Published in final edited form as:

Int J Drug Policy. 2017 November ; 49: 32–40. doi:10.1016/j.drugpo.2017.07.009.

Polydrug use and its association with drug treatment outcomes among primary heroin, methamphetamine, and cocaine users

Linwei Wang¹, Jeong Eun Min¹, Emanuel Krebs¹, Elizabeth Evans^{2,3}, David Huang², Lei Liu⁴, Yih-Ing Hser², and Bohdan Nosyk^{1,5}

¹BC Centre for Excellence in HIV/AIDS, 608-1081 Burrard Street, Vancouver, BC Canada V6Z 1Y6

²UCLA Integrated Substance Abuse Programs, 11075 Santa Monica Blvd., Ste. 200, Los Angeles, CA USA 90025

³Centre for the Study of Healthcare Innovation, Implementation & Policy, Veterans Affairs Health Service Research & Development, Greater Los Angeles Healthcare System, 1301 Wilshire Blvd (111G), Los Angeles, CA USA 90073

⁴Feinberg School of Medicine, Northwestern University, 303 E Chicago Ave, Chicago, IL USA 60611

⁵Faculty of Health Sciences, Simon Fraser University, Blusson Hall, 8888 University Drive, Burnaby, BC Canada V5A 1S6

Abstract

Background—Polydrug use may challenge effective treatment for substance use disorders. We evaluate whether secondary substance use modifies the association between treatment and primary drug use among primary heroin, cocaine and methamphetamine (MA) users.

Methods—Data were obtained from prospective cohort studies on people who use illicit drugs (PWUD) in California, USA. Using repeated monthly data on self-reported secondary substance use (heroin, cocaine, MA, alcohol or marijuana; 1 day in a month), primary drug use (1 day in a month), and treatment participation, collected via timeline follow-back, we fitted generalized linear mixed multiple regression models controlling for potential confounders to examine the

Corresponding Author: Bohdan Nosyk, PhD, BC Centre for Excellence in HIV/AIDS, St. Paul's Hospital, 613-1081 Burrard St., Vancouver, BC, Canada V6Z 1Y6, bnosyk@cfeet.ubc.ca, T: 604-806-8649, F: 604-806-8649.

Contributors: LW designed the study, performed analyses, and drafted the manuscript. JEM designed the study, managed data, performed analyses, and revised the manuscript. EK interpreted the results and drafted the manuscript. EE revised the manuscript and provided critical comments. DH revised the manuscript and provided critical comments. LL revised the manuscript and provided critical comments. YH revised the manuscript and provided critical comments. BN designed the study, interpreted the results, revised the manuscript and provided critical comments. LW and JEM had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. All authors approved of the final manuscript.

The authors declared no conflict of interest.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

interactions between treatment and secondary substance use on the odds of primary heroin, cocaine and MA use, respectively.

Results—Included in our study were 587 primary heroin, 444 primary MA, and 501 primary cocaine users, with a median of 32.4, 13.3 and 18.9 years of follow-up, respectively. In the absence of secondary substance use, treatment was strongly associated with decreased odds of primary drug use (adjusted odds ratios (aORs): 0.25, 95% CI: 0.24, 0.27, 0.07 (0.06, 0.08), and 0.07 (0.07, 0.09)) for primary heroin, MA, and cocaine users, respectively. Secondary substance use of any kind moderated these associations (0.82 (0.78, 0.87), 0.25 (0.21, 0.30) and 0.53 (0.45, 0.61), respectively), and these findings were consistent for each type of secondary substance considered. Moreover, we observed different associations in terms of direction and magnitude between secondary substance use and primary drug use during off-treatment periods across substance types.

Conclusions—This study demonstrates secondary substance use moderates the temporal associations between treatment and primary drug use among primary heroin, MA and cocaine users. Disparate patterns of polydrug use require careful measurement and analysis to inform targeted treatment for polydrug users.

Keywords

Polydrug use; heroin; cocaine; methamphetamine; alcohol; marijuana; treatment

1. Introduction

Heroin, cocaine, and methamphetamine (MA) have among the highest global burden of disease among illicit drugs (Degenhardt et al., 2013) and are associated with severe public health and social consequences such as mortality, morbidity, and criminality (Y. I. Hser, Evans, Huang, Brecht, & Li, 2008; UNODC, 2012; Wang et al., 2016). In addition, high levels of polydrug use have been reported among people who use illicit drugs (PWUD) in a wide variety of treatment and community settings internationally (Ball & Ross, 1991; Booth, Leukefeld, Falck, Wang, & Carlson, 2006; Byqvist, 2006; Darke & Hall, 1995; Ives & Ghelani, 2006; Leri, Bruneau, & Stewart, 2003; Leri et al., 2005). Compared to mono-drug use, polydrug use has been associated with greater psychopathology (Booth, et al., 2006; Medina & Shear, 2007; Sumnall, Wagstaff, & Cole, 2004); higher levels of risky health behaviors (Patterson, Semple, Zians, & Strathdee, 2005); decreased cognitive functioning (Dillon, Copeland, & Jansen, 2003); poorer treatment engagement (John, Kwiatkowski, & Booth, 2001) and treatment outcomes (Bovasso & Cacciola, 2003; DeMaria, Sterling, & Weinstein, 2000; Williamson, Darke, Ross, & Teesson, 2006b); and increased non-fatal overdoses as well as drug-related deaths (Coffin et al., 2003; Strang et al., 1999).

Treatment for opioid use disorders in the form of non-time limited opioid agonist treatment has been shown to be effective in numerous randomized trials, meta-analyses, and large-scale longitudinal studies (Amato et al., 2005; Faggiano, Vigna-Taglianti, Versino, & Lemma, 2003; Mattick, Kimber, Breen, & Davoli, 2008); however, the evidence for effective treatment of cocaine or MA use disorders is not as clear (Fischer et al., 2015). While psychosocial treatment has shown varying degrees of promise in clinical trials (Courtney &

Ray, 2014; Pérez-Mañá, Castells, Vidal, Casas, & Capellà, 2011), the search for pharmacological treatment for cocaine or MA use has yet to produce an effective medication (Brensilver, Heinzerling, & Shoptaw, 2013; Kishi, Matsuda, Iwata, & Correll, 2013; Minozzi et al., 2015). Development of effective treatment strategies for people who use multiple illicit drugs, or polydrug users, is further challenged by the variety of substances combinations and patterns of use (European Monitoring Centre for Drugs and Drug Addiction, 2009; Ives & Ghelani, 2006). As a consequence, clinical guidelines provide minimal guidance on the management and impact of polydrug use (American Psychiatric Association, 2006; Management of Substance Use Disorders Working Group, 2015; National Institute on Drug Abuse, 2012). For instance, the only suggestion found in treatment guidelines from the US Veterans Health Department and the National Institute on Drug Abuse was to manage multiple substance use disorders according to the recommendations made for each of those individual disorders (Management of Substance Use Disorders Working Group, 2015; National Institute on Drug Abuse, 2012).

