine dose (self-reported weekly), buprenorphine diversion (using buprenorphine differently than prescribed, self-reported weekly), UDTs for buprenorphine and other substances (weekly), current and previous use of medication for OUD (methadone or buprenorphine, baseline and final), status of current mental and physical health and lifetime and self-reported ever and past-30 illicit substance use via the Addiction Severity Index (ASI) (baseline and final).

Outcome Measures: At each visit, adherence to buprenorphine for the past seven days was assessed via self-report utilizing a modified calendar timeline follow-back (TLFB) procedure[75,78,79]. Non-adherence to buprenorphine (binary yes/no) was defined as not reporting taking the daily dose equal to the amount prescribed for at least one day of the past seven days.

Data analysis: In this study population, we expected certain baseline characteristics such as age, gender, race/ethnicity, and housing status to confound the relationship between methamphetamine UDT and buprenorphine adherence at every time point. Beyond this, however, there likely exists time-varying confounding that traditional logistic regression cannot properly address. By time-varying confounding, we mean confounding by factors that can change over time, such as someone's substance use. Our hypothesized causal model (**Figure 3.1: Hypothesized Causal Model)** is for the effect of meth UDT at the previous visit on the current visit's adherence. This model also assumes that buprenorphine adherence at each visit is confounding the subsequent week's association between methamphetamine UDT and the following week's adherence. To effectively account for this, we used inverse probability of treatment weighted (IPTW) estimation of a marginal structural model (MSM). This allowed us to determine the effect estimate of non-adherence for a potential outcomes comparison between people who hypothetically had a positive methamphetamine UDT at every visit versus those that never had a positive methamphetamine UDT. The MSM estimate tells us what effect a hypothetical intervention that moves people from the category of always testing positive for methamphetamine to never testing positive would theoretically have on buprenorphine non-adherence. It is important to note that while someone's methamphetamine use during a given week may impact their buprenorphine adherence in the same week or even day, we chose to focus on the relationship between the prior week's methamphetamine UDT on the following week's buprenorphine non-adherence. We did this in order to focus on an exposure-outcome relationship where the temporality assumption would not be violated, or in other words,

we knew for sure that the exposure preceded the outcome in time. Due to this, we believe our underlying causal model has less potential for bias.

Treatment Models: We first developed treatment models by modeling the probability of meth use at each visit directly preceding the visit for which we were assessing adherence. In our MSM treatment models, we adjusted for baseline confounders selected *a priori* based on supporting literature, which included age, gender, race, Hispanic ethnicity, and housing status. We included race and Hispanic ethnicity as a proxy for societal-level factors, particularly structural racism, that has been shown to be associated with both methamphetamine use and buprenorphine access and retention[80–85]. We used a cubic spline for time using visit as a proxy for time (0-12) and added two knots at visit 4 and 8 to allow for more temporal flexibility in the model. Our simplest MSM model included the prior week's methamphetamine UDT as the primary exposure, adherence from the week prior, time and the baseline confounders. From there, we added in two different variables to model exposure history (methamphetamine positive at the prior visit and proportion of prior visits with a positive methamphetamine UDT) and time-varying values for common opiate UDTs, amphetamine UDT, and polysubstance use (tested positive for >=2 substances at the prior visit). We calculated the untruncated weights for each model variation and selected the model that we adjusted most appropriately for confounding while also having weights with a mean close to 1 and with the least variance. We generated a table with the mean, variance, minimum, maximum, and 1st and 99th percentile weight values. Model #5 was selected (prior to running the response model to get effect sizes) as we thought this model

adequately adjusted for potential confounders while having a small negative impact on the mean and variance of the weights.

Response Models: Before including the weights in our response models, we truncated all weights at the 1st and 99th percentile for better stability. The response models estimated the likelihood of non-adherence at a given visit adjusting for the same baseline confounders and time. We used the truncated weights from each treatment model as the weighting term in each response model to generate odds ratios for each model variation. Finally, we included all response model effects estimates in the table alongside the weight data for the corresponding model. After completing this process among the entire patient population, we also completed the same process among only intermittent users (patients who tested positive and negative for meth at least once during the treatment period) as we were less concerned about an exchangeability violation among this population.

Non-MSM Model Comparisons: As a comparison to the MSM results, we used logistic regression (clustered on participant study ID) and generalized estimating equations (GEE) to generate comparison unadjusted and adjusted effect estimates for the effect of the prior week's methamphetamine UDT on the current week's non-adherence to buprenorphine. For the adjusted models, we include baseline confounders determined *a priori*, which included age, gender, race, Hispanic ethnicity, and housing status. From there we generated the effect estimates for increasingly complex models by adding in baseline opioid use, time-varying adherence and time-varying opioid UDT to eventually

generate a non-MSM model that was a close comparison to the final MSM model. We also conducted a subgroup analysis in which we used logistic regression (clustered on study ID) and GEE models to look at the effect estimate of methamphetamine UDT on non-adherence to buprenorphine by comparing those who were observed to have always tested positive for methamphetamine to those who never tested positive for methamphetamine.

Missing data: Due to a combination of participants missing entire visits (N=277/1,014: 27%) and missing UDT measurements, 32% (N=324/1014) of methamphetamine UDT and 27% of adherence information was missing for the 1,014 participant visits. We utilized multiple missing data strategies to account for these missing data. First, we censored individuals at the first of at least two consecutive missing adherence values. This left us with 737 remaining visits of the total 1,014 potential visits. For all remaining missing adherence data, we used a last-value-carry-forward approach to fill in the missing value with the adherence from the prior visit. To deal with the missing UDT data, we assumed that if all the UDT results at the available visits were negative, that the missing data points were negative. If there was at least one positive UDT for that substance in the patient's 13 visit history, we filled in any missed visits with a positive UDT. We also conducted two sensitivity analyses where we filled in the missing UDT data assuming 1) all negative test results and 2) all positive test results to see whether our choice had any large impacts on the results.

RESULTS

Demographic Characteristics of Study Population: A total of 78 patients completed at least the baseline visit. The average number of visits missed was 3.6 (SD: 3.7) out of 13. After censoring, 34 patients were censored at some point in the 12 week study period, with the average censoring time being the 5th visit. **Table 3.1** displays demographic characteristics by three methamphetamine use patterns: 1) patients who tested negative for meth at every visit (never positive; N=45), 2) patients who tested positive for meth at every visit (always positive; N=11) and 3) patients who had a combination of positive and negative visits (intermittent positive; N=22). The average age of all patients was 41.7 years (SD=11.9). Proportionally, patients were predominantly men (71.8%), white race (62.3%), non-Hispanic ethnicity (76.9%), and did not experience homelessness in the past 3 months (60.3%). Participants testing positive for methamphetamine intermittently or always were more likely to have experienced homelessness in the past 3 months than those who always tested negative (63.6% and 54.6% vs. 26.7%). Non-adherence to prescribed buprenorphine over the course of the study was common, with 69.2% of patients being non-adherent for at least one visit (post-censoring). Proportionally more patients were never adherent among the groups of patients that always and intermittently tested positive for methamphetamine compared to those who never tested positive (**Figure 3.2**; 45% vs. 4% vs. 0%).

Model Selection: The unadjusted and adjusted MSM model results are displayed in **Tables 3.2 and 3.3**. Based on the MSM model including meth exposure history and time-varying opioid UDT among all patients, the odds ratio of non-adherence to

buprenorphine was 2.56 (95% CI: 1.37-4.76) for a potential outcomes comparison between hypothetical patients always testing positive for methamphetamine versus those never testing positive for methamphetamine. (**Table 3.2**). Among only people testing positive for methamphetamine intermittently, the odds ratio of non-adherence to buprenorphine was 1.87 (95% CI: 0.89-3.96) for a potential outcomes comparison between hypothetical patients always testing positive for methamphetamine versus those never testing positive for methamphetamine (**Table 3.3**).

The effect sizes among the full study population for the sensitivity analyses of methamphetamine UDT missing data approaches are displayed in **Table 3.4 (all missing UDT's = negative: OR=2.95; 95% CI: 150-5.83; all missing UDT's = positive: OR=2.83; 95% CI: 1.72-4.64)**, where we show that these two differing approaches to handling the missing data did not make a significant impact on our results or interpretation for our primary analysis (model #5).

