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Impact of recent stimulant use on treatment outcomes amongst individuals initiating medications for opioid use disorders: Secondary analysis of a multisite randomized controlled trial

Cari Coles [a,*], Courtney Batts [a], Joanne Bae [a], Gabriela León [a], Alex Schmidt [a,b], Sterling M. McPherson [a,b], Crystal L. Smith [a,b], André C. Miguel [a,b]

[a] Washington State University Elson S. Floyd College of Medicine, USA
[b] Washington State University, Analytics and PsychoPharmacology Laboratory (APPL), USA

HIGHLIGHTS

- Stimulant co-use is highly prevalent among people seeking OUD treatment.
- Baseline stimulant use is associated with worse OUD within-treatment outcomes.
- Baseline stimulant use is associated with worse follow-up OUD treatment outcomes.
- The need for coordinated treatment for stimulant and opioid use is critical.

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ABSTRACT

Introduction: Illicit stimulant use among individuals initiating medication for opioid use disorder (MOUD) has significantly increased over the past decade. Co-use of these substances is associated with increased risk of mortality as well as worse treatment outcomes. This study examines the potential predictive role of stimulant urinalysis result at baseline on treatment retention and opioid and stimulant use outcomes amongst individuals initiating MOUD treatment.

Methods: This is a cross-sectional secondary analysis of data from a multi-site randomized clinical trial (CTN-0027). A total of 1269 individuals were randomized to receive 24 weeks of buprenorphine (n = 740) or methadone (n = 529) treatment across nine sites. Multiple linear and logistic regressions were conducted to determine the impact of baseline stimulant urinalysis results on treatment retention, and stimulant and opioid use outcomes.

Results: Individuals initiating MOUD with a stimulant negative urinalysis result at baseline submitted more negative stimulant (β=7.8; 95 % CI 6.8–8.7) and opioid (β=2.8; 95 % CI 1.8–3.8) urinalyses during treatment, were more likely to complete treatment (aOR=1.4; 95 % CI 1.1–1.7), and had better outcomes at six-month follow-up, measured as negative urinalysis for stimulant (aOR=5.3; 95 % CI 3.6–7.7), and opioid (aOR=1.8; 95 % CI 1.3–2.6).

Conclusion: Baseline stimulant use is associated with worse MOUD treatment outcomes, underscoring the need for novel integrated interventions designed to address opioid and stimulant co-use.

1. Introduction

The "fourth wave" of the opioid epidemic is marked by a drastic increase in opioid and illicit stimulant (mainly cocaine and methamphetamine) co-use (Ahmed et al., 2022; Ciccarone, 2021). It has been estimated that opioid and stimulant co-use has increased by over 80 % in the last decade (Ellis et al., 2018; Goodwin et al., 2021), with a recent cross-sectional study conducted in 10 states between 2018 and 2020 finding that 75 % of people with current opioid addiction reported illicit stimulant use in the past 30-days (Tsui et al., 2023).

* Correspondence to: Health Education & Research Bldg. (HERB), Washington State University, PO Box 1495, Spokane, WA 99210-1495, USA.
E-mail address: cari.coles@wsu.edu (C. Coles).

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Medications for opioid use disorder (MOUD), such as methadone and buprenorphine, effectively manage opioid withdrawal and reduce misuse and overdose risk (Bell and Strang, 2020). However, some studies suggest that the simultaneous use of opioids and illicit stimulants can hinder the effectiveness of MOUD by negatively affecting treatment adherence, opioid abstinence and increasing the risk of overdose (Frost et al., 2021; Russell et al., 2023; Warfield et al., 2022).

Using data from a large, multisite randomized controlled trial (RCT) (Saxon et al., 2013), this study aims to add to this literature by examining the association among recent illicit stimulant use on opioid use outcomes, stimulant use outcomes, and treatment retention among individuals initiating MOUD treatment. Based on prior evidence, we hypothesized that patients initiating MOUD with a positive stimulant urinalysis (UA) would achieve worse treatment outcomes, when compared to those initiating MOUD with a negative stimulant UA (Frost et al., 2021; Russell et al., 2023; Smith et al., 2023).