Previous studies have mainly evaluated the relationships between cocaine use and treatment outcomes among heroin dependent individuals. For example, prior observational studies have shown that cocaine use was associated with increased heroin use at treatment entry, poorer treatment outcomes including retention, and subsequent relapse into heroin use (Hartel et al., 1995; Sullivan et al., 2010; Termorshuizen, Krol, Prins, & van Ameijden, 2005; Williamson, Darke, Ross, & Teesson, 2006a; Williamson, et al., 2006b) among patients receiving opioid agonist treatment. However, there is substantially less evidence regarding polydrug use and treatment outcomes among individuals primarily use cocaine or MA. Furthermore, the majority of PWUD concurrently use alcohol or marijuana (Brecht, Huang, Evans, & Hser, 2008). One review study revealed that alcohol use post-drug treatment increased relapse to drug use, but evidence regarding whether alcohol could become a substitute addiction remained inconclusive (Staiger, Richardson, Long, Carr, & Marlatt, 2013). Evidence on the association between marijuana use and drug treatment outcomes also produced conflicting results, with some demonstrating beneficial effects and others showing an adverse impact (Zielinski et al., 2016)

We take advantage of a unique set of California-based prospective cohort studies, which tracked monthly drug use and treatment receipt for as long as three decades for PWUD characterized by the primary use of heroin, cocaine and MA. We considered the use of any substance other than the primary drug as secondary substance use, including heroin, cocaine, MA, alcohol and marijuana. Polydrug use was thus defined as self-reported use of any two substances in a given month during study follow-up. We conducted this study to test the hypothesis that secondary substance use would moderate the associations, if treatment was associated with decreased odds of primary drug use. In addition, we examined the relationships between secondary substance use and primary drug use in the absence of treatment to investigate natural polydrug use patterns.

2. Methods

2.1 Study design and subjects

Data were derived from four non-overlapping studies that collected monthly information of adult PWUD in California using the Natural History Interview (NHI): (1) the 33-year Civil Addict Program (CAP) (Y. I. Hser, Hoffman, Grella, & Anglin, 2001); (2) the cocaine treatment evaluation study (CTE) (Y. I. Hser et al., 2006); (3) the methamphetamine natural history study (METH) (Brecht, O'Brien, von Mayrhauser, & Anglin, 2004); and (4) the treatment process study (TXPR) (Y. I. Hser, Huang, Teruya, & Anglin, 2004), with baseline assessments executed in 1964, 1988–1989, 1995–1997, and 1995 respectively, and the last year of follow-up in 1997, 2002–2003, 1999–2002, and 1996 respectively. All studies recruited subjects from treatment settings only, and baseline drug use profiles across studies were previously presented (Nosyk et al., 2014).

We included all participants from the four studies and classified them into primary heroin, cocaine, and MA use categories according to the definitions adopted by the original studies (Brecht, et al., 2004; Y. I. Hser, et al., 2001; Y. I. Hser, et al., 2004; Y. I. Hser, Huang, Teruya, & Douglas Anglin, 2003; Y. I. Hser, et al., 2006). The primary drug use classification was determined at baseline by the drug for which the subject was receiving treatment. Such classification of primary drug use was found to present valid information about drug use patterns over time (Brecht, et al., 2008). In the current study, we analyzed participants' drug use histories from their first use of the primary drug. We excluded observations (15.5%) during incarceration because drug use information was not available for all studies during these periods.

Use of these data for the current analysis was reviewed and approved by the University of California Los Angeles Institutional Review Board.

2.2 Instruments/Measures

All four studies collected information using the NHI, which was adapted from instruments designed by Nurco and colleagues (Nurco, Bonito, Lerner, & Balter, 1975) and has been used with various drug-using populations. It was designed to collect retrospective longitudinal quantitative data on drug use and related behaviors. The instrument consists of "static" and "dynamic" forms that permit the capture of longitudinal, sequential data on drug use, employment, criminal involvement, treatment, and other behaviors over the life course of research participants (McGlothlin, Anglin, & Wilson, 1977). Using an illustrated timeline, the interviewee notes major life events and then identifies time periods associated with specific behaviors, with periods delineated by changes in behavior. These reported data are translated to longitudinal data of behaviors for each month. The NHI has been shown to have generally high reliability; correlation coefficients of inter-variable relationships, based on 46 variables measured at two interviews 10 years apart, ranged as high as 0.86 and 0.90 (Anglin, Hser, & Chou, 1993; Chou, Hser, & Anglin, 1996; Y.I. Hser, Anglin, & Chou, 1992).

For the purpose of the current study, self-reported substance use and treatment information within the same month based on the NHI data was used to construct the variables of interest.

The primary outcome of interest was a binary variable capturing any primary drug use (use for 1 day in a month) for the primary heroin, MA and cocaine use categories, respectively. Given the short timeframe between repeated measures, primary drug use measured in the current and subsequent month were highly correlated (*Pearson* correlation coefficient >0.95), and analyses performed using outcomes measured at both time points provided similar results.

The main covariates of interest were treatment participation and secondary substance use. Treatment participation was a binary variable capturing monthly self-reported treatment for the primary drug of use 1 day in the treatment, including all treatment modalities: opioid agonist treatment with methadone, inpatient, outpatient and residential treatment. We constructed binary variables capturing secondary substance use, defined as use for 1 day in a month of any other substance than the primary drug, including heroin, cocaine, MA, alcohol, and marijuana. In addition, several binary variables were created to capture secondary alcohol use (1 day in a month), secondary marijuana use (1 day in a month), and secondary illicit drug use (1 day in a month). Secondary illicit drugs including heroin, MA or cocaine were grouped together due to the small numbers of observations available.

In addition, we considered a range of individual characteristics as potential confounders, including age of first drug use, gender, race/ethnicity, marital status, highest completed level of education and employment. We also considered any history of incarceration as it has been shown to influence drug use behaviors (Farrington, 2003), calendar year (1960's, 1970's, 1980's, 1990's and after) and study cohort from which the individual-level data was drawn.

2.3 Statistical analysis

Our statistical analysis proceeded in four steps. First, we assessed the characteristics of study participants by primary drug type. Second, we described substance use patterns by examining the frequency of possible combinations of secondary substance use among all available monthly observations, stratified by treatment participation.

Third, we employed generalized linear mixed multiple regression models (GLMMs) (Raudenbush & Bryk, 2002) with a logit link, binomial distribution and random intercept to investigate the association between treatment participation and primary drug use for each primary drug group, measured within the same month. We first examined the association between treatment and primary drug use adjusting for the secondary substance use. To examine whether secondary substance use modified the association, we conducted the following models. First, we examined the interaction between treatment and any secondary substance use; we then examined the interaction between treatment and each type of secondary substance use, adjusting for the use of other secondary substances. In each model, we controlled for the covariates described above.

Fourth, we investigated the associations between secondary substance use and primary drug use in the absence of treatment using GLMMs, to explore natural polydrug use patterns. The models included each type of secondary substance use as a binary variable, adjusting for each other and the same set of covariates as previous models.

Finally, in order to assess the robustness of the results, we repeated analyses in steps three and four on daily primary drug use (<28 days vs <28 days in a month). All statistical analyses were executed in SAS version 9.4.

3. Results

A total of 1,532 participants were included in the study, including 587 primary heroin users, 444 primary MA users, and 501 primary cocaine users, with 159,240, 27,573 and 131,667 monthly observations, respectively.

As shown in Table 1, primary heroin users were mainly Hispanic (53.7%), male (91.5%), divorced or separated (57.0%), with less than a high school education (47.5%), and initiated heroin use prior to 1970 (84.0%) at a median age of 18. In contrast, primary MA users were primarily white (52.5%), male (52.0%), divorced or separated (95.0%), with a college education (34.5%), and initiated MA use in the 1980's and 1990's (80.8%) at a median age of 18. Most primary cocaine users were black (66.1%), male (75.6%), divorced or separated (56.8%), with a college education (45.2%), and initiated cocaine use in the 1970's and 1980's (90.2%) at a median age of 22. Over a median follow-up of 32.4, 13.3 and 18.9 years respectively, 91.8% of primary heroin users, 57.2% of primary MA users, and 42.3% of primary cocaine users had ever been incarcerated.