Non-MSM Models: **Table 3.5** displays a variety of unadjusted and adjusted non-MSM models among three study populations (all patients, patients only testing positive intermittently, and patients only testing positive always vs. never) that can be used as a comparison for the MSM effect estimates. While the effect estimates for all adjusted models were greater than one, they were not statistically significant. Generally, the adjusted model estimates were smaller than the unadjusted effect estimates. Among all patients, the logistic model that most closely corresponds to the final MSM model among all patients was smaller than our MSM effect estimate (OR=1.35, 95% CI: 0.73-

2.49) Similarly, among patients testing positive intermittently, the logistic model that most closely matches our MSM model among patients intermittently testing positive was also smaller than the MSM effect estimate (OR=1.71; 95% CI: 0.89-3.33).

DISCUSSION

In this study, we were able to effectively implement an MSM approach to address the complex, bi-directional relationship between methamphetamine use and buprenorphine adherence. We found a significant positive relationship between methamphetamine use and non-adherence to buprenorphine treatment for opiate use disorder when adjusting for baseline confounders and the time-varying effect of prior adherence and prior opioid and methamphetamine use. This finding should encourage researchers to further investigate ways to decrease methamphetamine use or interrupt the pathway through which methamphetamine use impacts buprenorphine adherence among populations of people with OUD seeking buprenorphine treatment. This is of particular importance as the concurrent use of methamphetamine and opioids is on the rise[23,69,70].

While Frost et al's systemic review found that methamphetamine/amphetamine use or use disorder was generally negatively associated with both retention in treatment programs and opioid abstinence[18], most of these studies focused on engagement in clinic appointments and receipt of prescriptions rather than direct assessments of daily buprenorphine adherence. Additionally, none of these studies utilized an MSM approach to adjust for the effect of buprenorphine on decreasing methamphetamine use[24–26]. The structure of our data allowed us to conduct a novel analysis of this relationship with

weekly adherence (based on self-report of daily adherence) using an MSM that more appropriately adjusted for the complex longitudinal relationship between these two time-varying variables as compared to past studies. To our knowledge, this study was also the first to use longitudinal study data to look at systematic assessments of both weekly methamphetamine use and weekly buprenorphine adherence throughout the treatment period for patients who have recently initiated buprenorphine and are in the "stabilization" phase.

This MSM approach had the effect that we expected based on the theory of how this model removes the confounding effect of time-varying confounders. As we might expect, assuming our causal diagram is correct, the effect estimate from our MSM model that adjusted for time varying confounding through inverse probability weighting was larger compared to the non-MSM approaches that adjust for time-varying confounding by regression-based conditioning that can both block causal pathways and induce collider stratification bias [citation]. In our non-MSM logistic regression model among all patients, the effect size was underestimated when adding the adjustment for adherence. This supports the theory that prior adherence is confounding the relationship between methamphetamine and buprenorphine adherence. However, we would expect this model to still be imperfect due to the collider stratification bias induced by adjusting for the effect of the prior week's adherence on the subsequent week's relationships between methamphetamine UDT and buprenorphine adherence. In attempting to include prior adherence in the non-MSM model, we see evidence of

adjusting away the mediated pathway of the effect that meth use has on long-term adherence via its effect on short-term adherence.

We were also interested in looking at the non-MSM estimates that were restricted to the patients who were either always or never testing positive for methamphetamine because this comparison is the most similar to the interpretation of the MSM estimate. The MSM estimate tells us what effect a hypothetical intervention that moves people from the category of always testing positive for methamphetamine to never testing positive would theoretically have on buprenorphine non-adherence, assuming all assumptions of the MSM model are met. The MSM model was larger compared to the real-life non-MSM comparison of people always testing positive vs. never testing positive. This could indicate that the non-MSM always vs. never comparison underestimated the real effect for which the MSM model does a better job at estimating. However, this could also be due to differences in the underlying study populations for each model as well. It is also important to note that both analyses may violate the exchangeability assumption. It is likely that patients who always tested positive for methamphetamine are substantially different from patients who never testing methamphetamine and we believe that it is likely that we were not able to include sufficient information in the adjustment for factors in our models to make these groups truly exchangeable due to concerned with overfitting our model. In contrast, we were less concerned about exchangeability among people intermittently testing positive for meth because these individuals were likely more similar and comparable to each other. Therefore, we would expect the MSM effect estimate that we generate using only people intermittently testing positive to be less biased. The effect size for this MSM

model showed a weaker effect of methamphetamine on buprenorphine adherence compared to the effect estimate for the same causal contrast derived from the MSM model that included all patients, although with a wider confidence interval likely due to the smaller sample size. We hypothesize a couple of different reasons for this. This could indicate more unmeasured confounding in the analysis among all patients, and that there is something about the patients who tested positive at every visit that made them less adherent as compared to intermittent users. Alternatively, the attenuation of the effect when the population is restricted to people intermittently testing positive may mean that the anticipated effect of an intervention that hypothetically moves everyone in a population of people intermittently using meth from always using meth to the status of never using meth would be smaller than the effect of the same hypothetical intervention among people always testing positive for methamphetamine. These results suggest that the relationship between methamphetamine use and buprenorphine adherence may be different within subcategories of individuals based on their different frequencies of using methamphetamine. It could be that the causal effect estimate among intermittent users may be the least biased and could represent more of what could be achievable with an intervention that targets intermittent methamphetamine users. In fact, this may suggest that these two groups of patients require different interventions entirely.

There were several limitations to this analysis. First, there was a large amount of missing data in this cohort due to participants missing visits or being lost to follow-up. However, we filled in missing UDT values informed by other available UDT data for each participant, and the sensitivity analyses indicated that other approaches to filling in this

data did not have a large impact on our results. We also filled in missing adherence data using the preceding visit's value and censored individuals with two or more consecutive missing adherence values in order to limit making assumptions about adherence beyond one week. Second, adherence to buprenorphine was based on self-report and may have resulted in some measurement error. If people testing positive for methamphetamine were more or less likely to correctly report their adherence in the past week compared to people not testing positive for methamphetamine, this could have resulted in an effect estimate spuriously closer or farther from the null (respectively) due to non-differential misclassification of adherence. However, as we asked about adherence in the prior 7 days rather than for a longer period of time, we believe this reduces the possibility of measurement error at least due to misremembering. Third, as we discussed above, our final MSM model may have violated the exchangeability assumption, primarily regarding people always testing positive for methamphetamine to those never testing positive. This was the motivation for a secondary analysis among only people intermittently testing positive for meth. Since all of these individuals tested positive and negative for methamphetamine at least once, we are much less concerned here that there are unmeasured confounders making individuals in this group non-exchangeable. While the confidence interval is much wider for this sub-analysis, likely due to a loss of power from a smaller sample size, we still saw a positive association between methamphetamine UDT and non-adherence. Fourth, there may have been a violation of the well-defined intervention (consistency) assumption, since all patterns of methamphetamine use are likely not equal in terms of their effect on adherence. By nature of our exposure being

methamphetamine UDT, we have not clearly defined an intervention that could theoretically, consistently move someone from the status of using methamphetamine to not using methamphetamine (exposure to unexposed. Fifth, the people never testing positive for meth may have almost a zero probability of using methamphetamine, which would be a violation of positivity. While we cannot say for sure, people may have characteristics that made it very unlikely for them to ever use methamphetamine, and therefore very unlikely to ever have the exposure. However, we were less concerned about this violation in the analysis restricted to people testing positive intermittently.

Using IPTW estimation of an MSM allowed us to more clearly evaluate the relationship between methamphetamine UDT and buprenorphine adherence. This analysis approach is becoming more popular as it enables researchers to answer complex scientific questions with much less bias than traditional methods[73,86,87]. While it is true that we found somewhat different point estimates depending on the model and the subgroup, overall the results were qualitatively quite consistent, and the sensitivity analyses didn't drastically change our results. Our study was novel in being the first of our knowledge to apply this MSM approach to the relationship between methamphetamine use and adherence to a medication for opioid use disorder. We found that methamphetamine use appears to result in a higher odds of non-adherence to treatment and there is evidence of a feedback loop between methamphetamine use, adherence and subsequent methamphetamine use. Our results also indicated that there may be a need for a differentiated approach to treatment for people who are always using methamphetamine versus those who are intermittently using methamphetamine.