2. Methods

2.1. Secondary data source

Cross-sectional secondary analyses were conducted using publicly available data (http://datashare.nida.nih.gov) from a multisite randomized controlled trial (RCT) sponsored by the National Institute on Drug Abuse Treatment Clinical Trials Network. The original study (n = 1269) compared the hepatotoxicity of 24 weeks of buprenorphine and methadone treatment for individuals seeking MOUD. Measures from this trial included weekly opioid and stimulant UA results during the 24-week intervention period and a six-month follow-up assessment. For a full description of the methodology, consort diagram, and primary outcomes of this study see Saxon et al.,. (2013).

2.2. Statistical analysis

Baseline demographics and clinical characteristics were compared by baseline stimulant UA result using ANOVA for continuous variables and chi square tests for categorical variables (presented in odds ratio).

To evaluate the predicative effect of baseline stimulant UA result on MOUD treatment response we conducted two multiple linear regressions and three multiple logistic regressions. For these models, each of the following measures were assigned separately as the primary outcome; total negative Stimulant UAs submitted during treatment; total negative opioids UAs submitted during treatment, treatment completion (retained until the 24th week of treatment), negative stimulant UA result at 6-month follow-up, and negative opioid UA result at 6-month follow-up. For all models, baseline stimulant UA result was assigned as the primary predictor of interest while baseline opioid UA result, treatment condition (methadone or buprenorphine), age, sex, and race/ethnicity were assigned as pre-specified covariates. In addition, we ran these same models stratified by treatment condition (i.e., buprenorphine and methadone) to explore the impact of baseline stimulant UA result on treatment outcomes when being treated with either medication. For all analyses, inferential results are presented as adjusted odds ratios (aOR) with 95 % confidence intervals (CI) for binary outcomes, and unstandardized regression coefficients (β) with 95 % CI for continuous outcomes. Analyses were conducted using STATA 15 with the alpha level set at 0.05. For the purpose of this study, only associations between the treatment outcomes and the primary predictor of interest (i.e., baseline stimulant UA result) are presented.

Lastly, we conducted Kaplan-Meier survival analysis to explore the impact of baseline stimulant UA result on treatment retention. Analyses were conducted using STATA 15 with the alpha level set at 0.5.

3. Results

3.1. Baseline characteristics

As can be seen in Table 1, of the total sample of 1269 participants, 543 (42.8 %) had a stimulant positive UA at baseline, while 726 (57.2 %) tested negative for stimulants. The baseline characteristics of the participants showed that those with a stimulant positive urinalysis were significantly more likely to be assigned to the methadone treatment group (OR=1.4, $p < 0.01$), to identify as Black (OR=2.0, $p < 0.01$), and to have a diagnosis of stimulant use disorder (OR=3.5, $p < 0.01$). Additionally, they were more likely to test positive for opioids at baseline (OR=3.1, $p < 0.01$). No significant differences were found between the groups for other demographic variables such as age, sex, or other substance use disorders.

3.2. Treatment outcomes

As can be seen in Table 2, participants with a stimulant negative UA at baseline submitted on average more stimulant negative UAs during treatment (β=7.8, 95 % CI 6.8–8.7), more opioid negative UAs during treatment (β=2.8, 95 % CI 1.8–3.8), and were more likely to complete the 24 weeks of treatment (aOR=1.4, 95 % CI 1.1–1.7) when compared to those with a stimulant positive baseline UA. At the six-month follow-up, participants with a stimulant negative UA at baseline were also more

Table 1
Baseline Characteristics by Baseline Stimulant Urinalysis Result.

