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# Methamphetamine use and illicit opioid use during buprenorphine treatment

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ABSTRACT

*Introduction:* Although methamphetamine use is rising in the United States, its impacts on patient outcomes among persons undergoing treatment for opioid use disorder (OUD) remain unclear. This study aims to assess the association between baseline methamphetamine/amphetamine (MA/A) use and subsequent illicit opioid use among patients with OUD initiating buprenorphine in an office-based setting.

*Methods:* We conducted a secondary analysis of a pilot randomized controlled trial of a behavioral mobile health intervention for buprenorphine adherence conducted over a 12-week study period at two clinic sites. The study defined baseline MA/A use by a positive urine drug test (UDT) and/or self-report of use within the past 30-days. Separate Poisson regression models with robust standard errors evaluated associations between MA/A and: i) illicit opioid use measured by weekly UDT (primary) and ii) self-reported past 30-day use at end of study (secondary). Other secondary outcomes included buprenorphine positive UDTs throughout the study and retention in OUD treatment at both weeks 12 and 24 post-randomization.

*Results:* At baseline, 28 (36 %) of the 78 participants had MA/A use and use was associated with a statistically significant increase in risk of testing positive for illicit opioids on UDT during the study follow-up period (adjusted relative risk (aRR) = 1.54; 95 % CI = 1.09–2.17; $p = 0.015$), as well as an increased risk for reported past 30-day illicit opioid use at week 12 (aRR = 3.86; 95 % CI = 1.47–10.18; $P = 0.006$). The study found no significant associations between MA/A use and buprenorphine positive UDT or retention in OUD treatment.

*Conclusions:* In this sample of patients initiating buprenorphine, methamphetamine/amphetamine use at baseline was associated with illicit opioid use over a 12-week period. These findings demonstrate how co-use of methamphetamine can impede attainment of ideal OUD treatment outcomes.

## 1. Introduction

The substantial health impacts of the opioid crisis have made the crisis the primary focus of drug policy within the United States for the past decade. Although recent efforts in prevention and intervention have been made to address opioids, recent law enforcement data and news reports point to a new and concerning increase in the availability and use of methamphetamine in the United States, particularly in the West (Al-Tayyib et al., 2017). According to a national survey from the Substance Abuse and Mental Health Services Administration (SAMHSA), the percentage of past-year methamphetamine users, aged 26 years old or older, increased from 0.5 % (or 1.1 million people) in 2016 to 0.8 % (or

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1.7 million people) in the United States in 2019 (Substance Abuse and Mental Health Services Administration, 2019). This rise in methamphetamine use is particularly concerning viewed in the context of increases in overdose deaths involving both opioids and stimulants. A report issued by the Centers for Disease Control (CDC) using data from January through June 2019 among 24 states and the District of Columbia, reported 16,236 drug overdose deaths, of which 5301 (32.6 %) involved a combination of opioids and stimulants and 2056 (12.7 %) involved stimulants alone (O'Donnell et al., 2020). The report described regional differences with a larger proportion of stimulant-related deaths occurring in the West; however, subsequent reports have confirmed the trend of increasing psychostimulant (e.g., methamphetamine) overdose deaths with the largest relative increases occurring outside of the West, reflecting a spread in use throughout the country (Al-Tayyib et al., 2017; Fischer et al., 2021; Gladden et al., 2019; Hedegaard et al., 2018; Mattson et al., 2021; McKetin et al., 2008).

Among persons with opioid use disorder (OUD) who seek care, studies have shown concurrent methamphetamine use is increasing (Ellis et al., 2018; Jones et al., 2020). Studies have suggested a pattern of negative health consequences associated with concurrent use of methamphetamine among individuals with OUD including increased emergency department visits and hospitalizations (Howell et al., 2021), early discharges against medical advice and readmissions (Merchant et al., 2020), and high risk sex and drug use behaviors leading to increased risk for blood borne infections such as HIV and hepatitis C (Cai et al., 2020; Glick et al., 2021; Jawa et al., 2021; Nerlander et al., 2018). A recent systematic review examining the effects of methamphetamine use on MOUD treatment outcomes reported that most, but not all, studies found a negative association with treatment retention and abstinence from opioids (Frost et al., 2021). Weaknesses in the studies included small sample sizes and cross-sectional designs, as well as use of abstinence as the outcome rather than opioid use over time. A need exists for longitudinal studies with repeated assessments of substance use using biomarkers to establish the effects of methamphetamine on opioid use over time.