Further research should explore what common patterns of methamphetamine use look like in buprenorphine treatment programs and ways for providers to identify these patient populations. Identification of a patient's methamphetamine use pattern will likely rely on well-developed relationships between providers and patients that involve open communication about a patient's substance use habits. Additionally, it will be important to research effective interventions to reduce methamphetamine use in the context of OUD treatment. Contingency management, or the practice of providing vouchers in exchange for negative drug tests, has been one intervention shown as a successful method to decrease methamphetamine use[88]. Case management, where patients receive help with coordination, planning and accessing resources to improve their overall health and wellbeing, has also been shown to improve treatment outcomes[88]. By helping patients manage other challenges in their lives, they may be able to focus more investment on their health as a result. It is also worth noting that there is evidence that people who were retained in buprenorphine treatment have decreased methamphetamine use over time[89], programs that improve retention may likely result in decreased methamphetamine use from regular use of the buprenorphine itself. Interventions to reduce methamphetamine use and keep patients in treatment could vary in intensity and be used in different combinations to address different levels of methamphetamine use. Investment in research to determine what interventions work best for people with different methamphetamine use patterns must be prioritized for the development of treatment programs that work for groups with increased barriers to mOUD adherence and retention.

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Tables and Figures

Figure 3.1: Hypothesized Causal Model for the Relationship Between Methamphetamine UDT and Buprenorphine Adherence