	Total Sample (n = 1269)	Stimulant Negative Baseline UA (n = 726; 57.21 %)	Stimulant Positive Baseline UA (n = 543; 42.79 %)	OR/ F*	P-Value
Treatment (n (%))					
Buprenorphine	740 (58.3)	448 (61.7)	292 (53.8)	**1.4**	**0.005**
Methadone	529 (41.7)	278 (38.3)	251 (46.2)		
Age, (Mean ± SD)	37.4 ± 11.1	36.4 ± 11.3	38.9 ± 10.7	1.7*	0.198
Sex (n (%))				1.1	0.591
Male	861 (67.9)	497 (68.5)	364 (67.1)		
Female	408 (32.2)	229 (31.5)	179 (33)		
Race/Ethnicity (n (%))					
White	892 (70.3)	516 (71.1)	376 (69.3)	1.1	0.480
Hispanic	206 (16.2)	127 (17.5)	79 (14.6)	1.3	0.160
Black	114 (9)	47 (6.5)	67 (12.3)	**2**	**0.001**
Others*	57 (4.5)	36 (5)	21 (3.9)	1.3	0.354
DSM Diagnosis (n (%))					
Stimulant Use Disorder	422 (33.5)	173 (23.8)	249 (45.9)	**3.5**	**0.001**
Cannabis Use Disorder	223 (17.6)	136 (18.7)	87 (16)	0.9	0.571
Alcohol Use Disorder	251 (19.7)	150 (20.7)	101 (18.6)	0.9	0.872
Sedative Use Disorder	153 (12.1)	96 (13.2)	57 (10.5)	0.9	0.353
Smokes Tobacco	737 (58.1)	399 (55)	338 (62.3)	1.2	0.225
Positive Urinalysis (n (%))					
Benzodiazepine	236 (18.6)	126 (17.4)	110 (20.3)	1.2	0.189
Opiate	1103 (86.9)	596 (82.1)	507 (93.4)	**3.1**	**0.001**
THC	300 (23.6)	171 (23.6)	129 (23.8)	1	0.933

N = Sample; UA = Urinalysis; SD= Standard Deviation; OR = Odds Ratio; * = F-statistic;
Bold = statistically significant;
* Others under Race/Ethnicity includes all races and ethnicities that were marked other than "white," "black," or "Hispanic."

Table 2
Treatment Response by Baseline Stimulant Urinalysis Result.

For the Total Sample	Stimulant Negative Baseline UA (n = 726)	Stimulant Positive Baseline UA (n = 543)	β	aOR	95 % CI	p-value
Total negative Stimulant UAs submitted during treatment, mean (SD)	12.4 (9.1)	4.9 (6.9)	**7.8**	-	6.8 – 8.7	**0.001**
Total negative Opiate UAs submitted during treatment, mean (SD)	10.7 (9.1)	7.6 (8)	**2.8**	-	1.8 – 3.8	**0.001**
Treatment Completion, *n* (%)	549 (69.1)	306 (64.6)	-	**1.4**	1.1 – 1.7	**0.019**
Negative Stimulant UA at 6-month follow-up, *n* (%)	296 (79.6)	86(40.8)	-	**5.3**	3.6 – 7.7	**0.001**
Negative Opiate UA at 6-month follow-up, *n* (%)	258 (69.2)	109 (51.7)	-	**1.8**	1.3 – 2.6	**0.002**
For those Receiving Buprenorphine Treatment	(n = 488)	(n = 252)				
Total negative Stimulant UAs submitted during treatment, mean (SD)	10.7 (8.9)	4.1 (6.4)	**6.5**	-	5.2 – 7.8	**0.001**
Total negative Opiate UAs submitted during treatment, mean (SD)	9.4 (9.1)	6.7 (8.1)	**2.4**	-	1.1 – 3.7	**0.001**
Treatment Completion, n (%)	307 (62.9)	148 (58.7)	-	1.2	0.9 – 1.7	0.149
Negative Stimulant UA at 6-month follow-up, n (%)	135 (76.3)	39 (47.6)	-	**3.2**	1.8 – 5.7	**0.001**
Negative Opiate UA at 6-month follow-up, n (%)	118 (66.7)	45 (54.9)	-	1.5	0.8 – 2.6	0.176
For those Receiving Methadone Treatment	(n = 307)	(n = 222)				
Total negative Stimulant UAs submitted during treatment, mean (SD)	15.2 (8.7)	5.7 (7.3)	**9.3**	-	7.9 – 10.8	**0.001**
Total negative Opiate UAs submitted during treatment, mean (SD)	12.6 (8.7)	8.7 (7.7)	**3.3**	-	1.9 – 4.7	**0.001**
Treatment Completion, n (%)	242 (78.8)	158 (71.2)	-	**1.7**	1.1 – 1.7	**0.034**
Negative Stimulant UA at 6-month follow-up, n (%)	161 (82.6)	47 (36.4)	-	**7.6**	4.5 – 12.9	**0.001**
Negative Opiate UA at 6-month follow-up, n (%)	140 (71.4)	64 (49.6)	-	**2.2**	1.4 – 3.7	**0.001**