We conducted the investigation reported on here to assess the association between methamphetamine use and treatment outcomes among participants receiving buprenorphine treatment for OUD. We hypothesized that individuals who were using methamphetamine at the time of treatment initiation would have higher illicit opioid use during treatment, lower adherence to buprenorphine, and worse retention, compared with nonusers of methamphetamines.

## 2. Methods

### 2.1. Study design and population

This is secondary analysis of data collected in the Trial of Adherence Application for Buprenorphine treatment (TAAB) study, a two-site pilot randomized controlled trial of a behavioral mHealth intervention that has been described previously (Schramm et al., 2020; Tsui et al., 2021). Briefly, the TAAB study evaluates a mobile health adherence tool of video directly observed therapy ("DOT") for patients receiving office-based opioid treatment (OBOT) with buprenorphine. The study recruited participants from OBOT programs at primary care and psychiatric clinics in Seattle, WA, and Boston, MA. All the clinic sites within the study utilized a health care model based on the Massachusetts Collaborative Care Model in which nurse care managers collaborate with buprenorphine-waivered physicians to provide health care services (Alford et al., 2011). The parent study did not show any differences in outcomes between the intervention (mobile DOT app + treatment-as-usual (TAU)) and control (TAU) arms (Tsui et al., 2021).

The study recruited participants through clinic referrals and flyers posted in clinic. Participant eligibility criteria included: 18 years or older, within their first 28 days of either starting or restarting prescribed sublingual buprenorphine treatment from the office-based treatment program recruitment sites, and able to read and understand English. The study considered participants to be ineligible if they were unable or unwilling to use the mobile application, cognitively impaired and unable to provide informed consent, had immediate plans to move such that they could not complete study visits, or were aware of imminent incarceration. Weekly study visits that included urine drug testing (UDT) occurred over a 12-week period. Participants received $50USD for completing baseline and final visits, and $20USD for completing each weekly follow-up visit. The study received approval from the University of Washington and Boston University Medical Campus Institutional Review Boards.

### 2.2. Data collection and procedures

At the baseline research visit participants completed an assessment that included demographics, lifetime illicit substance use, and past 30-day illicit substance use (Addiction Severity Index [ASI]) (McLellan et al., 1992). Participants were considered employed if they reported working either a full- or part-time job and unemployed if they reported being temporarily/permanently unemployed, disabled, a homemaker, student, retired, or for some other reason. The study considered as homeless participants who reported staying at least one night in a shelter or on the streets in the past 90 days. Baseline assessments also included measures of mental and physical health (Veteran-RAND 12 [VR-12]) (Jones et al., 2001); depression (Patient Health Questionnaire 8 [PHQ-8]) (Razykov et al., 2012); and anxiety (Generalized Anxiety Disorder 7 [GAD-7]) (Spitzer et al., 2006). Participants provided a urine sample at the baseline visit for urine toxicology. Following the baseline research visit, participants were scheduled for 12 weekly postrandomization assessments. At each of the 12 weekly follow-up visits, the study assessed the participants' self-reported adherence to buprenorphine using a 7-day timeline follow-back procedure and urine toxicology. Urine samples were initially tested with Alere 14 Drug Panel iCups and later tested with Identify Diagnostic cup, due to discontinuation of production of Alere iCups mid-study. We assessed fentanyl use using Fentanyl test strips with a preset 300 ng/ml cutoff level throughout the study. In the event that participants failed to complete one of the 12 weekly follow-up assessments, the study used clinical urine drug test (UDT) results performed as part of routine clinical care when available.