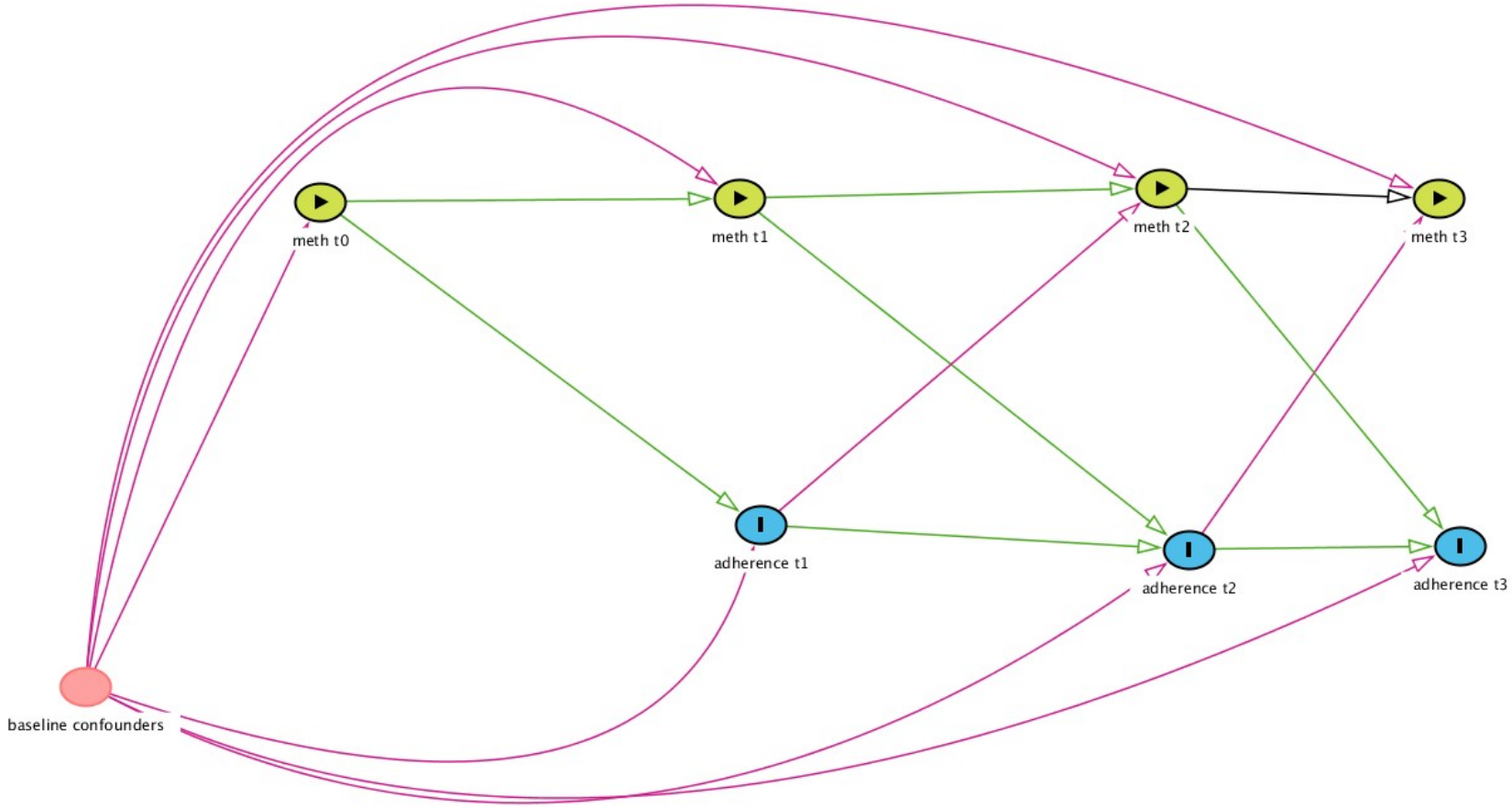

Figure 3.2: Study Population Adherence Patterns by Methamphetamine Use Patterns

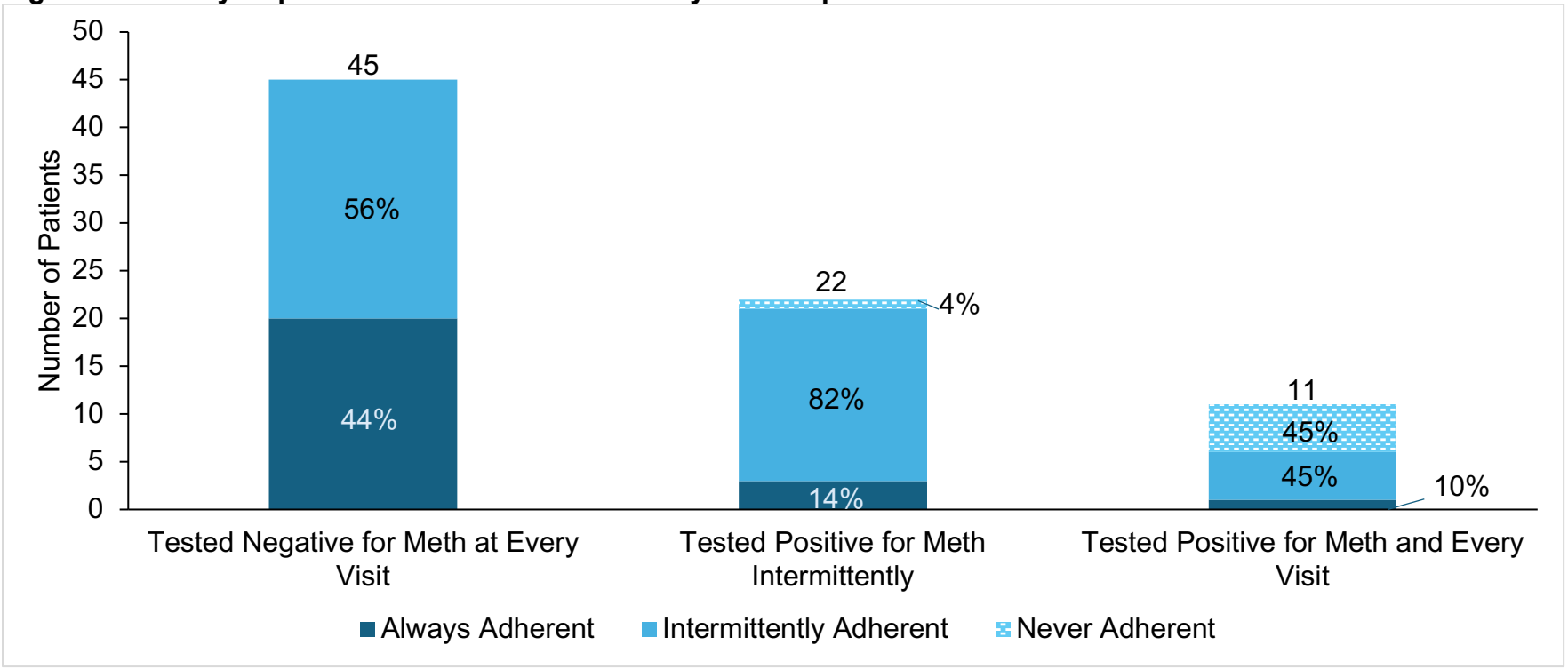

Table 3.1: Study Population Characteristics by Methamphetamine Use Patterns								
Characteristic	**Tested Negative for Meth at Every Visit (N=45)**		**Tested Positive for Meth Intermittently (N=22)**		**Tested Positive for Meth at Every Visit (N=11)**		**All Patients (N=78)**	
	n	%	n	%	n	%	n	%
Age (mean, SD)	42.07	12.4	42.05	12.4	39.55	9.5	41.71	11.9
Gender								
Man	31	68.9	18	81.8	7	63.6	56	71.8
Woman	13	28.9	4	18.2	3	27.3	20	25.6
Other	1	2.2	0	0.0	1	9.1	2	2.6
Race								
White/Caucasian	31	68.9	13	61.9	4	36.4	48	62.3
Black/African American	5	11.1	2	9.5	1	9.1	8	10.4
Other	9	20.0	6	28.6	6	54.6	21	27.3
Hispanic Ethnicity								
Yes	10	22.2	4	18.2	4	36.4	18	23.1
No	35	77.8	18	81.8	7	63.6	60	76.9
Experienced Unstable Housing, past 3 months								
Yes	12	26.7	12	54.6	7	63.6	31	39.7
No	33	73.3	10	45.5	4	36.4	47	60.3
Positive Urine Drug Test (Baseline)								
Heroin (n=15)	1	2.2	4	18.2	10	90.9	15	19.2
Fentanyl (n=1)	1	2.2	0	0.0	0	0.0	1	1.3
Oxycodone (n=5)	2	4.4	2	9.1	1	9.1	5	6.4
Amphetamine (n=19)	3	6.7	5	22.7	11	100.0	19	24.4

Table 3.2: Treatment Model Weights[a] and Response Model Effect Estimates for all Model Variations[a] (All Patients)								
Model	**Mean**	**Variance**	**Min**	**Max**	**1%**	**99%**	**Effect**	**95% CI**
1.Base model[b]	1.0604	0.3398	0.0787	4.6530	0.1306	3.6174	1.328	0.6151-2.8662
Exposure History Parameterization								
2.Meth	0.9963	0.0112	0.5446	1.5519	0.6648	1.3344	2.3458	1.2317-4.4677
3.%Meth[c]	1.0016	0.0047	0.7796	1.5045	0.8240	1.2788	2.5673	1.3779-4.7832
4.Meth + %Meth[c]	1.0011	0.0034	0.8146	1.4311	0.8537	1.2376	2.5594	1.3734-4.7698
Time-Varying Confounders								
5.Meth +%Meth[c]+Opiate[d]	1.0026	0.00997	0.4718	1.5405	0.7031	1.4218	**2.5561**	**1.3731-4.7584**
6.Meth +%Meth[c]+Opiate+Amph	1.0104	0.0445	0.1714	2.3746	0.3085	1.8933	2.7215	1.4535-5.0959
7.Meth +%Meth[c]+Opiate+Polys	1.0403	0.1754	0.0966	6.1851	0.2658	3.3651	2.7314	1.4916-5.0018
8.Meth +%Meth[c]+Opiate+Polys+Amph	1.0387	0.1757	0.1050	6.3994	0.2499	3.1530	2.7346	1.4879-5.0261

Meth: Binary variable indicating whether someone tested positive or negative for meth at the prior visit.
%Meth: Variable indicating the proportion of prior visits at which someone testing positive for methamphetamine.
Opiate: Binary variable indicating whether someone tested positive or negative for heroin, oxycodone, or fentanyl at the prior visit.
Polys: Binary variable indicating whether someone tested positive for two or more substances (heroin, oxycodone, fentanyl, meth, or amphetamine) at the prior visit.
[a]All models also include adjustment for age, gender, race, Hispanic ethnicity, housing status, and time. All weights summary values are prior to truncation at the 1st and 99th percentiles.
[b]Baseline model = lagged meth UDT (treatment) and double-lagged adherence
[c]Only single lagged variable -rest of variables are double lagged to precede primary methamphetamine exposure
[d] Final selected model

Table 3.3: Treatment Model Weights and Response Model Effect Estimates for all Model Variations[a] for the Relationship Between Methamphetamine Use and Buprenorphine Nonadherence(Among Only Patients with Intermittent Methamphetamine Positive Tests[b,] N=22)

Model	Mean	Variance	Min	Max	1%	99%	Effect	95% CI
Base model[c]	0.9983	0.0052	0.8051	1.1926	0.8245	1.1615	1.6678	0.79168-3.5137
Exposure History Parameterization								
Meth	1.0002	0.00035	0.9472	1.0496	0.9589	1.0424	1.7632	0.8362-3.7175
%Meth[d]	0.9901	0.0094	0.7849	1.3093	0.7945	1.3085	1.8548	0.85590-4.01972
Meth + %Meth[d]	0.9906	0.00725	0.8124	1.2882	0.8265	1.2670	1.8364	0.8507-3.9643
Time-Varying Confounders								
Meth +%Meth[d]+Opiate[e]	0.9948	0.04193	0.3444	1.7210	0.3671	1.5658	**1.8708**	**0.8850-3.9548**
Meth +%Meth[d]+Opiate+Amph	0.9921	0.1053	0.2919	2.9494	0.3727	2.0074	1.9451	0.9393-4.0277
Meth +%Meth[d]+Opiate+Polys	1.0785	0.4711	0.1054	5.7744	0.1835	4.1725	1.8348	0.8918-3.7748
Meth +%Meth[d]+Opiate+Polys+Amph	1.0709	0.4618	0.1132	5.9491	0.1966	3.9975	1.8178	0.8850-3.7338

Meth: Binary variable indicating whether someone tested positive or negative for meth at the prior visit.
%Meth: Variable indicating the proportion of prior visits at which someone testing positive for methamphetamine.
Opiate: Binary variable indicating whether someone tested positive or negative for heroin, oxycodone, or fentanyl at the prior visit.
Polys: Binary variable indicating whether someone tested positive for two or more substances (heroin, oxycodone, fentanyl, meth, or amphetamine) at the prior visit.
[a]All models also include adjustment for age, gender, race, Hispanic ethnicity, housing status, and time. All weights summary values are prior to truncation.
[b] Intermittent methamphetamine positive means the patients tested positive and negative at least once
[c] Baseline model = lagged meth UDT (treatment) and double-lagged adherence
[b] Only single lagged variable -rest of variables are double lagged to precede primary methamphetamine exposure
[e] Final selected model

Table 3.4: Odds Ratios from the Sensitivity Analyses for the Final Model Among the Total Population for the Relationship Between Methamphetamine Use and Buprenorphine Nonadherence

Model	Effect	95% CI
All Missing UDTs Set Equal to Negative	2.9538	1.4957-5.8333

All Missing UDTs Set Equal to Positive	2.8271	1.7224-4.6403

[a]*All models include adjustment for age, gender, race, Hispanic ethnicity, housing status, and time.*

Table 3.5: Non-MSM Model Effect Estimates for the Relationship Between Methamphetamine Use and Buprenorphine Nonadherence(