The patterns of substance use among each primary drug group were summarized in Table 2. The majority of primary heroin, MA and cocaine users (89.6%, 95.0% and 93.4% respectively) concurrently used two or more substances in the same month over study follow-up. For primary heroin users, the most common drug use pattern was heroin use only, followed by the concurrent use of heroin and alcohol at the same month, each comprising 27.4% and 17.2% of all monthly observations. For primary MA users, the most common drug use pattern was concurrent use of MA, alcohol and marijuana (15.2%), followed by the use of MA only (10.9%), and the concurrent use of MA and alcohol (10.2%). For primary cocaine users, concurrent use of cocaine, alcohol and marijuana was the most common (18.0%), followed by the concurrent use of cocaine and alcohol (16.2%), and the concurrent use of alcohol and marijuana (11.3%). Table 2 also showed that a small proportion of time was spent on treatment among each primary drug group, with the proportion on treatment among all monthly observations being 17.3%, 5.3% and 5.7% for primary heroin, MA, and cocaine users, respectively.

Results of the multiple regression analyses are presented in Table 3. We found secondary substance use consistently moderated associations between treatment and primary drug use. During months without any secondary substance use, treatment was strongly associated with decreased odds of primary drug use. The adjusted odds ratios (aORs) were 0.25 (95% confidence interval (CI): 0.24, 0.27), 0.07 (0.06, 0.08), and 0.07 (0.07, 0.09) for primary heroin, MA, and cocaine users, respectively. With the use of any secondary substance, the adjusted odds ratios were 0.82 (0.78, 0.87), 0.25 (0.21, 0.30) and 0.53 (0.45, 0.61) for primary heroin, MA, and cocaine users, respectively. In addition, the findings were consistent for each type of secondary substance use. Without secondary use of alcohol, marijuana or secondary illicit drugs, respectively, treatment was associated with decreased

odds of primary drug use; however, these associations were smaller or non-significant in the presence of the secondary use of alcohol, marijuana or other drugs (Table 3). Moreover, results from our sensitivity analyses on daily primary drug use supported the main findings (Table S1).

Table 4 shows the relationship between secondary substance use and the use of primary drug, in the absence of treatment. We found secondary cocaine and MA use were associated with increased odds of primary heroin use (3.60 (3.30, 3.91), 1.16 (1.07, 1.27), respectively), while secondary alcohol and marijuana use were associated with decreased odds of primary heroin use (0.77 (0.73, 0.80)), 0.92 (0.87, 0.98), respectively). In contrast, secondary heroin, alcohol and marijuana use were associated with increased odds of primary MA use (6.72 (5.71, 7.91), 3.31 (3.12, 3.52) and 5.95 (5.57, 6.36), respectively). Similarly, secondary heroin, alcohol and marijuana use were associated with increased odds of primary cocaine use (4.21 (3.78, 4.68), 9.56 (9.06, 10.1) and 1.09 (1.04, 1.14), respectively), although effect sizes differed greatly. Our results from the sensitivity analyses on daily primary drug use generally supported the main findings, except that secondary MA use was associated with increased odds of primary heroin use (1.16 (1.07, 1.27)), but associated with decreased odds of daily primary heroin use (0.52 (0.48, 0.56)). In addition, any MA use and any cocaine use were not associated among both primary MA and primary cocaine users, but they were associated with decreased odds of daily use of the other drug (0.78 (0.73, 0.83), 0.65 (0.57, 0.74), respectively).

4. Discussion

To summarize, despite observing varying associations between secondary substance use and primary use of heroin, MA or cocaine, secondary substance use consistently moderated the temporal associations between treatment and primary drug use.

Our findings suggest that secondary substance use compromises the effects of drug treatment. Existing evidence supports that use of cocaine compromises treatment outcomes among heroin users, including poorer treatment retention and increased risk of heroin use relapse (Bovasso & Cacciola, 2003; DeMaria, et al., 2000; Downey, Helmus, & Schuster, 2000; Hartel, et al., 1995; Sullivan, et al., 2010; Termorshuizen, et al., 2005; Williamson, et al., 2006a, 2006b). Brecht et al. found secondary use of cocaine or heroin was associated with not completing treatment among MA users (Brecht, Greenwell, & Anglin, 2005), which was in line with our results, although treatment participation rather than completion was measured in the current study. Evidence was less consistent, however, regarding the impact of alcohol use or marijuana use on drug treatment outcomes (Ottomanelli, 1999; Staiger, et al., 2013; Zielinski, et al., 2016). Ottomanelli conducted a literature review on alcohol use by methadone patients and found no evidence that alcohol abuse diminished treatment retention (Ottomanelli, 1999). On the other hand, a more recent review revealed that alcohol use increased the likelihood of relapse to drug use (Staiger, et al., 2013). Similarly, Wasserman et al. found marijuana use was associated with greater risk of relapse to heroin use among individuals on opioid agonist treatment (Wasserman, Weinstein, Havassy, & Hall, 1998), while Epstein and Preston did not observe an association between marijuana use and treatment retention (Epstein & Preston, 2003). The heterogeneous findings

might be partially explained by the different treatment outcome measures used. Regardless, our findings serve to further underline the importance of screening for ongoing multiple substances use among PWUD who initiate treatment. Existing drug treatment programs should be equipped to deal with people who use polydrugs.

In addition, we found high levels of alcohol and marijuana use among all groups. Both secondary alcohol and marijuana use were positively associated with primary MA use, and primary cocaine use. These results were consistent with several previous studies (Barrett, Darredeau, & Pihl, 2006; Brecht, et al., 2008; Bujarski et al., 2014; Furr, Delva, & Anthony, 2000; McKay, Alterman, Rutherford, Cacciola, & McLellan, 1999) and might indicate users' desire to counterbalance the effects of stimulant use (Brecht, et al., 2008). In contrast, there appeared to be negative associations between secondary alcohol and marijuana use with primary heroin use. One recent study also reported reduced opioid use frequency among people who inject drugs in California who also used marijuana compared to who did not (Kral et al., 2015). However, the potential role of medical marijuana use as a harm reduction approach among opioid-using populations is still under debate and requires more research (Lucas et al., 2016). Anglin et al. (Anglin, Almog, Fisher, & Peters, 1989) and Almog et al. (Almog, Anglin, & Fisher, 1993) found an inverse relationship between alcohol use and heroin use among heroin dependent individuals in opioid treatment programs in California and the pattern was evident in addiction, treatment and post-discharge stages of individuals' drug use career (Anglin, et al., 1989). The inverse pattern suggested that primary heroin users might substitute alcohol for heroin to compensate for a reduction in their use of heroin (Almog, et al., 1993). The strong negative association between secondary alcohol use and daily primary heroin use observed in our study further supported this.

Moreover, our results of the positive association between heroin and cocaine use are consistent with heroin-cocaine co-use patterns previously reported in the literature (Brecht, et al., 2008; Kreek, 1997; Leri, et al., 2003; Leri, et al., 2005; Roy, Richer, Arruda, Vandermeerschen, & Bruneau, 2013). Brecht *et al.* (Brecht, et al., 2008) found the average days of use per month of heroin and cocaine were positively related for primary heroin and cocaine users. Simultaneous use of heroin and cocaine in the form of "speedball" is also common (Leri, et al., 2003). Moreover, heroin users often report the sequential use of cocaine after heroin to enhance euphoria or to reduce the withdrawal symptoms experienced during their typical day (Leri, et al., 2003) or to counteract the physical depressive effects of opioids (Roy, et al., 2013). Cocaine users also sequentially use cocaine followed by heroin to self-mediate side effects of chronic cocaine administration (Kreek, 1997).