This investigation allocated participants into two groups based on whether they were or were not using methamphetamines/amphetamines at the time of their baseline research visit. The study defined use as a self-report of using methamphetamine/amphetamine within the past 30 days of the baseline visit and/or a UDT positive for methamphetamines or amphetamines at the baseline visit. We wanted to identify those who may have responded as not using in the past 30 days at baseline but had a positive UDT to categorize them as positive to gain a better sense of use. Conversely, if self-reported use was present but the UDT was negative, the study would categorize the participant as positive because of concern over false negative tests.

### 2.3. Outcomes

The primary outcome was the number of weekly UDTs that were positive for opioids, including opiates/morphine, methadone, oxycodone, and fentanyl, during the 12-week study period. Samples that were missing were presumed to be positive. The secondary outcome was self-reported use of illicit opioids, including the above-mentioned substances as well as other prescription opioids without a doctor's prescription or in greater amounts than prescribed, in the past 30 days assessed at the end of study (week 12). The analysis excludes missing self-report data at week 12.

Additional secondary outcomes included 1) engagement in treatment at week 12 per EHR review, 2) engagement in treatment at week 24 per EHR review, and 3) percentage of weekly UDTs negative for buprenorphine as a measure of medication non-adherence/

discontinuation. The study defined engagement in treatment as not having gone >7 days without medication based on EHR review at the 12- and 24-week time points, and based on whether the participant had an active script for buprenorphine within the 7 days prior to the week 12 visit or week 24 postenrollment date.

### 2.4. Statistical analysis

The study evaluated differences in baseline demographics and substance use characteristics between methamphetamine/amphetamine groups using chi-square or Fisher's exact test for categorical variables, and *t*-test for difference in means for continuous variables.

For the primary outcome of UDT positive for illicit opioids over the 12-week study period, Poisson regression models with robust standard errors tested the null hypothesis of no difference in the proportion of positive UDT when comparing those with and without baseline methamphetamine/amphetamine use. Results are reported as the rate ratio for the rate of an opioid positive UDT in the methamphetamine/amphetamine positive group compared to the negative group. We conducted a sensitivity analysis with missing UDT as missing to determine the influence of missing assumed as positive on the magnitude of the effect estimate.

We also used Poisson regression models with robust standard errors to test the secondary outcomes of self-reported days of illicit opioid use in the past 30 days at week 12, proportion of 12 weekly UDTs negative for buprenorphine with missing UDTs excluded from analysis, proportion of participants engagement in treatment at week 12, and proportion of participants engagement in treatment at week 24 postenrollment. The study evaluated unadjusted and adjusted models including covariates for age, sex and study site. We selected these covariates a priori based on our knowledge of the subject matter and published literature.

The research team conducted statistical tests with Stata statistical software (16.1, StataCorp LLC, College Station, TX). All analyses are reported with 95 % confidence intervals and 2-sided tests of the null hypothesis at a significance level of 0.05.

## 3. Results

Of the 104 potential participants who screened as eligible, the TAAB study enrolled 38 participants at the Seattle site and 40 at the Boston site, for a total of 78 participants. Of the 78 participants in the sample, 28 (36 %) had baseline methamphetamine/amphetamine (MA/A) use; most (20/28) were enrolled from the Seattle site. We show participant demographic and clinical characteristics by baseline methamphetamine and/or amphetamine positive and negative groups, with tests for significant differences between groups, in Table 1. Overall, the two groups were similar on demographics and mental health and quality of life measures. However, past 30-day use of cannabis, cocaine, and heroin were all more common among patients with MA/A use compared to those without MA/A use, with heroin use being statistically significant ($p < 0.001$). Also notable, a larger percentage of the participants in the positive MA group reported being homeless (46 %) compared to the negative MA group (36 %).