Model	Effect	95% CI
All Patients (N=78)		
Unadjusted Models[a]		
Logistic	2.9925	1.5977-5.6048
Gee	1.8817	1.2042-2.9404
Logistic + Lagged adherence	1.9844	1.1622-3.3883
Gee + lagged adherence	2.0229	1.2370-3.3080
Adjusted Models[b]		
Logistic (+ baseline opioid UDT)	1.6505	0.8709-3.1279
GEE (+ baseline opioid UDT)	1.4626	0.8605-2.4859
Logistic + Time-varying Opioid UDT	1.4437	0.8052-2.5885
GEE + Time-varying Opioid UDT	1.5981	0.9640-2.6495
Logistic +Time-varying Opioid UDT + Lagged adherence	1.3523	0.7344-2.4903
GEE +Time-varying Opioid UDT + Lagged adherence	1.6033	0.9243-2.7810
Patient Testing Positive Intermittently (N=22)		
Unadjusted Models[a]		
Logistic	1.7919	0.8454-3.7980
Gee	1.4035	0.8212-2.3989
Logistic + Lagged adherence	1.7859	0.9049-3.5249
Gee + lagged adherence	1.5153	0.8523-2.6943
Adjusted Models[b]		
Logistic + baseline opioid UDT	1.6564	0.8594-3.1924
GEE + baseline opioid UDT	1.4399	0.7819-2.6515
Logistic + Time-varying Opioid UDT	1.5595	0.7995-3.0421
GEE + Time-varying Opioid UDT	1.4755	0.8002-2.7207
Logistic +Time-varying Opioid UDT + Lagged adherence	1.7193	0.8875-3.3306
GEE +Time-varying Opioid UDT + Lagged adherence	1.5963	0.8424-3.0252
Always vs. Never Positive for Methamphetamine Comparison Only (N=56)		

Unadjusted Models[a]		
Logistic	5.3980	2.3883-12.2002
GEE	7.4121	2.3644-23.2363
Adjusted Models[c]		
Logistic	1.5666	0.45102-5.44161
GEE	1.8114	0.26647-12.3141

[a]*All unadjusted models also include time.*
[b]*Also includes adjustment for opioid UDT (heroin or oxycodone or fentanyl) age, gender, race, Hispanic ethnicity, housing status, and time.*
[c]*Also includes adjustment for baseline opioid UDT (heroin or oxycodone or fentanyl) age, gender, race, Hispanic ethnicity, and time. Housing status excluded due to co-linearity with opioid UDT.*

Chapter 4: Association Between Buprenorphine Injection and HIV Risk Factors

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ABSTRACT

Background

Injection of sublingual buprenorphine, a behavior associated with increased risk of infectious disease transmission and other injection-related harms, has not been well described in the U.S. A better understanding of this behavior will allow for more

informed discussion between patients and providers.

Methods

As part of the multi-site NIDA-funded Rural Opioid Initiative, we surveyed people who use drugs (PWUD) from January 2018-March 2020 regarding substance use and associated health behaviors in 65 rural counties in 10 U.S. states. Participants either used opioids or reported injecting any drug “to get high” in the past 30 days. We described unadjusted differences in the prevalence of demographic and behavioral characteristics comparing those who reported buprenorphine injection to those who did not in the past 30 days. We analyzed qualitative one-on-one interview data to further elucidate the context of this behavior.

Results

Among PWUD (n=2,369) who reported injection drug use in the past 30 days, 27% (642) reported injecting buprenorphine. People who injected buprenorphine more proportionally reported injecting drugs daily (79% vs 63%), shared syringes (51% vs 38%), shared injection equipment (61% vs 45%), traded sex for money (12% vs 10%), had condomless sex (66% vs 59%), received buprenorphine from a provider/program in the past month (19% vs 10%), had experienced an overdose (61% vs 49%), and had a history of hepatitis C (HCV, 40% vs 35%) more commonly. People reported different reasons for injecting buprenorphine, including maintenance, harm reduction, management of withdrawal from injecting buprenorphine and addiction to the behavior of injecting

Conclusions

PWUD who injected buprenorphine more commonly reported sex- and drug-related risk behaviors for HCV and other bloodborne viruses. Further research is needed to develop preventive and harm reduction strategies, as well as understand the context in which these behaviors occur.

BACKGROUND

Buprenorphine has been an important tool in treating opioid use disorder (OUD) in the United States for decades[28,90]. It is most commonly prescribed as a film or tablet co-formulated with naloxone, which is believed to confer lower abuse potential due to the inclusion of naloxone which is minimally absorbed in an oral/sublingual route but will result in the highly aversive experience of precipitated withdrawal if injected[28]. Yet, the phenomenon of people injecting oral or sublingual buprenorphine monoproduct is recognized, and there are reports of people injecting the combined buprenorphine/naloxone product (BUP/NX)[28,29,91]. Extra-medical use of buprenorphine (use of a prescription differently than how it was prescribed or by someone other than who it was prescribed to) has been the subject of investigation in the U.S. as well as other countries[90,92–98], yet less is known specifically about the practice of buprenorphine injection. While Bozinoff et all's recent systematic review identified 88 studies from around the world that reported on dose, frequency and adverse events among people injecting buprenorphine, including of the co-formulation, only three were conducted in the U.S.[91]. Harms from injecting buprenorphine include the risk of bloodborne transmission, local complications at the injection site, acute hepatitis, and pancreatitis[99–105]. Understanding the frequency and finding feasible alternatives for people engaging in

this behavior that meet their needs is important to prevent these adverse health outcomes.

While this behavior carries potential risks, recent research highlights the potential for extramedical use of buprenrophine to serve as a harm reduction strategy for people who use drugs (PWUD). Buprenorphine use may reduce the risk of opioid overdose if replacing other substances like fentanyl and heroin. Extramedical buprenorphine use has been used to self-medicate in an attempt to achieve “stability” and management of use of other opioids in addition to recreational use[90]. Studies show that barriers to accessing or participating in traditional drug treatment therapy programs may drive non-prescribed use of buprenrophine[92,106–109]. Research has also suggested that extramedical buprenorphine use may provide PWUD options for use as a substitute for other opioids, to manage the time prior to accessing traditional treatment, and as a way of achieving some level of recovery on their own terms[90,92,110–112]. Barriers to OUD treatment are heightened in rural areas, where accessibility to medications for OUD (MOUD) can often be lower than in urban areas[113,114]. Relatedly, infectious disease concerns among PWID in rural areas have risen in the past decade. In a 2016 CDC national vulnerability assessment, the majority of U.S. counties at highest risk of rapid HIV spread and with high rates of HCV infection identified were rural[115,116]. Despite this, the amount of research in rural areas among PWID is primarily focused on urban areas[115]. As rural areas differ in factors such as drug availability, systemic and social context, stigma, harm reduction and healthcare availability and access to transportation, urban-based research likely is not generalizable to rural areas, necessitating focused rural research efforts[115,117–121].

We sought to better understand the phenomenon of extramedical buprenorphine injection, using mixed quantitative and qualitative methods in a large multisite cohort of rural PWUD. The goal of this research is to improve our understanding of what groups are more likely to report injecting buprenorphine and allow for future research to engage with these populations to design better treatment solutions.

METHODS

Study Design/Setting: We conducted analyses using quantitative and qualitative data from the Rural Opioid Initiative (ROI), a multi-agency funded collaboration that was created to improve understanding and address the rural opioid crisis in the U.S.[122]. Briefly, ROI includes 8 studies across 65 rural counties in 10 states, including Illinois, Kentucky, Massachusetts, New Hampshire, North Carolina, Oregon, Ohio, Vermont, West Virginia, Wisconsin. Rurality was defined according to the Health Resources and Services Administration (HRSA). All sites obtained local IRB approval.

Recruitment and Eligibility: To be eligible for the quantitative survey, participants had to either have used opioids (for example: heroin, fentanyl, pharmaceutical pain medication) in the past 30-days “to get high” or report injecting any drug “to get high” in the past 30 days. We conducted respondent-driven sampling (RDS) between January 2018–March 2020. Seeds from SSPs and community outreach programs were provided with coupon incentives to recruit their peers. Incentives of $10-$20 were provided per peer recruited, and $40-$60 was provided for participation in the study. Computer-

Assisted Self- interviews or interviewer administered surveys were used to collect quantitative information on substance use and healthcare access and utilization.

PWUD were eligible for qualitative interviews if age 18 or over and reported use of non-prescribed opioids in the past 30 days (**Table 4.1**). Participants were recruited from community-based programs and street outreach at some sites. Qualitative researchers lead an informed consent process with participants per local site IRB protocols and conducted interviews in-person at each site, which were digitally recorded and transcribed verbatim. Participants were compensated $25-$50 for completing the interview depending on the site.