Cocaine and MA are the most prevalent stimulants among those with use disorders (Degenhardt et al., 2014) and are both characterized by intense and short-lived effects (National Institute on Drug Abuse; National Institute on Drug Abuse). While we found both drugs were associated with increased odds of any heroin use, MA use was strongly associated with decreased odds of daily heroin use as opposed to the positive association between cocaine and daily heroin use. We postulate that these differences could be partially driven by either or both following facts: (i) the drug half-life for MA is substantially longer than that of cocaine (National Institute on Drug Abuse; National Institute on Drug Abuse), which could explain different patterns of strategic co-use of these stimulants with heroin;

and (ii) the expansion of widespread availability of MA in the U.S. and California occurred during the 1990s (Gonzales, Mooney, & Rawson, 2010), a period after a vast majority of individuals in our study sample initiated first use of either substance.

Furthermore, our sensitivity analyses suggested that primary users of MA or cocaine may substitute one stimulant for another, findings that would appear intuitive given that the physical and mental effects of cocaine and MA use are similar (National Institute on Drug Abuse; National Institute on Drug Abuse). Markedly, secondary use of cocaine or MA was associated with decreased odds of daily primary use of the other. Our study represents a significant contribution to a previously-scarce evidence base on co-use patterns of these drugs (Cox, Jacobs, Leblanc, & Marshman, 1983; Ellinwood, Eibergen, & Kilbey, 1976) and helps clarify patterns of substitution and co-use among polydrug users.

Our study had several limitations that require consideration. First, our data came from self-reported interviews at a maximum 10-year intervals from which monthly records of drug use and other variables were constructed. Reports of days of drug use may be influenced by recall bias given the long duration between follow-up interviews, although recall bias was minimized by using records-based anchors. Recall may be differential for different drug types, and in periods with and without multiple drug use. Nonetheless, a comparison of drug use trajectories measured by days of use obtained using Addiction Severity Index and NHI data showed comparable temporal patterns of alcohol, heroin, cocaine, methamphetamine, and marijuana use, supporting these instruments' reliability for longitudinal examination of self-reported drug use (Murphy, Hser, Huang, Brecht, & Herbeck, 2010). In our analysis, we used binary classifications of drug use rather than the reported exact days of use, which could have reduced the recall bias. Sensitivity analysis on daily primary drug use also supported the findings from the main analysis on any primary drug use, further strengthening our results.

Second, we could not distinguish different treatment modalities in our dataset, a level of measurement error which was likely to differ across drug use groups and patients. We expected there be less variation in treatment programs for opioid users than stimulant users. No pharmacological treatment is available for stimulant use, and a heterogeneous mix of psychosocial treatment was likely captured in the 'treatment' indicator. Treatment for opioid use disorders may have incorporated some psychosocial treatment, however pharmacological treatment with methadone was likely a common feature across all programs. Third, although we considered both any and daily primary drug use in the analysis, we did not distinguish the frequency of non-primary drug use and potential impact of the secondary substance use frequency on the outcomes of interest. Fourth, although we controlled for a number of covariates which are potentially associated with the outcome, we could not rule out unmeasured confounding, potentially due to motivational and psychosocial characteristics, as well as measures of treatment adherence. Careful measurement of these factors in future studies may further inform the design and target clientele for multi-drug treatment programs. Lastly, the results might not reflect polydrug use patterns for other drug use populations, as our study samples represented three groups of people who primarily use heroin, cocaine, or MA in California. Our samples might not be representative of PWUD in the current drug use era, as they were primarily recruited in the

1960's, 1980's and 1990's for primary heroin, cocaine, and MA users respectively. However, samples of each primary drug use group were followed for an extended period (Table 1) and the current analysis might have captured the average drug use patterns over time. Our main findings that secondary substance use moderated the temporal associations between treatment and primary drug use were also consistent across three primary drug groups, despite differential recruitment periods. Otherwise, the treatment options for opioid users included primarily methadone maintenance treatment for our study periods, and the findings might not be generalizable to opioid agonist treatment using buprenorphine.

In conclusion, our results indicate that secondary substance use moderates the association between treatment and primary drug use among primary heroin, MA and cocaine users. Diverse polydrug use patterns should be carefully examined and the underlying pharmacological, psychosocial and behavioral reasons for certain substance combinations need to be better understood to inform the development of targeted treatment options for polydrug users.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by US National Institutes of Health, National Institute on Drug Abuse [R01DA032551]; and for the UCLA ISAP Center for Advancing Longitudinal Drug Abuse Research (CALDAR) [P30 DA016383]. Dr. Bohdan Nosyk is supported by a Michael Smith Foundation for Health Research Scholar award.

Abbreviations

MA	methamphetamine
CAP	the Civil Addict Program
CTE	the cocaine treatment evaluation study
METH	the methamphetamine natural history study
TXPR	the treatment process study
TUE	the treatment utilization and effectiveness study
NHI	Natural History Interview
GLMM	generalized linear mixed multiple regression model

References

- Almog YJ, Anglin MD, Fisher DG. Alcohol and Heroin Use Patterns of Narcotics Addicts - Gender and Ethnic-Differences. *American Journal of Drug and Alcohol Abuse*. 1993; 19(2):219–238. DOI: 10.3109/00952999309002682 [PubMed: 8484358]
- Amato L, Davoli M, Perucci CA, Ferri M, Faggiano F, Mattick RP. An overview of systematic reviews of the effectiveness of opiate maintenance therapies: available evidence to inform clinical practice and research. *J Subst Abuse Treat*. 2005; 28(4):321–329. [PubMed: 15925266]