### 3.1. Primary outcome

At baseline, 21 (27 %) participants had a positive UDT for methamphetamine and/or amphetamine, comprising 21/28 (75 %) of the positive MA group. The mean and standard deviation (SD) for the number of positive UDT for illicit opioids during the 12-week study period was 4.2 (3.6) compared to 6.9 (4.3) for the MA negative and positive groups, respectively (Fig. 1, Table 2; adjusted relative risk [aRR] = 1.54 (95 % confidence interval [CI]: 1.09–2.17; $p = 0.015$)). The sensitivity analysis of assuming missing UDT for opioids as missing resulted in a greater incidence rate ratio estimate but a larger confidence interval due to a loss in power. The *p*-value still shows statistical

**Table 1**
Baseline characteristics of study participants receiving buprenorphine treatment, overall, and stratified by baseline methamphetamine/amphetamine use, n (%).

| Participant characteristics | METH/AMP negative (N = 50) | METH/AMP positive (N = 28) | Overall (N = 78) | P-value[a] |
|---|---|---|---|---|
| Study site, n (%) | | | | |
| Seattle | 18 (36 %) | 20 (71 %) | 38 (49 %) | 0.003 |
| Boston | 32 (64 %) | 8 (29 %) | 40 (51 %) | |
| Age, mean (SD), range | 42.49 (13.08), 19–70 | 39.43 (9.24), 24–62 | 41.71 (11.90), 19–70 | 0.17[b] |
| Gender (n, %)[c] | | | | |
| Women | 14 (28 %) | 6 (21 %) | 20 (26 %) | 0.81[d] |
| Men | 35 (70 %) | 21 (75 %) | 56 (72 %) | |
| Non-binary | 1 (2 %) | 1 (3.6 %) | 2 (2.6 %) | |
| Race, n (%)[e] | | | | |
| White/Caucasian | 33 (66 %) | 15 (54 %) | 48 (62 %) | 0.25 |
| Black/African American | 6 (12 %) | 2 (7 %) | 8 (10 %) | |
| All others | 11 (22 %) | 10 (36 %) | 21 (27 %) | |
| Refusal | 0 (0 %) | 1 (4 %) | 1 (1 %) | |
| Hispanic ethnicity, n (%) | 11 (22 %) | 7 (25 %) | 18 (23 %) | 0.76 |
| Education, n (%) | | | | |
| Less than high school diploma | 6 (12 %) | 7 (25 %) | 13 (17 %) | 0.23 |
| High school diploma or GED | 25 (50 %) | 8 (29 %) | 33 (42 %) | |
| Some post-high school | 10 (20 %) | 8 (29 %) | 18 (23 %) | |
| College degree | 9 (18 %) | 5 (18 %) | 14 (18 %) | |
| Homeless, n (%) | 18 (36 %) | 13 (46 %) | 31 (40 %) | 0.37 |
| Unemployed, n (%) | 41 (82 %) | 20 (71 %) | 61 % (78 %) | 0.28 |
| History of injection drug use, n (%) | 41 (82 %) | 22 (79 %) | 63 (81 %) | 0.71 |
| Married/living with partner | 2 (4 %) | 0 (0 %) | 2 (3 %) | 0.38[d] |
| PHQ-8, mean (SD), range | 9.76 (6.1), 0–23 | 9.64 (7.1), 0–24 | 9.71 (6.4), 0–24 | 0.94[b] |
| GAD-7, mean (SD), range | 9.34 (6.2), 0–21 | 9.11 (6.3), 0–21 | 9.3 (6.2), 0–21 | 0.88[b] |
| VR-12, mean (SD), range | | | | |
| Physical component summary | 40.7 (14.6), 7.3–62.9 | 41.9 (11.7), 18.5–62.2 | 41.1 (13.6), 7.3–62.9 | 0.71 |
| Mental component summary | 37.2 (15.4), 6.6–61.4 | 37.4 (14.7), 14.8–62.8 | 37.3 (15.1), 6.6–62.8 | 0.95 |
| Past 30-day heavy alcohol use[f] | 3 (6 %) | 2 (7 %) | 5 (7 %) | 0.61[d] |
| Past 30-day cannabis use | 20 (40 %) | 18 (64 %) | 38 (49 %) | 0.17[d] |
| Past 30-day cocaine use | 4 (8 %) | 7 (25 %) | 11 (14 %) | 0.05[d] |
| Past 30-day fentanyl use | 5 (10 %) | 1 (4 %) | 6 (8 %) | 0.41[d] |
| Past 30-day heroin use | 8 (16 %) | 16 (57 %) | 24 (31 %) | <0.001 |
| Past 30-day illicit opioid use[g] | 5 (42 %) | 6 (86 %) | 11 (58 %) | 0.08 |