Quantitative Survey Measures: The survey included questions on drug use, socioeconomic status, ever and past 30-day substance use, access to injection equipment, drug injection practices, substance use treatment, healthcare utilization, engagement in harm reduction services and sexually transmitted infections. For this analysis, demographic/clinical characteristics examined included age (continuous), gender (man, woman, transgender/other), race/ethnicity (Non-Hispanic White, Non-Hispanic Black/African American, Non-Hispanic American Indian, Other/Mixed/Unknown, Hispanic ethnicity), education (high school or less, some college/trade school, college graduate or above), experienced homelessness (past 6 months, yes/no), no current health insurance (yes/no), ever diagnosed with hepatitis C virus (HCV) or HIV (yes/no). Behavioral characteristics included injection frequency (daily or more, at least weekly (<daily), at least monthly (<weekly)), syringe and injection

equipment sharing, traded sex for money, sex without a condom, heavy alcohol consumption and cigarette smoking (past 30 days, yes/no), drug treatment (ever, yes/no), received buprenorphine from a doctor/program (ever and past 30 days, yes/no), could not get buprenorphine from doctor/program (past 6 months, yes/no), current drug preference (heroin, fentanyl, opioid painkillers, synthetic opioids, buprenorphine, methadone, prescription anxiety drugs, cocaine/crack, methamphetamine/amphetamine, other), perceived ease of accessing buprenorphine in treatment programs (strongly agree, somewhat agree, uncertain, somewhat disagree, strongly disagree) and ever experienced an overdose.

Outcome: We used the following question to determine whether someone injected buprenorphine in the past 30 days: “How many of the last 30 days have you injected buprenorphine – like Suboxone or Subutex etc. – to get high?” Anyone that answers 0 days for this question will serve as the comparison group compared to those that report injecting buprenorphine in the last 30 days at least once.

Qualitative analysis: Since the quantitative and qualitative data were collected concurrently, we utilized a convergent mixed method design to integrate the two forms of data[123]. We conducted initial deductive coding of all interview data using Dedoose qualitative software. Data coded as MOUD use was downloaded into Excel documents for inductive coding. Two coders separately open-coded this data to identify themes within mentions of illicit MOUD use, and subsequently met to reconcile differences in interpretation.

RESULTS

Quantitative Survey

Study Population Characteristics

A total of 3,084 people who use drugs (PWUD) were enrolled across all sites. Of 2,587 participants reported injecting drugs in the past 30 days, 92% (2,369) of participants answered the question of whether they injected buprenorphine and were included in this quantitative analysis from the eight ROI sites. Of the 2,369 PWID, the mean age was 35.7 years (SD=10.0) and proportionally most of the participants were male (57.1%) and White race (83.5%). The most common current drug preference was heroin (39.2%) followed closely by methamphetamine (38.0%). A total of 642 participants (27.1%) reported injecting buprenorphine in the past 30 days, 276 (11.9%) reported receiving buprenorphine from a doctor/program in the past 30 days and 940 (40.6%) reported receiving buprenorphine from a doctor/program ever.

Demographic Characteristics by Buprenorphine Injection Status

The mean age of participants reporting injecting buprenorphine was 34.7 years (SD=9.4), as compared with 36.1 (SD=10.2) years among those not reporting the behavior (**Table 4.2**). Proportionally more men (60.6% vs. 55.8%), people reporting white race (84.9% vs 82.9%) people with a high school education or less (73.6% vs. 67.3%) and those reporting ever being diagnosed with HCV (39.8% vs. 34.8%) or HIV (1.4% vs. 1.2%) injected buprenorphine in the past 30 days compared to those that did not inject buprenorphine.

Behavioral Characteristics by Buprenorphine Injection Status

Daily frequency of injecting drugs was more common among those injecting buprenorphine in the past 30 days compared to those that did not inject in the past 30 days (78.8% vs. 63.3%, **Table 4.3**). Syringe sharing (50.7% vs. 38.3%), injection equipment sharing (61.2% vs. 45.1%), trading sex for money (12.4% vs. 9.5%), sex without a condom (65.6% vs. 59.1%) and heavy alcohol consumption (57.8% vs. 44.9%) were more common among people reporting injecting vs. not injecting buprenorphine. People who injected buprenorphine more commonly reported ever receiving drug treatment (80.9% vs. 78.2%) and ever receiving buprenorphine from a doctor/program (52.6% vs. 36.0%) as compared to those that did not inject buprenorphine. Also more common among those reporting injecting buprenorphine in the past 30 days included a current drug preference of heroin (41.7% vs. 38.1%) or buprenorphine (7.0% vs. 0.9%), strongly disagreeing that accessing buprenorphine in treatment programs was easy (40.7% vs. 35.4%) and ever experiencing an overdose (60.5% vs. 49.1%).

Qualitative Interviews

Study Population Characteristics

A total of 349 people were interviewed. Interview participants were proportionally more likely to be male (56%) and White race (61%). Almost the entire population reported current injection drug use (91%) and over 60% of participants reported injecting heroin, methamphetamine and other drugs in the past 30 days (61%, 64%, 65% respectively). Twenty-two percent of the population reported injecting fentanyl in the past 30 days.

Qualitative Interview Data: Recurring Themes

There were 126 interviews of 349 total that included mention of buprenorphine injection that were reviewed. Thematic coding revealed two types of utterances regarding buprenorphine injection: how it was accessed, and reasons for use. Themes surrounding access included purchasing it off the street, through peers, or through a treatment program/provider. Themes surrounding reasons for injecting buprenorphine included: to get high; to help with withdrawal from other substances; as harm reduction to avoid using other drugs; and due to missing the ritual of needle use. Quotes supporting each of these themes are included in **Table 4.4**.

DISCUSSION

Our study found that the frequency of buprenorphine injection is somewhat common among rural PWID in the U.S. Infectious disease risk factors such as sharing needles and injection equipment, exchanging sex for money, unprotected sex, and heavy alcohol use were more common among people who injected buprenorphine in this study population. People reported different reasons for injecting buprenorphine, including maintenance, harm reduction, management of withdrawal from injecting buprenorphine and addiction to the behavior of injecting.

The finding that buprenorphine injection is occurring among PWID is supported by a growing body of research[28,29,91]. A few studies outside of the U.S. have reported on characteristics associated with buprenorphine injection similar to this analysis, although our results are descriptive. Some of these studies also found associations between injecting buprenorphine and factors associated with infectious disease transmission,

such as sharing needles and injecting other drugs[124,125]. Other associated characteristics in these prior studies included male gender, prior imprisonment, homelessness, receiving opioid substitution therapy, injection related health problems, having a history of suicide ideation or attempt, and patient perception of the first buprenorphine dose not being adequate [99,125,126]. While none of these studies were conducted in the rural U.S., we similarly saw that factors associated with infectious disease risk were more common among those injecting buprenorphine.

The qualitative interview data enhanced our understanding of buprenorphine injection by telling us more about why and how PWID in rural areas were engaging in this behavior. Harm reduction and maintenance were commonly reported reasons which have also been identified previously in the literature[28,90,127]. However, in our study, participants also reported injecting buprenorphine due to a desire for the ritual of using the needle itself. This is supported by prior research that has reported “needle fixation” behaviors in which people are fixated on the practice of injecting itself, and may inject inert substances such as water[128–130]. Study participants also reported that they injected either a personal buprenorphine prescription or were obtaining extramedical buprenorphine from peers or purchasing off of the street. These findings are not surprising as purchasing buprenorphine off of the street and injecting a personal prescription are already reported occurrences in the literature[28]. While it was somewhat surprising that participants did not often describe precipitated withdrawal from injecting buprenorphine (especially if they were injecting them buprenorphine/naloxone

combination) in the qualitative surveys, we cannot say to what extent this was happening from the data as we did not directly ask about it in the interviews.