UA= urinalysis; aOR = adjusted odds ratio; CI = confidence interval; SD = standard deviation
β= unstandardized regression coefficients; **Bold** = statistically significant

likely to have a stimulant negative UA (aOR=5.3, 95 % CI 3.6–7.7) and an opioid negative UA (aOR=1.8, 95 % CI 1.3–2.6) when compared to those with a stimulant positive baseline UA. Among those receiving buprenorphine treatment, participants with a stimulant negative UA at baseline submitted on average more stimulant negative UAs during treatment (β=6.5, 95 % CI 5.2 – 7.8), more opioid negative UAs during treatment (β=2.4, 95 % CI 1.1 – 3.7), and were more likely to submit a stimulant negative UA at the 6-month follow-up assessment (aOR=3.2, 95 % CI 1.8 – 5.7). Among those receiving methadone treatment, participants with a baseline negative stimulant UA submitted on average more stimulant negative UAs (β= 9.3, 95 % CI 7.9 – 10.8) and more opioid negative UAs during treatment (β=3.3, 95 % CI 1.9–4.7). They were also more likely to complete the 24 weeks of treatment (aOR=1.7, 95 % CI 1.1 – 1.7), and to submit negative stimulant (aOR= 7.6, 95 % CI 4.5 – 12.9) and opioid (aOR=2.2, 95 % CI 1.4–3.7) UAs at the 6-month follow-up assessment, when compared to those with a baseline positive stimulant UA.

Lastly, as can be seen in Fig. 1, our survival analysis indicates no significant effect of baseline stimulant UA result on treatment retention for the entire sample, nor among those receiving buprenorphine or methadone treatment.

4. Discussion

Opioid and illicit stimulant co-use has increased dramatically in the last decade (Ellis et al., 2018; Goodwin et al., 2021) and is directly associated with worse MOUD treatment outcomes (Frost et al., 2021; Russell et al., 2023). Almost half of the sample (42.8 %) tested positive for stimulants at baseline, highlighting the high prevalence of opioid and stimulant co-use among individuals initiating MOUD treatment. As hypothesized, and consistent with the existing literature (Frost et al., 2021; Russell et al., 2023), our findings highlight the significant association between recent illicit stimulant use and worse treatment outcomes (i.e., opioid use, illicit stimulant use) among individuals undergoing MOUD treatment. In addition, the lower rates of opioid and stimulant abstinence (confirmed via UA results) at the 6-month follow-up, points to a long-term negative effect of illicit stimulant co-use on MOUD treatment response. It is mentionable that some studies have found that prescription stimulants, such as those for attention deficit hyperactive disorders, may lead to improved buprenorphine treatment retention among people with opioid addiction (Mintz et al., 2022; Tardelli et al., 2023). Therefore, it is important to make a distinction between prescribed and illicit stimulant use among individuals receiving MOUD.