- American Psychiatric Association. Practice Guideline for the Treatment of Patients With Substance Use Disorders Second Edition. 2006.
- Anglin MD, Almog IJ, Fisher DG, Peters KR. Alcohol-Use by Heroin-Addicts - Evidence for an Inverse Relationship - a Study of Methadone-Maintenance and Drug-Free Treatment Samples. *American Journal of Drug and Alcohol Abuse*. 1989; 15(2):191–207. DOI: 10.3109/00952998909092720 [PubMed: 2729226]
- Anglin MD, Hser YI, Chou CP. Reliability and Validity of Retrospective Behavioral Self-Report by Narcotics Addicts. *Evaluation Review*. 1993; 17(1):91–108. DOI: 10.1177/0193841x9301700107
- Ball, J., Ross, A. The effectiveness of methadone maintenance treatment. New York: Springer-Verlag; 1991.
- Barrett SP, Darredeau C, Pihl RO. Patterns of simultaneous polysubstance use in drug using university students. *Human Psychopharmacology-Clinical and Experimental*. 2006; 21(4):255–263. DOI: 10.1002/hup.766 [PubMed: 16783813]
- Booth BM, Leukefeld C, Falck R, Wang JC, Carlson R. Correlates of rural methamphetamine and cocaine users: Results from a multistate community study. *Journal of Studies on Alcohol*. 2006; 67(4):493–501. [PubMed: 16736068]
- Bovasso G, Cacciola J. The long-term outcomes of drug use by methadone maintenance patients. *Journal of Behavioral Health Services & Research*. 2003; 30(3):290–303. DOI: 10.1007/Bf02287318 [PubMed: 12875097]
- Brecht ML, Greenwell L, Anglin MD. Methamphetamine treatment: Trends and predictors of retention and completion in a large state treatment system (1992–2002). *Journal of Substance Abuse Treatment*. 2005; 29(4):295–306. DOI: 10.1016/j.jsat.2005.08.012 [PubMed: 16311182]
- Brecht ML, Huang D, Evans E, Hser YI. Polydrug use and implications for longitudinal research: Ten-year trajectories for heroin, cocaine, and methamphetamine users. *Drug and Alcohol Dependence*. 2008; 96(3):193–201. DOI: 10.1016/j.drugalcdep.2008.01.021 [PubMed: 18329825]
- Brecht ML, O'Brien A, von Mayrhauser C, Anglin MD. Methamphetamine use behaviors and gender differences. *Addictive Behaviors*. 2004; 29(1):89–106. DOI: 10.1016/S0306-6403(03)00082-0 [PubMed: 14667423]
- Brensilver M, Heinzerling KG, Shoptaw S. Pharmacotherapy of amphetamine-type stimulant dependence: An update. *Drug and Alcohol Review*. 2013; 32(5):449–460. [PubMed: 23617468]
- Bujarski S, Roche DJO, Lunny K, Moallem NR, Courtney KE, Allen V, ... Ray LA. The relationship between methamphetamine and alcohol use in a community sample of methamphetamine users. *Drug and Alcohol Dependence*. 2014; 142:127–132. DOI: 10.1016/j.drugalcdep.2014.06.004 [PubMed: 24975477]
- Byqvist S. Patterns of drug use among drug misusers in Sweden. Gender differences. *Substance Use & Misuse*. 2006; 41(13):1817–1835. DOI: 10.1080/10826080601006805 [PubMed: 17118818]
- Chou CP, Hser YL, Anglin MD. Pattern reliability of narcotics addicts' self-reported data: A confirmatory assessment of construct validity and consistency. *Substance Use & Misuse*. 1996; 31(9):1189–1216. DOI: 10.3109/10826089609063972 [PubMed: 8853237]
- Coffin PO, Galea S, Ahern J, Leon AC, Vlahov D, Tardiff K. Opiates, cocaine and alcohol combinations in accidental drug overdose deaths in New York City, 1990–98. *Addiction*. 2003; 98(6):739–747. DOI: 10.1046/j.1360-0443.2003.00376.x [PubMed: 12780362]
- Courtney KE, Ray LA. Methamphetamine: an update on epidemiology, pharmacology, clinical phenomenology, and treatment literature. *Drug and Alcohol Dependence*. 2014; 143:11–21. [PubMed: 25176528]
- Cox, TC., Jacobs, MR., Leblanc, AE., Marshman, JA. *Drugs and drug abuse: a reference text*. Vol. 1983. Addiction Research Foundation; 1983.
- Darke S, Hall W. Levels and Correlates of Polydrug Use among Heroin Users and Regular Amphetamine Users. *Drug and Alcohol Dependence*. 1995; 39(3):231–235. DOI: 10.1016/0376-8716(95)01171-9 [PubMed: 8556972]
- Degenhardt L, Baxter AJ, Lee YY, Hall W, Sara GE, Johns N, ... Vos T. The global epidemiology and burden of psychostimulant dependence: findings from the Global Burden of Disease Study 2010. *Drug and Alcohol Dependence*. 2014; 137:36–47. [PubMed: 24559607]

- Degenhardt L, Whiteford HA, Ferrari AJ, Baxter AJ, Charlson FJ, Hall WD, ... Engell RE. Global burden of disease attributable to illicit drug use and dependence: findings from the Global Burden of Disease Study 2010. *The Lancet*. 2013; 382(9904):1564–1574.
- DeMaria PA, Sterling R, Weinstein SP. The effect of stimulant and sedative use on treatment outcome of patients admitted to methadone maintenance treatment. *American Journal on Addictions*. 2000; 9(2):145–153. [PubMed: 10934576]
- Dillon P, Copeland J, Jansen K. Patterns of use and harms associated with non-medical ketamine use. *Drug and Alcohol Dependence*. 2003; 69(1):23–28. Pii S0376-8716(02)00243-0. DOI: 10.1016/S0376-8716(02)00243-0 [PubMed: 12536063]
- Downey KK, Helmus TC, Schuster CR. Treatment of heroin-dependent poly-drug abusers with contingency management and buprenorphine maintenance. *Experimental and Clinical Psychopharmacology*. 2000; 8(2):176–184. DOI: 10.1037/1064-1297.8.2.176 [PubMed: 10843300]
- Ellinwood EH, Eibergen RD, Kilbey MM. Stimulants - Interaction with Clinically Relevant Drugs. *Annals of the New York Academy of Sciences*. 1976; 281(Dec10):393–408. DOI: 10.1111/j.1749-6632.1976.tb27948.x [PubMed: 14585]
- Epstein DH, Preston KL. Does cannabis use predict poor outcome for heroin-dependent patients on maintenance treatment? Past findings and more evidence against (vol 98, pg 269, 2003). *Addiction*. 2003; 98(4):538–538.
- European Monitoring Centre for Drugs and Drug Addiction. polydrug use: patterns and responses. 2009
- Faggiano F, Vigna-Taglianti F, Versino E, Lemma P. Methadone maintenance at different dosages for opioid dependence. *Cochrane Database Syst Rev*. 2003; (3):CD002208. [PubMed: 12917925]
- Farrington DP. Developmental and life-course criminology: Key theoretical and empirical issues - The 2002 Sutherland Award Address. *Criminology*. 2003; 41(2):221–255. DOI: 10.1111/j.1745-9125.2003.tb00987.x
- Fischer B, Kuganesan S, Gallassi A, Malcher-Lopes R, van den Brink W, Wood E. Addressing the stimulant treatment gap: A call to investigate the therapeutic benefits potential of cannabinoids for crack-cocaine use. *International Journal of Drug Policy*. 2015; 26(12):1177–1182. [PubMed: 26500166]
- Furr CDM, Delva J, Anthony JC. The suspected association between methamphetamine ('ice') smoking and frequent episodes of alcohol intoxication: data from the 1993 National Household Survey on Drug Abuse. *Drug and Alcohol Dependence*. 2000; 59(1):89–93. DOI: 10.1016/S0376-8716(99)00078-2 [PubMed: 10706978]
- Gonzales R, Mooney L, Rawson R. The methamphetamine problem in the United States. *Annual Review of Public Health*. 2010; 31:385.
- Hartel DM, Schoenbaum EE, Selwyn PA, Kline J, Davenny K, Klein RS, Friedland GH. Heroin Use during Methadone-Maintenance Treatment - the Importance of Methadone Dose and Cocaine Use. *American Journal of Public Health*. 1995; 85(1):83–88. DOI: 10.2105/Ajph.85.1.83 [PubMed: 7832267]
- Hser YI, Anglin MD, Chou CP. Reliability of retrospective self-report by narcotics addicts. *Psychological Assessment*. 1992; 4(2):207.
- Hser YI, Evans E, Huang D, Brecht ML, Li L. Comparing the dynamic course of heroin, cocaine, and methamphetamine use over 10 years. *Addictive Behaviors*. 2008; 33(12):1581–1589. DOI: 10.1016/j.addbeh.2008.07.024 [PubMed: 18790574]
- Hser YI, Hoffman V, Grella CE, Anglin MD. A 33-year follow-up of narcotics addicts. *Archives of General Psychiatry*. 2001; 58(5):503–508. DOI: 10.1001/archpsyc.58.5.503 [PubMed: 11343531]
- Hser YI, Huang D, Teruya C, Anglin MD. Diversity of drug abuse treatment utilization patterns and outcomes. *Evaluation and Program Planning*. 2004; 27(3):309–319. DOI: 10.1016/j.evalproplan.2003.07.002
- Hser YI, Huang D, Teruya C, Douglas Anglin M. Gender comparisons of drug abuse treatment outcomes and predictors. [Comparative Study Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. *Drug and Alcohol Dependence*. 2003; 72(3):255–264. [PubMed: 14643942]