There are several limitations to this analysis. First, the qualitative data did not focus on asking about injecting buprenorphine specifically, or the reasons why someone did it. Second, the quantitative survey was purely cross-sectional in nature and does not allow us to speculate on the direction of any of the exploratory associations reported. Third, we did not do any statistical testing as these analyses were exploratory in nature, as we wanted to focus on descriptively reporting on a range of patient characteristics to support hypothesis-generation and aid in guiding future research in this area. Fourth, while we saw that buprenorphine injection was more common among cisgender men and people reporting White race, this also represents the majority of participants in our study population. As societal level factors such as structural racism influence substance use and OUD treatment[47–49,52], further research on buprenorphine injection must prioritize including participants of ethnic and gender minorities to fully understand this behavior in all rural populations and design equitable treatment solutions. Qualitative studies could be especially useful for learning about the experience of these individuals that otherwise represent small numbers in quantitative studies. In addition to these limitations, our study also has notable strengths, including that we used both quantitative and qualitative data to get at a more holistic understanding of the behavior of injecting buprenorphine. Second, this study was conducted at multiple sites in different regions, allowing us to include multiple different patient settings and perspectives. Finally, we focused on rural sites in 10 different U.S. states. Research on buprenorphine injection practices in rural areas is necessary to ensure populations at

elevated risk of infectious disease exposure and injection related harms are receiving the focus deserved.

The finding that buprenorphine injection is a common occurrence in rural U.S. settings reinforces the need to integrate harm reduction activities into addiction treatment programs. Prior studies have found that due to the relative scarcity of easily-accessible MOUD programs and other harm reduction tools such as naloxone in rural areas, PWUD often take harm reduction into their own hands. Examples of this include people using methamphetamine along with heroin or fentanyl to limit adverse side effects or in an attempt to reverse overdose[131]. Additionally, PWUD in rural areas may be less likely to call 911 in response to overdose due to fear of law enforcement[132]. In our study, some interview participants who injected buprenorphine reported they were doing so out of an attempt at reducing their risk of overdose or minimizing other drug use, both of which are forms of harm reduction. As PWUD in rural areas are already using harm reduction, this indicates an opportunity to engage with patients on this topic of interest. HIV and HCV screening needs to be regular and active in buprenorphine programs as patients who receive treatment are still at risk of these infectious diseases. Similarly, HIV and HCV treatment providers should be providing buprenorphine to their patients who are interested. Naloxone should be offered to these patients for the prevention of overdose. Providers could also discuss and offer kits with injecting supplies to patients receiving MOUD if they are continuing to inject.

Physicians must be willing to have open conversations with patients to not only screen for buprenorphine injection, but to also offer other treatments that can reduce infectious disease and injection-related harms. It is worth noting that only the minority of

participants who reported injecting buprenorphine had been prescribed buprenorphine in the past 30 days (19%), yet it was more common to report recent buprenorphine treatment among those who reported injecting buprenorphine compared to those who did not. This speaks to on-going needs for HIV prevention (such as PrEP) for those in addiction treatment. For patients and providers seeking ways to reduce risk for injecting buprenorphine, alternative treatments could include options such as methadone, long-acting injectable formulations of buprenorphine or adherence tools to ensure buprenorphine is being taken as directed. Methadone, another MOUD, may have increased retention and treatment outcomes as compared to buprenorphine, according to some studies[65,133]. Research has shown that injectable buprenorphine can be useful for patients interested in treatment solutions that require fewer visits and/or no daily medication[134–136]. Asynchronous video directly-observed-therapy (DOT) of buprenorphine involves patients recording brief videos of themselves taking their medication via smartphone which can later be reviewed by a provider in an attempt to increase/confirm adherence, although further research is needed to determine for which patients this intervention is useful[137–139]. Ensuring that the patient understands the range of options available to them may allow for better provider-patient relationships as well as the implementation of more individually-tailored treatment and harm reduction strategies.

Based on these results, future research should more thoroughly explore the natural history of buprenorphine injection, perceptions and reasons behind the behavior, and whether there are ways to prevent or provide alternatives to injecting buprenorphine that still respect the agency or outcomes they are seeking. As previously suggested by Sud

et al, there is a need to move beyond the dichotomy of harm-reducing versus harm-producing effects and instead prioritize the needs and perspectives of PWUD as we design more effective forms of health care and programs for this population. Further research could benefit from qualitative interviews of people who inject buprenorphine and providers who prescribe buprenorphine. Possible qualitative work could delve deeper into 1) why people are injecting buprenorphine, including delving into factors at the individual (housing status, mental health), community (peer support), and societal levels (social determinants of health, supply and demand), 2) whether patients describe precipitated withdrawal when injecting buprenorphine/naloxone, 3) what barriers exist to accessing buprenorphine through healthcare providers, or why might someone prefer to use buprenorphine outside of a traditional treatment setting or differently than prescribed, 4) what barriers exist to taking their medication sublingually or orally as intended and 5) the natural history of how people begin injecting buprenorphine. Answering such questions will be necessary in order to develop treatment programs that adequately serve people with OUD, so that injecting buprenorphine becomes less common.

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Tables and Figures

Table 4.1: Inclusion criteria for quantitative questionnaire and for qualitative interviews	
State	**Inclusion Criteria**
Illinois	○ Questionnaire: ≥ 15 yo**, injected drug to get high in last 30 days OR used any opioid by any route in last 30 days**, English speaking and can provide consent (not high), passes drug screening test ○ Interview: Completes PWID survey, accepts referral to Harm Reduction services
Kentucky	○ Questionnaire: age ≥ 18, English speaking, current resident in 12 county area**, injected drugs or used opioids to get high within past 30 days**; Urine drug screen to verify drug use. ○ Interview: Same eligibility criteria as for questionnaire, "In 4 communities, drawn from our survey cohort. Elsewhere, recruited from local SSPs" per email 8/21/2020. ○
North Carolina	○ Questionnaire: age ≥ 18, English speaking, current resident in study area and intends to stay 12 months, **opioid injection or methamphetamine injection (30 days)**; verification by stigmata or appropriate description of injection practices. ○ Interview: (Consent form says "We are asking you to be in this study because you told us that you have injected painkillers or heroin") ○
New England	○ Questionnaire: age ≥ 18; **Injected drugs or used opioids to get high within past 30 days (self-report**); living within the targeted regions; English speaking; and ability to provide informed consent. ○ Interview: "people who inject drugs and/or use opioids as key informants in rural locations in each of our 3 target states." Per email 8/1/2019: "We recruited a convenience sample of in-depth interview participants through street outreach, venue-based recruitment, and respondent driven sampling that was part of the larger study." ○
Ohio	○ Questionnaire: Are at least 18 years of age, are a resident of Scioto, Pike, or Jackson counties, **have used heroin or prescription opioids OR have injected any type of drug to get high in the past 30days**, are capable and willing to provide informed consent to participate. "Where doubts about eligibility remain, staff or volunteers may pose additional (non-standardized) questions confirm true eligibility" ○ Interview: PWID will be purposively selected (15 men and 15 women); half of the individuals selected will have accessed health-or drug-related services in the past year, with subsamples

	of individuals who have recently transitioned to injection and women with experiences with NAS. "PWID will be recruited with the help of community partners and key informants." ○
Oregon	○ Questionnaire: live in the study area, **have injected drugs or report recreational opioid use without injection in the last 30 days**, are age 18 or greater, and are willing to provide consent for risk survey and future linkage of biologic and survey data to administrative data, and able to communicate in English. No eligible participants are excluded. ○ Interview: "PWUD qualitative interview participants will be recruited through advertisement in community-based and service locations, and through direct recruitment by service provider and outreach staff; … PWUD will be included as community stakeholders and be offered participation in qualitative interviews. No PWUD will be excluded from the qualitative interviews." (Community Action Team members are also invited to interview, and may include PWUDs). ○
Wisconsin	○ Questionnaire: 15 years of age or older**, have injected any opioid drug in the past 1 month**, and reside in a rural community. ○ Interview: "Clients who participate in the cross-sectional study described above will be systematically invited (e.g., every nth person) to also participate in a qualitative interview." ○
West Virginia	○ Questionnaire: age ≥ 18, English speaking, current resident in 7 counties of study area, **injection in past 30 days/ Verification: "self-report (primarily recruited from SSPs**)" ○ Interview: N/A ○

Table 4.2: Demographic Characteristics by Buprenorphine Injection Status Among People who Injected Drugs in the Past 30 Days

Characteristic	Injected Buprenorphine (past 30 days) (N=642, %)	Did not inject Buprenorphine (past 30 days) (N=1,727, %)
Age (mean, SD)		
	34.7 (9.4)	36.1 (10.2)
Gender		
Man	389 (60.6)	963 (55.8)
Woman	251 (39.1)	752 (43.6)
Transgender/Other	2 (0.3)	11 (0.6)
Race		
White	545 (84.9)	1433 (82.9)
Black/African American	12 (1.9)	51 (3.0)
American Indian	43 (6.7)	128 (7.4)
Other/Mixed/Unknown	24 (3.7)	53 (3.1)
Hispanic Ethnicity[a]	18 (2.8)	62 (3.6)
Education		
High school or less	472 (73.6)	1160 (67.3)
Some college/Trade School	154 (24.0)	528 (30.6)
College graduate or above	15 (2.3)	37 (2.1)
Experienced homeless (past 6 mo.)	349 (55.0)	953 (56.1)
No current health insurance	463 (75.0)	1,271 (75.8)
HCV Diagnosis (ever)	244 (39.8)	578 (34.8)
HIV Diagnosis (ever)	9 (1.4)	20 (1.2)

[a]Race and Hispanic ethnicity are mutually exclusive.