Abbreviations: SD: standard deviation; GED: general education diploma; PHQ-8: Patient Health Questionnaire-8; GAD-7: general anxiety disorder–7; VR-12: veteran rand-12.

[a] P-value derived from chi-square test unless otherwise denoted.

[b] Independent sample *t*-test assuming unequal variances.

[c] The non-binary category for gender includes those who self-identified as transgender female-to-male, transgender male-to-female, transgender unspecified, or other gender identities that do not fit the normative gender binary of man or woman.

[d] P-value derived from Fisher's exact test.

[e] The "all other" race category includes participants who described their race as exclusively non-white, non-black, or as multiple races and ethnicities.

[f] Heavy alcohol use defined as 5 or more drinks for men and 4 or more for women on one occasion as per NIAAA.

[g] Includes illicit opioid use (heroin, methadone, fentanyl) and other prescription opioid medication use without a doctor's prescription or in greater amounts than prescribed.

significance but to a lesser degree than the original finding (aRR = 1.83 (1.02–3.28); $p = 0.043$).

### 3.2. Secondary outcomes

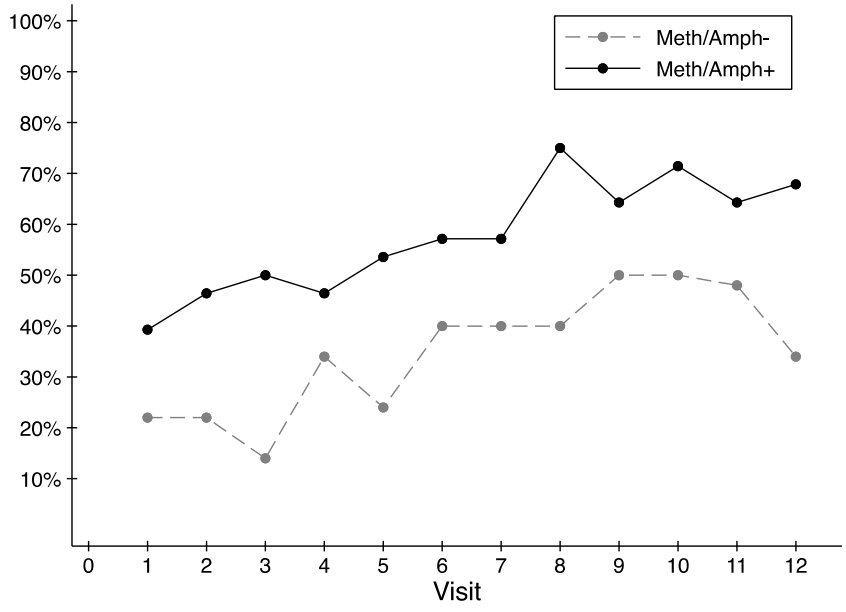
Out of the 50 participants in the negative MA group, 37 (74 %) completed the final week 12 visit, and out of those 37, 4 (11 %) self-reported illicit opioid use in the past 30 days (Table 2). Out of the 28 participants in the positive MA group, 17 (61 %) completed the week 12 visit, and 7 out of the 17 (41 %) self-reported illicit opioid use, aRR = 3.86 [95 % CI: 1.47–10.18; $p = 0.006$] (Table 2).