When considering our stratified analyses, we have observed that the treatment completion outcome did not differ significantly by baseline stimulant UA result for those receiving buprenorphine treatment. In addition, the effect of baseline stimulant UA result observed for all outcomes (i.e., β and aOR) were smaller for those receiving buprenorphine treatment than those receiving methadone treatment. Such findings may suggest that baseline stimulant UA result may have a more pronounced effect on treatment response among those receiving

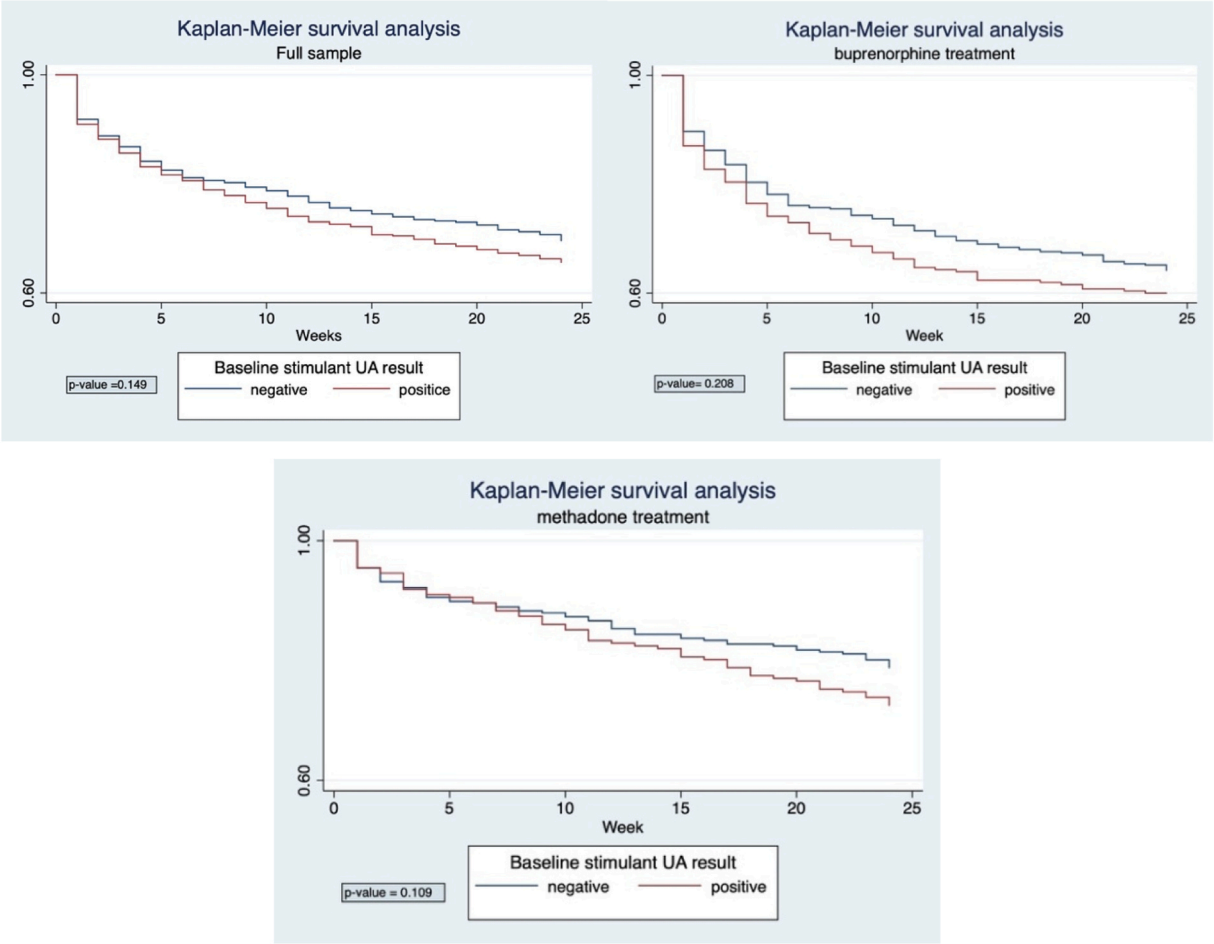

Fig. 1. Kaplan-Meier survival analysis: Treatment Retention by baseline stimulant UA result.

methadone treatment when compared to those receiving buprenorphine treatment.

