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Short communication

Event-level relationship between methamphetamine use significantly associated with non-adherence to pharmacologic trial medications in event-level analyses

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ABSTRACT

Background: Methamphetamine use has been previously associated with poor medication adherence, but, to date, there have been no studies that have conducted event-level analyses on correlates of medication adherence in studies of pharmacologic agents for methamphetamine dependence.
Methods: We pooled data from two previous, randomized controlled trials (using bupropion and mirtazapine, respectively) for methamphetamine dependence and used a mixed effects logistic model to examine correlates of daily opening of the medication event monitoring system (MEMS) cap as a repeated measure. We explored whether periods of observed methamphetamine use via urine testing were associated with study medication adherence based on MEMS cap openings.
Results: We found a significant negative association between methamphetamine-urine positivity and event-level study medication adherence as measured by MEMS cap openings (AOR: 0.69; 95% CI: 0.49–0.98). In addition, age (AOR: 1.07; 95% CI: 1.02–1.11) and depressive symptoms (AOR: 0.78; 95% CI: 0.64–0.90) were significantly associated with adherence. Finally, participants were more likely to open their study medication bottles on days when they presented for in-person urine testing.
Conclusions: Our event-level analysis shows that methamphetamine use can be associated with reduced medication adherence as measured by MEMS cap openings in pharmacologic trials, which corroborates prior research. These findings may suggest that medication adherence support in pharmacologic trials among methamphetamine users may be needed to improve study compliance and could be targeted towards periods of time when there are more likely to not open their study medication pill bottles.

1. Introduction

Methamphetamine is a psychostimulant with significant physical and psychological consequences (Darke et al., 2008) that has been linked with high-risk sexual behavior (Rawson et al., 2002) and HIV and STI incidence for men who have sex with men (MSM; Koblin et al., 2006; Colfax et al., 2011). Researchers have evaluated various medications in clinical trials to treat methamphetamine dependence, but there is currently no pharmacotherapy approved by the Food and Drug Administration (FDA) for this use (Elkashef et al., 2007; Colfax et al., 2011). Many trials among methamphetamine-dependent populations have been inconclusive and complicated by challenges including low levels of medication adherence (Longo et al., 2009; Colfax et al., 2011; Anderson et al., 2012).

Methamphetamine use is broadly associated with decreased medication adherence, particularly for HIV antiretroviral therapy (Hinkin et al., 2004, 2006; Marquez et al., 2009; Reback et al., 2003). Previous studies have described how methamphetamine use can negatively affect medication adherence via disrupted sleep, altered eating behavior, difficulty maintaining a schedule, and planned medication holidays during methamphetamine binges (Reback et al., 2003; Hinkin et al., 2006). In addition, methamphetamine

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use can lead to psychiatric symptoms such as depression and neurocognitive changes that may also affect adherence (Hinkin et al., 2006; Zweben et al., 2004). Studies of interventions for methamphetamine dependence have had difficulty retaining participants (Elkashef et al., 2007; Shoptaw et al., 2008), but even among those studies with good retention, adherence to pharmacologic therapies has made results difficult to interpret. A trial of modafinil showed no effect, but adherence was at most 50% (Anderson et al., 2012). We documented a significant reduction in methamphetamine use with mirtazapine, although adherence by MEMS caps was only 48% overall; the effect of mirtazapine was positively associated with adherence (Colfax et al., 2011). Self-report has been observed to overestimate medication adherence (Das et al., 2010); using more complex methods such as medication labeling, which is limited by preparation and analysis costs, and electronic medication event monitoring systems (MEMS) based on pill bottle opening may provide data that is more objective than self-report despite several MEMS measurement limitations (e.g., if a person is using an additional, external device to store pills or has removed several capsules during a pill bottle opening; Liu et al., 2001; Colfax et al., 2011). Nevertheless, the direct effect of methamphetamine on medication adherence in these trials is poorly understood. We were unable to identify any studies that conducted an event-level analysis on the correlates of medication adherence in pharmacologic trials for methamphetamine dependence using MEMS as a primary measurement outcome. We evaluated the predictors of events or observed periods of medication adherence within-person and hypothesized that days of weekly urine collection and periods of methamphetamine use would be associated with periods of adherence to study medications.