- Hser YI, Stark ME, Paredes A, Huang D, Anglin MD, Rawson R. A 12-year follow-up of a treated cocaine-dependent sample. *Journal of Substance Abuse Treatment*. 2006; 30(3):219–226. DOI: 10.1016/j.jsat.2005.12.007 [PubMed: 16616166]
- Ives R, Ghelani P. Polydrug use (the use of drugs in combination): A brief review. *Drugs-Education Prevention and Policy*. 2006; 13(3):225–232. DOI: 10.1080/09687630600655596
- John D, Kwiattkowski CF, Booth RE. Differences among out-of-treatment drug injectors who use stimulants only, opiates only or both: implications for treatment entry. *Drug and Alcohol Dependence*. 2001; 64(2):165–172. DOI: 10.1016/S0376-8716(01)00120-X [PubMed: 11543986]
- Kishi T, Matsuda Y, Iwata N, Correll CU. Antipsychotics for cocaine or psychostimulant dependence: systematic review and meta-analysis of randomized, placebo-controlled trials. *The Journal of clinical psychiatry*. 2013; 74(12):1169–1180.
- Kral AH, Wenger L, Novak SP, Chu D, Corsi KF, Coffa D, ... Bluthenthal RN. Is cannabis use associated with less opioid use among people who inject drugs? *Drug and Alcohol Dependence*. 2015; 153:236–241. DOI: 10.1016/j.drugalcdep.2015.05.014 [PubMed: 26051162]
- Kreek MJ. Opiate and cocaine addictions: Challenge for pharmacotherapies. *Pharmacology Biochemistry and Behavior*. 1997; 57(3):551–569. DOI: 10.1016/S0091-3057(96)00440-6
- Leri F, Bruneau J, Stewart J. Understanding polydrug use: review of heroin and cocaine co-use. *Addiction*. 2003; 98(1):7–22. DOI: 10.1046/j.1360-0443.2003.00236.x [PubMed: 12492751]
- Leri F, Stewart J, Fischer B, Jurgens R, Marsh DC, Brissette S, ... Tyndall MW. Patterns of opioid and cocaine co-use: A descriptive study in a Canadian sample of untreated opioid-dependent individuals. *Experimental and Clinical Psychopharmacology*. 2005; 13(4):303–310. DOI: 10.1037/1064-1297.13.4.303 [PubMed: 16366760]
- Lucas P, Walsh Z, Crosby K, Callaway R, Belle-Isle L, Kay R, ... Holtzman S. Substituting cannabis for prescription drugs, alcohol and other substances among medical cannabis patients: The impact of contextual factors. *Drug and Alcohol Review*. 2016; 35(3):326–333. DOI: 10.1111/dar.12323 [PubMed: 26364922]
- Management of Substance Use Disorders Working Group. VHA/DoD clinical practice guideline for the management of substance use disorders. Version 3.0. Washington (DC): Veterans Health Administration, Department of Defense; 2015.
- Mattick R, Kimber J, Breen C, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev*. 2008; (2)
- McGlothlin, WH., Anglin, MD., Wilson, B. An evaluation of the California civil addict program. Rockville, Md. Washington: National Institute on Drug Abuse; for sale by the Supt. of Docs., U.S. Govt. Print. Off; 1977.
- McKay JR, Alterman AI, Rutherford MJ, Cacciola JS, McLellan AT. The relationship of alcohol use to cocaine relapse in cocaine dependent patients in an aftercare study. *Journal of Studies on Alcohol*. 1999; 60(2):176–180. [PubMed: 10091955]
- Medina KL, Shear PK. Anxiety, depression, and behavioral symptoms of executive dysfunction in ecstasy users: Contributions of polydrug use. *Drug and Alcohol Dependence*. 2007; 87(2–3):303–311. DOI: 10.1016/j.drugalcdep.2006.09.003 [PubMed: 17074449]
- Minozzi, S., Amato, L., Pani, PP., Solimini, R., Vecchi, S., De Crescenzo, F., ... Davoli, M. The Cochrane Library. 2015. Dopamine agonists for the treatment of cocaine dependence.
- Murphy DA, Hser YI, Huang D, Brecht ML, Herbeck DM. Self-Report of Longitudinal Substance Use: A Comparison of the UCLA Natural History Interview and the Addiction Severity Index. *Journal of Drug Issues*. 2010; 40(2):495–515. [PubMed: 21212856]
- National Institute on Drug Abuse. Cocaine. Retrieved June 29, 2016, from <https://www.drugabuse.gov/publications/drugfacts/cocaine>
- National Institute on Drug Abuse. Methamphetamine. Retrieved June 29, 2016, from <https://www.drugabuse.gov/publications/drugfacts/methamphetamine>
- National Institute on Drug Abuse. Principles of drug addiction treatment: A research-based guide. 3. National Institute on Drug Abuse, National Institutes of Health; 2012.
- Nosyk B, Li L, Evans E, Huang D, Min J, Kerr T, ... Hser YI. Characterizing longitudinal health state transitions among heroin, cocaine, and methamphetamine users. *Drug and Alcohol Dependence*. 2014; 140:69–77. DOI: 10.1016/j.drugalcdep.2014.03.029 [PubMed: 24837584]