According to EHR review done at week 12, 39 (78 %) of the MA negative group participants were still engaged in treatment, compared to 20 (71 %) among the MA positive group, RR = 0.92 (95 % CI: 0.69–1.23; $p = 0.59$) (Table 2). EHR review at week 24 showed 27/50 (54 %) of MA negative group participants still engaged in treatment, compared to only 11/28 (39 %) among the MA positive group, aRR = 0.66 (95 % CI: 0.38–1.15; $p = 0.14$) (Table 2).

The mean (SD) number of urine samples negative for buprenorphine during the 12-week study period was 0.3 (0.8) among the MA negative group, compared to 0.5 (1.5) among the MA positive group, aRR = 1.32 (95 % CI: 0.44–3.97; $p = 0.62$) (Table 2).

## 4. Discussion

This study of persons who initiated office-based buprenorphine for




Number of Weekly Opioid Positive UDTs

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Meth/Amp+ (N=28)** | 11 | 13 | 14 | 13 | 15 | 16 | 16 | 21 | 18 | 20 | 18 | 19 |
| **Meth/Amp- (N=50)** | 11 | 11 | 7 | 17 | 12 | 20 | 20 | 20 | 25 | 25 | 24 | 17 |

**Fig. 1.** Weekly percentage of opioid positive UDTs by Methamphetamine/Amphetamine group. Number of weekly opioid positive UDTs shown in table.

**Table 2**
Descriptive statistics and Poisson regression results of primary and secondary outcomes by baseline methamphetamine/amphetamine use, n (%).

| | METH/ AMP- *(N = 50)* | METH/ AMP+ *(N = 28)* | Overall *(N = 78)* | Unadjusted RR (95 % CI) | p-Value | Adjusted[a] RR (95 % CI) | p-Value |
|---|---|---|---|---|---|---|---|
| Primary outcome | | | | | | | |
| Number of urine samples positive for illicit opioids[b], mean (SD), range | 4.2 (3.6), 0–12 | 6.9 (4.3), 0–12 | 5.2 (4.0), 0–12 | 1.66 (1.19–2.30) | 0.002 | 1.54 (1.09–2.17) | 0.015 |
| Secondary outcomes | | | | | | | |
| Self-reported illicit opioid use in past 30 days at 12 weeks, n/N (%)[c] | 4/37 (11 %) | 7/17 (41 %) | 11/54 (20 %) | 3.81 (1.27–11.40) | 0.017 | 3.86 (1.47–10.18) | 0.006 |
| Engaged in treatment at week 12, n (%) | 39 (78 %) | 20 (71 %) | 59 (76 %) | 0.91 (0.69–1.21) | 0.54 | 0.92 (0.69–1.23) | 0.59 |
| Engaged in treatment at week 24, n (%) | 27 (54 %) | 11 (39 %) | 38 (49 %) | 0.73 (0.43–1.24) | 0.24 | 0.66 (0.38–1.15) | 0.14 |
| Number of urine samples negative for buprenorphine, mean (SD), range | 0.3 (0.8), 0–4 | 0.5 (1.5), 0–6 | 0.4 (1.1), 0–6 | 1.67 (0.45–6.12) | 0.44 | 1.32 (0.44–3.97) | 0.62 |

Abbreviations: RR = risk ratio, CI = confidence interval, UDT = urine drug test.
[a] Adjusted for study site, participant age, and sex at baseline.
[b] Includes heroin, methadone, fentanyl, and oxycodone without a prescription or in greater amounts than prescribed.
[c] Includes heroin, methadone, fentanyl, and other prescription opioids without a doctor's prescription or in greater amounts than prescribed.

treatment of OUD in two sites observed that baseline methamphetamine/amphetamine use was prospectively associated with increased risk of illicit opioid use over the subsequent 3 months based on weekly urine drug testing. Overall, we found that just over a third had methamphetamine/amphetamine use, and that use was more common at the Seattle site compared to Boston, which is consistent with prior literature demonstrating regional differences in use (Ellis et al., 2018). We did not observe significant associations between methamphetamine/amphetamine use and retention at 12 or 24 weeks, nor did we observe a significant association with nonadherence to buprenorphine as evidenced by buprenorphine negative UDTs.