2. Methods

2.1. Study design

A total of 90 participants were pooled from two previously published placebo-controlled medication trials that evaluated bupropion ($n = 30$) and mirtazapine ($n = 60$). Full details of each study were previously described (Das et al., 2010; Colfax et al., 2011). Briefly, participants were MSM aged 18–60 years with methamphetamine dependence (verified by the Structured Clinical Interview for DSM-IV) who were interested in reducing their methamphetamine use or abstaining completely. To be eligible for the study, participants needed at least one methamphetamine-positive urine toxicology test during the initial screening period. Both trials excluded men with any acute medical or psychiatric conditions, abnormal baseline laboratory studies, a history of major depression, or men with HIV infection and a CD4 count less than 200 cells/μL.

2.2. Measures and study procedures

Participants presented for weekly urine collection and received substance use counseling based on a manualized treatment using both motivation interviewing and cognitive behavioral therapy techniques. At 4-week intervals, subjects had a repeat physical exam, laboratory testing, and behavioral assessments. We used audio computer-assisted self-interview (ACASI) to collect information about various participant characteristics including drug use (including frequency, type of drug, and route of administration), substance use treatment, and sexual risk behavior. We assessed depression symptoms based on the Center for Epidemiologic Studies-Depression Scale (CES-D; Andresen et al., 1994). Based on previous literature, we deemed participants with a score higher than 16 as having significant depressive symptoms (Andresen et al., 1994). Participants who also reported use of one or more illicit substances (e.g., marijuana, poppers, crack-cocaine, powdered cocaine, heroin, GHB, MDMA, ketamine, or hallucinogens) in addition to methamphetamine were classified as polysubstance users.

2.3. Primary outcome

Our primary outcome of interest was adherence to study medications as recorded by the daily opening of the MEMS cap as a repeated measure. For each participant, days with a record of a MEMS cap opening were classified as an adherent day.

2.4. Statistical analysis

To assess whether there were significant differences in demographic characteristics in the two trials pooled for this study, we performed Wilcoxon–Mann–Whitney or Fisher's exact tests, depending on whether the demographic variable of interest was continuous or categorical, respectively. We fitted a mixed effects logistic regression model that examined the relationship between daily opening of the MEMS cap as a repeated measure and predictors of interest, including methamphetamine use (defined as the last collected methamphetamine-positive urine test result carried forward for the days between urine tests), age, treatment group (placebo vs. active arm), presence of significant depressive symptoms (i.e., CES-D score was greater than 16), HIV status, number of days since the last urine result, polysubstance use, and whether the participant was in the bupropion or mirtazapine study. In our mixed effects logistic regression model, we accounted for repeated measures of our main predictor of interest and covariates whose values could change across the course of the study periods (e.g., CES-D score, polysubstance use). In order to assess for differential medication adherence in the two studies, we included an interaction term examining the association between the last collected urine result and the specific study sample. We also flexibly modeled trends in the baseline rate of bottle opening using a cubic spline in days since randomization.

3. Results

3.1. Sample characteristics

Participants enrolled in the two trials were similar with respect to age, race, education level, and employment status. The mean age for the pooled participants was 39 years (standard deviation = 9.2), approximately 12% reported no income, and 60% were unemployed. Most participants (93%) had at least a high school education and 66% had a regular healthcare provider. White, Caucasian, or European Americans made up 59% of the sample followed by people who were Asian-American or Pacific Islander (16%), Latino (14%), mixed or multiracial (6%), African-American (3%), or Native-American (2%). Most subjects (92%) reported using other substances in addition to methamphetamine. The mean CES-D score at baseline was 18.12 (standard deviation = 11.01). Over 57% of the study sample used methamphetamine at least three times per week, and over 78% of the participants had tried to stop or reduce their methamphetamine use in the past.

3.2. Event-level analyses

Results of the mixed effects logistic model revealed a significant, negative association between a methamphetamine-positive urine test and event-level medication adherence (AOR: 0.69; 95% CI: 0.49–0.98). There was a significant, positive association between age and event-level medication adherence (AOR: 1.07; 95% CI: 1.02–1.11). Having a significant level of depressive symptoms