Table 4.3: Behavioral Characteristics by Buprenorphine Injection Status Among People who Injected Drugs in the Past 30 Days

Characteristic	Injected Buprenorphine (past 30 days) (N=642, %)	Did not inject Buprenorphine (past 30 days) (N=1,727, %)
Frequency of Injecting Drugs		
Daily or more	504 (78.8)	1,080 (63.3)
At least weekly (< daily)	89 (13.9)	349 (20.5)
At least monthly (< weekly)	47 (7.3)	278 (16.3)
Syringe sharing (past 30 days)	310 (50.7)	628 (38.3)
Injection Equipment Sharing (past 30 days)	375 (61.2)	739 (45.1)
Drug Treatment (ever)	516 (80.9)	1,327 (78.2)
Traded sex for money (last 30 days)	65 (12.4)	125 (9.5)
Sex without a condom (last 30 days)	342 (65.6)	763 (59.1)
Received buprenorphine from doctor/program (ever)	334 (52.6)	606 (36.0)
Received buprenorphine from doctor/program (past 30 days)	123 (19.4)	153 (9.1)
Could not get buprenorphine from doctor/program, past 6 months	49 (7.7)	80 (4.9)
Current Drug Preference		
Heroin	268 (41.7)	658 (38.1)
Street fentanyl/carfentanil	16 (2.5)	36 (2.1)
Opiate painkillers	54 (8.4)	105 (6.1)
Synthetic opioids	14 (2.2)	5 (0.3)
Buprenorphine	45 (7.0)	16 (0.9)
Methadone	8 (1.3)	26 (1.5)
Prescription anxiety drugs	11 (1.7)	20 (1.2)
Cocaine/crack	32 (5.0)	99 (5.7)
Methamphetamine/crystal meth/amphetamine	183 (28.5)	714 (41.3)
Other[a]	10 (1.6)	41 (2.4)
Heavy Alcohol Consumption (>=4/5 drinks in one day in past 30 days)	369 (57.8)	764 (44.9)

Cigarette Smoking (past 30 days)	594 (92.7)	1,569 (91.1)
Perceived ease of accessing buprenorphine in treatment programs		
Strongly agree	60 (9.5)	183 (10.9)
Somewhat agree	62 (9.8)	129 (7.7)
Uncertain	127 (20.0)	487 (28.9)
Somewhat disagree	127 (20.0)	291 (17.3)
Strongly disagree	258 (40.7)	597 (35.4)
Ever experienced an overdose	379 (60.5)	830 (49.1)

[a]Other includes gabapentin, Neurontin and clonidine

Table 4.4: Qualitative Quotes by Theme Among People Who Use Drugs

1. Reasons for Injecting Buprenorphine	
a. Getting High from Buprenorphine	• *"Respondent: If you're not getting high and you take Suboxone, if you don't have a habit and you start taking them, they'll get you high."* *Interviewer: Is it used for getting high or for maintenance?* *Respondent: I don't do my dose that I'm prescribed, but I guess for getting high too yeah, and maintenance, a little bit of both.* • *"I use Suboxone because it has such a long half life, and the stigma is different, different opiate receptors than heroin. It stimulates the same receptors, but it's got a muted euphoria. You don't really feel that euphoria. You feel relaxation, and you have the analgesia, you feel the pain relief. I feel an increase in motivation, more confidence and it mutes my anxiety, but it lasts a very long time. So, I would do it usually, I always wanna say just once a day, but I do a shot go to work and have a great day at work and not be in any pain."*
b. Alternative to Medical Care (Withdrawal or Alternative to Traditional Drug Treatment Therapy)	• "I *get a prescription for it. I'm in a clinic. So I guess technically a lot of people say that I'm not clean, but I am because it's my medicine. I don't do it the wrong way. I actually don't take the dose I'm supposed to. I try to lower myself down. So when I do come off of it it's not going to be as painful."*

	• *"…but we don't get high. We just don't get sick, you know what I mean?"*
c. Alternative to Other Drugs (Harm Reduction)	• *Participant: "…now I don't want to back to doing heroin or meth no more, you know, so, I'm keeping on the Suboxone because it keeps me- you know, because you can't mix Suboxone with heroin or else you'll get sick. You know, because the opiate- or the, um- the Suboxone blocks out the opiates. And I'm on Suboxone, so."* *Interviewer: "Does it make you feel different or better than when you used heroin?"* *Participant: "No, it's really- I don't really feel anything, it just makes me feel better, you know? It's- I don't know, it feels like it's helping me keep away from the heroin and the meth. "* *Interviewer: "OK. So, you think staying away from heroin at this point in your life is a good thing for you?"* *Participant: "Yeah."* *Interviewer: "OK, and the Suboxone helps with that?"* *Participant: "Helps, yeah."*
d. Manage Addiction to the Needle Itself	• *"I don't feel anything when I do the Suboxone. Heroin makes me want to nod off and just I don't know, drool all over yourself, and Suboxone, I feel my normal self, and I don't know if the reason I keep doing it is because- like, smoking a cigarette, when you stop smoking, you take a pencil and find yourself, kind of, with the motion of a cigarette. I don't know if I- my main thing, I'm doing Suboxone is just to still have that needle and still have something to inject. Like, the cigarette pencil addiction, kind of, the needle addiction. I don't know, like, I feel like I almost still need to do that."*
2. Buprenorphine Provision	• *Interviewer: So now you're having to buy your Suboxone.* *Respondent: Yeah.* *Interviewer: Yeah. Okay. Is there a regular person that you buy it from or do you have a couple of different people or -* *Respondent: I just more/less have a friend that helps me out.* • *Interviewer: Okay. And then, during the time whenever you were using Suboxone, were you getting it from someone who got it from the maintenance…* *Respondent: Yeah.* *Interviewer: …clinic?* *Respondent: Yeah, I was getting it from somebody.* • *Respondent: - and I went to a Suboxone clinic for the last three and a half years.* *Interviewer: Okay. You actively go to the Suboxone clinic -* *Respondent: Yeah.* *Interviewer: - but you're injecting it -* *Respondent: Yes.*

Chapter 5: Conclusion

While the three studies outlined here all involve differing subjects within the wider topic area of substance use, they all exist in the broader, and increasingly dire, context of a devastating burden of opioid overdose. As fentanyl, xylazine, and other novel substances continue to penetrate the drug market, there will be implications for public health, substance use disorder treatment, and injection-related harm and overdose prevention efforts. Working towards real-time substance use monitoring, with methods such as dried blood spot testing, will help public health professionals stay on top of emerging threats to public health and provide PWUD with relevant information about drugs they may encounter in their communities. Harm reduction must be upscaled and practiced across different settings to increase accessibility, including in SSPs and in clinical treatment settings. Methods for harm reduction such as fentanyl test strips (or other drug testing services), naloxone, syringe service programs and safe-injection sites[140–143] are all examples of tools that we can advocate for and hope to deliver effectively to communities of people who use drugs. Continual research and development of treatment programs and interventions to help people with OUD is necessary to determine the services that meet the needs of a diverse range of individuals that have different lived-experiences[144,145] and different personal definitions for treatment success. Ensuring we are conducting research in the context of societal factors, such as structural racism and other systems of oppression, is important to ensure equitable health outcomes[113,118,121,146,147]. Research relating to substance use and OUD absolutely must continue efforts to integrate PWUD perspectives and a health

equity lens to design treatment programs and intervention strategies that work for all groups of people and can truly be successful.

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