The results of this study add to existing literature on adverse health care outcomes for those individuals seeking OUD treatment who are concurrently using methamphetamine/amphetamine. A recent study conducted in Vancouver, Canada, found that pretreatment use of stimulants (cocaine or methamphetamines/amphetamines) was strongly associated with self-reported ongoing illicit opioid use during treatment with opioid agonist therapy (buprenorphine or methadone) (Dong et al., 2021). Our findings are similar to an older study that observed an association between baseline cocaine use and opioid positive UDTs among individuals treated with buprenorphine (Sullivan et al., 2010).

Interestingly, we did not detect an association between methamphetamines/amphetamine use and nonretention in buprenorphine treatment for OUD. These findings differ from previous large studies demonstrating associations between methamphetamine use and nonretention among those being treated with medications for OUD (Krawczyk et al., 2021; Tsui et al., 2020). This finding can likely be attributed to our small sample size and limited power to detect differences in retention between the two groups. A recent systematic review on this topic found that most, but not all, studies found a positive association between methamphetamine use and nonretention in opioid agonist treatment and noted that the discrepancy could be explained by many studies having a small sample size (Frost et al., 2021). Any true association between methamphetamine use and retention may be modest in effect size because over time clinics have adopted a more "harm-reduction" approach that does not "penalize" patients for substance use during treatment (Hood et al., 2020; Payne et al., 2019). Although prior studies suggest programs exist that may discharge patients for using non-opioid substances (Baker et al., 2021), anecdotal evidence suggests that this approach is less common, particularly since the COVID pandemic has underscored the need for flexible care models to keep patients engaged in care (Becker & Fiellin, 2020).

This study has several strengths and limitations. One strength is the use of two sites, which were located on opposite sides of the country and thus reflecting different geographic trends of methamphetamine use. Other strengths were the focus on individuals initiating OUD treatment and rigorous methods to ascertain opioid use with weekly UDT in addition to self-report. However, restricting the study to two similar programs that used a nurse-care manager model for office-based buprenorphine treatment may limit generalizability. This was a post-hoc analysis of data collected from a study with a small sample size with limitations to power that may limit our conclusions, as we have described earlier. Finally, out of the total possible UDT, 305/1014 (30 %) were missing and the assumption of missing UDT results being opioid positive was a limitation. However, our results based on self-report were consistent with UDT giving further strength to our findings.

### 4.1. Conclusion

In summary, this study of persons initiating treatment with buprenorphine for OUD found that baseline use of methamphetamines and/or amphetamines was prospectively associated with illicit opioid use determined by UDT and self-reported use. These results underscore the consequences of rising methamphetamine use in parts of the country and how it may impede efforts to maintain cessation from opioids among persons starting buprenorphine treatment.

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## CRediT authorship contribution statement

**Zoë Kratina-Hathaway:** Formal analysis, Writing – original draft. **Andrea C. Radick:** Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft. **Brian G. Leroux:** Data curation, Formal analysis, Investigation, Methodology, Supervision, Validation, Writing – original draft. **Kendra Blalock:** Data curation, Formal analysis, Investigation, Project administration, Resources, Validation, Visualization, Writing – review & editing. **Theresa W. Kim:** Conceptualization, Funding acquisition, Investigation, Project administration, Supervision, Writing – review & editing. **James Darnton:** Conceptualization, Supervision, Writing – review & editing. **Andrew J. Saxon:** Funding acquisition, Supervision, Writing – review & editing. **Jeffrey H. Samet:** Funding acquisition, Supervision, Writing – review & editing. **Judith I. Tsui:** Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing – original draft.

## Declaration of competing interest

None.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.

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