- Nurco DN, Bonito AJ, Lerner M, Balter MB. Studying Addicts over Time - Methodology and Preliminary Findings. *American Journal of Drug and Alcohol Abuse*. 1975; 2(2):183–196. DOI: 10.3109/00952997509002733 [PubMed: 1211378]
- Ottomanelli G. Methadone patients and alcohol abuse. *Journal of Substance Abuse Treatment*. 1999; 16(2):113–121. DOI: 10.1016/S0740-5472(98)00030-0 [PubMed: 10023608]
- Patterson TL, Semple SJ, Zians JK, Strathdee SA. Methamphetamine-using HIV-positive men who have sex with men: Correlates of polydrug use. *Journal of Urban Health-Bulletin of the New York Academy of Medicine*. 2005; 82(1):1120–1126. DOI: 10.1093/jurban/jti031 [PubMed: 15738313]
- Pérez-Mañá C, Castells X, Vidal X, Casas M, Capellà D. Efficacy of indirect dopamine agonists for psychostimulant dependence: A systematic review and meta-analysis of randomized controlled trials. *Journal of Substance Abuse Treatment*. 2011; 40(2):109–122. [PubMed: 21036508]
- Raudenbush, SW., Bryk, AS. Hierarchical linear models: Applications and data analysis methods. 2. Vol. 1. Newbury Park: Sage; 2002.
- Roy E, Richer I, Arruda N, Vandermeersch J, Bruneau J. Patterns of cocaine and opioid co-use and polyroutes of administration among street-based cocaine users in Montreal, Canada. *International Journal of Drug Policy*. 2013; 24(2):142–149. DOI: 10.1016/j.drugpo.2012.10.004 [PubMed: 23182550]
- Staiger PK, Richardson B, Long CM, Carr V, Marlatt GA. Overlooked and underestimated? Problematic alcohol use in clients recovering from drug dependence. [Research Support, Non-U.S. Gov't Review]. *Addiction*. 2013; 108(7):1188–1193. DOI: 10.1111/j.1360-0443.2012.04075.x [PubMed: 23075415]
- Strang J, Griffiths P, Powis B, Fountain J, Williamson S, Gossop M. Which drugs cause overdose among opiate misusers? Study of personal and witnessed overdoses. *Drug and Alcohol Review*. 1999; 18(3):253–261.
- Sullivan LE, Moore BA, O'Connor PG, Barry DT, Chawarski MC, Schottenfeld RS, Fiellin DA. The Association between Cocaine Use and Treatment Outcomes in Patients Receiving Office-Based Buprenorphine/Naloxone for the Treatment of Opioid Dependence. *American Journal on Addictions*. 2010; 19(1):53–58. DOI: 10.1111/j.1521-0391.2009.00003.x [PubMed: 20132122]
- Sumnall HR, Wagstaff GF, Cole JC. Self-reported psychopathology in polydrug users. *Journal of Psychopharmacology*. 2004; 18(1):75–82. DOI: 10.1177/0269881104040239 [PubMed: 15107188]
- Termorshuizen F, Krol A, Prins M, van Ameijden EJC. Long-term outcome of chronic drug use - The Amsterdam Cohort Study among Drug Users. *American Journal of Epidemiology*. 2005; 161(3): 271–279. DOI: 10.1093/aje/kwi035 [PubMed: 15671259]
- UNODC. World Drug Report 2012. 2012. (No. (United Nations publication, Sales No. E.12.XI.1))
- Wang LW, Panagiotoglou D, Min JE, DeBeck K, Milloy MJ, Kerr T, ... Nosyk B. Inability to access health and social services associated with mental health among people who inject drugs in a Canadian setting. *Drug and Alcohol Dependence*. 2016; 168:22–29. DOI: 10.1016/j.drugalcdep.2016.08.631 [PubMed: 27610937]
- Wasserman DA, Weinstein MG, Havassy BE, Hall SM. Factors associated with lapses to heroin use during methadone maintenance. *Drug and Alcohol Dependence*. 1998; 52(3):183–192. DOI: 10.1016/S0376-8716(98)00092-1 [PubMed: 9839144]
- Williamson A, Darke S, Ross J, Teesson M. The association between cocaine use and short-term outcomes for the treatment of heroin dependence: findings from the Australian Treatment Outcome Study (ATOS). *Drug and Alcohol Review*. 2006a; 25(2):141–148. DOI: 10.1080/09595230500537381 [PubMed: 16627303]
- Williamson A, Darke S, Ross J, Teesson M. The effect of persistence of cocaine use on 12-month outcomes for the treatment of heroin dependence. *Drug and Alcohol Dependence*. 2006b; 81(3): 293–300. DOI: 10.1016/j.drugalcdep.2005.08.010 [PubMed: 16154714]
- Zielinski L, Bhatt M, Eisen RB, Perera S, Bhatnagar N, MacKillop J, ... Samaan Z. Association between cannabis use and treatment outcomes in patients receiving methadone maintenance treatment: a systematic review protocol. *Systematic reviews*. 2016; 5(1):139.doi: 10.1186/s13643-016-0317-2 [PubMed: 27530914]

Table 1

Characteristics of study participants at baseline by primary drug type (N=1532).

	Primary Heroin Users (N=587)	Primary MA Users (N=444)	Primary Cocaine Users (N=501)
Characteristics (N (%))			
Follow-up, years (Median [IQR])	32.4 [21.8, 38.4]	13.3 [9.3, 19.0]	18.9 [13.6, 24.3]
Female	50 (8.5)	213 (48.0)	122 (24.4)
Age at first use (Median [IQR])	18 [16, 20]	18 [15, 22.5]	22 [18, 27]
Race/Ethnicity			
Black	51 (8.7)	61 (13.7)	330 (66.1)
Hispanic	315 (53.7)	120 (27.0)	39 (7.8)
White	212 (36.1)	233 (52.5)	111 (22.2)
Other	9 (1.5)	30 (6.8)	19 (3.8)
Education			
College	102 (18.6)	153 (34.5)	226 (45.2)
High school/GED	186 (33.9)	145 (32.7)	171 (34.2)
Less than high school	261 (47.5)	146 (32.9)	103 (20.6)
Marital status			
Married	148 (26.7)	22 (5.0)	129 (25.8)
Divorced/separated	316 (57.0)	422 (95.0)	284 (56.8)
Single	90 (16.2)	0 (0.0)	87 (17.4)
Employed	207 (35.8)	171 (38.5)	214 (42.8)
Crime			
Age at first arrest (Median [IQR])	15 [13, 17]	18 [15, 22]	19 [16, 25]
Incarcerated, ever ^a	539 (91.8)	254 (57.2)	212 (42.3)
% of months incarcerated among who were ever incarcerated (Median [IQR])	21.7 [11.9, 37.0]	10.8 [3.2, 26.7]	4.4 [1.3, 10.9]
^a % of months on treatment (Median [IQR])	15.4 [7.2, 29.5]	4.3 [2.1, 8.2]	4.3 [1.1, 10.0]
Calendar year at first use			
<=1960's	493 (84.0)	12 (2.7)	26 (5.2)
1970's	43 (7.3)	73 (16.4)	187 (37.3)
1980's	33 (5.6)	188 (42.3)	265 (52.9)
1990's	18 (3.1)	171 (38.5)	23 (4.6)
Study			
CAP	472 (80.4)	0 (0.0)	0 (0.0)
CTE	0 (0.0)	0 (0.0)	319 (63.7)
METH	0 (0.0)	350 (78.8)	0 (0.0)
TXPR	115 (19.6)	94 (21.2)	182 (36.3)

^a Characteristics at the end of study follow-up;

Abbreviations: MA: methamphetamine; IQR: interquartile range; CAP: the Civil Addict Program; CTE: the cocaine treatment evaluation study; METH: the methamphetamine natural history study; TXPR: the treatment process study.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 2

Patterns of self-reported monthly substance use by primary drug type and treatment participation (N=1532, monthly observations=340,926) ^a.