Lastly, different from our initial hypothesis and the existing literature (Frost et al., 2021; Russell et al., 2023), we did not observe an effect of baseline stimulant UA result on treatment retention. While the reasons for this are unclear, such findings suggest that baseline stimulant UA result may play a more prominent role in stimulant and opioid use rather than on treatment retention.

Overall, our findings suggest that routine screening for illicit stimulant use at the initiation of MOUD treatment should be encouraged as it may be key in identifying individuals at higher risk of poor treatment outcomes and those that may require additional support to respond favorably to MOUD treatment.

4.1. Strengths and limitations

Among the strengths of this study are the availability of urinalysis results for stimulant and opioid use, large sample size (n = 1269), the long duration of the intervention phase (24-weeks), and the conduct of the study across multiple MOUD treatment programs (9 sites). However, some important limitations should be taken into consideration when evaluating our findings. First, data collection for this study was completed in 2010, which may not fully reflect current trends and patterns of opioid and stimulant co-use. Second, the dataset lacked detailed demographic information, such as education, job status, and financial status, which could provide a more comprehensive understanding of participants' clinical profile. Third, we were unable to adjust our analyses for site differences due to the process of stripping site identification out of the data prior to releasing it to the public. Fourth, our study had a substantial number of missing data at the 6-month-follow-up assessments (around 50 %). In that regard, it is possible that stimulant-co use and within treatment outcome responses may have influenced patients' attrition from the studies. As such, it is important to consider that different results might have been seen if data from these participants were included in these analyses. Finally, this study examined the cross-sectional associations between our primary predictor of interest and treatment outcomes, which does not allow us to make any inference pertaining to causality.

5. Conclusions

Given the rising prevalence of opioid and illicit stimulant co-use in the United States and its negative effect on MOUD treatment response, it is imperative to develop and evaluate novel treatment approaches to improve MOUD treatment outcomes among this population. Research indicates that the combination of MOUD with evidence-based stimulant use treatments, such as contingency management, may offer a promising solution. Bolívar et al. (2021) conducted a systemic review and meta-analysis which demonstrated the effectiveness of contingency management in promoting treatment retention and reducing stimulant use among individuals receiving MOUD. These findings suggest that integrating contingency management could enhance overall treatment outcomes, addressing both opioid and stimulant use in a more holistic manner. Therefore, incorporating more evidence-based stimulant use treatments, like contingency management, could serve as a potential solution for improving MOUD treatment outcomes in individuals with

opioid and illicit stimulant co-use.

CRediT authorship contribution statement

Coles Cari: Writing – review & editing, Writing – original draft, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Bae Joanne:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Batts Courtney:** Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Schmidt Alex:** Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **León Gabriela:** Writing – review & editing, Investigation, Conceptualization. **Smith Crystal L:** Writing – review & editing, Supervision, Project administration, Methodology, Formal analysis. **McPherson Sterling M:** Writing – review & editing, Supervision, Resources. **Miguel André C.:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Sterling M. McPherson reports a relationship with Alkermes Inc that includes: consulting or advisory. Sterling M. McPherson reports a relationship with Altimmune Inc that includes: consulting or advisory. Sterling M. McPherson reports a relationship with Idorsia Pharmaceuticals Ltd that includes: consulting or advisory. Sterling M. McPherson reports a relationship with Managed Health Connections that includes: funding grants. Sterling M. McPherson reports a relationship with Optimize Health that includes: funding grants. Sterling M. McPherson is an Associate Editor at Drug and Alcohol Dependence Reports but was not involved in the management or review of this manuscript. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Co-author Sterling M. McPherson has the following disclosure:

Sterling M. McPherson is an Associate Editor at Drug and Alcohol Dependence Reports but was not involved in the management or review of this manuscript. He has consulted for Alkermes, Altimmune, and Idorsia biopharmaceutical companies. He has also received funding from Managed Health Connections and Optimize Health that originated with NIH. This funding is in no way related to what is reported here.

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