	Total	On treatment	Off treatment
Primary heroin users (N=587)			
Number of monthly observations (N(%))	159,240 (100)	27,573 (17.3)	131,667 (82.7)
Any secondary substance use ^b (N(%))	88,170 (55.4)	13,875 (50.3)	74,295 (56.4)
Substance use pattern ^c (%)			
Heroin only	27.4	23.4	28.2
No drug use	17.2	26.2	15.4
Heroin and alcohol	15.7	14.2	16
Alcohol only	11.7	10.5	11.9
Heroin, alcohol and marijuana	5.4	5.4	5.4
Alcohol and marijuana	4.5	1.9	5
Heroin and marijuana	3.9	4.8	3.8
Other combinations	14.2	13.6	14.3
Primary MA users (N=444)			
Number of monthly observations (N(%))	71,553 (100)	3,825 (5.3)	67,728 (94.7)
Any secondary substance use ^b (N(%))	48,625 (68.0)	771 (20.2)	47,831 (70.6)
Substance use pattern ^c (%)			
No drug use	21.1	72.9	18.2
MA, alcohol and marijuana	15.2	3.2	15.9
MA only	10.9	7.0	11.1
MA and alcohol	10.2	3.5	10.6
MA and marijuana	7.8	2.5	8.1
Alcohol only	6.6	4.7	6.7
Alcohol and marijuana	5.7	1.2	5.9
Cocaine, MA, alcohol and marijuana	5.1	0.1	5.4
Cocaine, alcohol and marijuana	2.9	0.0	3.1
Other combinations	14.5	4.9	15.0
Primary cocaine users (N=501)			
Number of monthly observations (N(%))	110,133 (100)	6,317 (5.7)	103,816 (94.3)
Any secondary substance use ^b (N(%))	77,520 (70.4)	1083 (17.1)	76,437 (75.0)
Substance use pattern ^c (%)			
No drug use	21.6	76.0	18.3
Cocaine, alcohol and marijuana	18.0	3.4	18.8
Cocaine and alcohol	16.2	4.4	17.0
Alcohol and marijuana	11.3	0.9	11.9
Alcohol only	10.2	3.6	10.6

	Total	On treatment	Off treatment
Cocaine only	8.0	6.9	8.0
Other combinations	14.7	4.8	15.4

^aSubstance use was defined as self-reported use of the substance for 1 day in a month;

^bAny secondary substance use was defined as the use of any substance other than the primary drug, with or without concurrent use of the primary drug;

^cSubstance use patterns considered the use of the following five substances (heroin, MA, cocaine, alcohol and marijuana) and their combinations at each month, resulting in a total of 31 mutually-exclusive combinations; the table presented the most common combinations which accounted for over 85% of all the monthly observations for each primary drug group. The remainder were summarized in the “other combinations” category. The proportion of each substance use pattern among all monthly observations was presented;

Abbreviations: MA: methamphetamine.

Table 3

Adjusted associations between self-reported treatment participation and primary drug use, stratified by secondary substance use (N=1532, monthly observations=340,926) ^a.

Subgroups	Treatment participation	Primary heroin use (N=587)	Primary MA use (N=444)	Primary cocaine use (N=501)
		Outcome: primary drug use Adjusted ^d odds ratios (95% Confidence Intervals)		
Overall	No	1.00	1.00	1.00
	Yes	0.46 (0.44, 0.48)	0.12 (0.11, 0.13)	0.16 (0.15, 0.18)
Any secondary substance use ^b				
Yes	No	1.00	1.00	1.00
	Yes	0.82 (0.78, 0.87)	0.25 (0.21, 0.30)	0.53 (0.45, 0.61)
No	No	1.00	1.00	1.00
	Yes	0.25 (0.24, 0.27)	0.07 (0.06, 0.08)	0.07 (0.07, 0.09)
Test of interaction ^e		<0.001	<0.001	<0.001
Alcohol use ^c				
Yes	No	1.00	1.00	1.00
	Yes	0.89 (0.83, 0.95)	0.39 (0.31, 0.49)	0.59 (0.50, 0.70)
No	No	1.00	1.00	1.00
	Yes	0.31 (0.29, 0.32)	0.08 (0.07, 0.09)	0.08 (0.07, 0.09)
Test of interaction ^e		<0.001	<0.001	<0.001
Marijuana use ^c				
Yes	No	1.00	1.00	1.00
	Yes	1.13 (1.03, 1.24)	0.40 (0.31, 0.51)	1.21 (0.95, 1.53)
No	No	1.00	1.00	1.00
	Yes	0.39 (0.37, 0.41)	0.08 (0.07, 0.09)	0.10 (0.09, 0.11)
Test of interaction ^e		<0.001	<0.001	<0.001
Secondary illicit drug use ^c				
Yes	No	1.00	1.00	1.00
	Yes	0.95 (0.84, 1.07)	0.90 (0.50, 1.60)	0.36 (0.24, 0.54)
No	No	1.00	1.00	1.00
	Yes	0.42 (0.40, 0.44)	0.11 (0.10, 0.12)	0.15 (0.14, 0.16)
Test of interaction ^e		<0.001	<0.001	<0.001

^aPrimary drug use: use of the primary drug 1 day in a month; multiple regression models were run separately for each primary drug group, with the outcome being use of heroin, MA, and cocaine for primary heroin users, primary MA users and primary cocaine users, respectively;

^bAny secondary substance use included the use of any substance other than the primary drug for 1 day in a month: including heroin, cocaine, MA, alcohol, and marijuana; the model included one set of interaction between any secondary substance use and treatment;

^cThese multiple regression models included one set of interaction terms between one type of secondary substance use and treatment, adjusting for the other two; where secondary illicit drug use was defined as the use of heroin, MA or cocaine other than the primary drug for 1 day in a month; the use of secondary illicit drugs were grouped together due to the small number of observations available;

^dAll multiple regression models additionally adjusted for the following covariates: age at first use, male, white, marital status, education, employment, incarcerated, calendar year of observation (1990's, 1980's, 1970's, and 1960's), and the study cohort (CAP, CTE, METH, TXPR);

^eLikelihood ratio tests were performed for test of interactions in all models, and a p-value<0.05 rejected the null hypothesis of no interaction.

Abbreviations: MA: methamphetamine.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 4

Adjusted associations between self-reported secondary substance use and primary drug use, in the absence of treatment (N=1532, monthly observations=303,211) ^a.

	Primary heroin use (N=587)	Primary MA use (N=444)	Primary cocaine use (N=501)
	Adjusted ^b odds ratios (95% Confidence Intervals)		
Outcome: any primary drug use			
Secondary heroin use ^c	N/A	6.72 (5.71, 7.91)	4.21 (3.78, 4.68)
Secondary cocaine use ^c	3.60 (3.30, 3.91)	0.98 (0.92, 1.04)	N/A
Secondary MA use ^c	1.16 (1.07, 1.27)	N/A	1.05 (0.96, 1.14)
Secondary alcohol use ^c	0.77 (0.73, 0.80)	3.31 (3.12, 3.52)	9.56 (9.06, 10.1)
Secondary marijuana use ^c	0.92 (0.87, 0.98)	5.95 (5.57, 6.36)	1.09 (1.04, 1.14)
Outcome: daily primary drug use			
Secondary heroin use ^c	N/A	2.24 (1.93, 2.61)	3.66 (3.27, 4.09)
Secondary cocaine use ^c	4.95 (4.58, 5.34)	0.78 (0.73, 0.83)	N/A
Secondary MA use ^c	0.52 (0.48, 0.56)	N/A	0.65 (0.57, 0.74)
Secondary alcohol use ^c	0.31 (0.30, 0.32)	2.10 (1.97, 2.24)	5.11 (4.76, 5.49)
Secondary marijuana use ^c	0.48 (0.46, 0.51)	3.80 (3.55, 4.07)	1.08 (1.02, 1.15)

^a Multiple regression models were run separately for each primary drug group, with the outcome being use of heroin, MA, and cocaine among primary heroin users, primary MA users and primary cocaine users, respectively; for each primary drug, the primary outcome was any primary drug use defined as use of the primary drug 1 day in a month (yes vs no); and the secondary outcome was daily primary drug use defined as use of the primary drug 28 days in a month (yes vs no);

^b Models additionally adjusted for the following covariates: age at first use, male, white, marital status, education, employment, ever incarcerated, calendar year of observation (1990's, 1980's, 1970's, and 1960's), and the study cohort (CAP, CTE, METH, TXPR);

^c Secondary substance use: use of the secondary substance for 1 day in a month; Abbreviations: MA: methamphetamine.