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The Effects of Heroin Administration and Drug Cues on Impulsivity

Jermaine D. Jones^{1,*}, Nehal P. Vadhan², Rachel R. Luba, and Sandra D. Comer¹

¹Division of Substance Abuse, New York State Psychiatric Institute, Columbia University Medical Center, 1051 Riverside Drive, Unit 120, New York, NY 10032

²Department of Psychiatry and Behavioral Science, Stony Brook School of Medicine, 101 Nicolls Road, Stony Brook NY 11794

Abstract

Drug addiction is a chronic relapsing disorder characterized by compulsive drug seeking and continued use despite negative consequences. Behavioral impulsivity is a strong predictor of the initiation and maintenance of drug addiction. Preclinical data suggest that heroin may exacerbate impulsive characteristics in an individual but this has yet to be assessed in clinical samples. The current secondary data analysis sought to investigate the effects of heroin on impulsivity along with the effects of exposure to drug cues. Using the current data set, we also tentatively assessed the etiological relationship between impulsivity and heroin abuse. Sixteen heroin-dependent participants were recruited to complete IMT/DMT and GoStop tasks following repeated heroin administration, acute heroin administration and following a drug cue exposure session. Four preceding days of active heroin availability, compared to four preceding days of placebo drug availability, increased impulsivity assessed using the IMT and DMT. Presentation of drug cues similarly acted to increase impulsivity assessments on all three tasks. It also appears that heavier users were more susceptible to the influence of drug cues on impulsivity. The present study represents a step toward a more comprehensive understanding of the interaction between opioid abuse and impulsivity. A better understanding of these factors could provide critical insight into the maintenance of heroin use and relapse.

Keywords

Heroin; Opioid abuse; Impulsivity; Immediate Memory Task; Delayed Memory Task; GoStop

*Corresponding author: Jermaine D. Jones, Ph.D., Ph: 646-774-6113, Fx: 646-774-6111, Jonesje@NYSPI.Columbia.edu, JermaineDJones@gmail.com.

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Conflicts of Interest: Over the past three years, SDC has received compensation (in the form of partial salary support) from investigator-initiated studies supported by Reckitt-Benckiser Pharmaceuticals, Schering-Plough Corporation, Johnson & Johnson Pharmaceutical Research & Development, Endo Pharmaceuticals, and MediciNova and served as a consultant to the following companies: AstraZeneca, Camurus, Collegium, Cytogel, Guidepoint Global, Janssen, Mallinckrodt, Neuromed, Orexo, Pfizer, Salix, and Shire. The other authors have no conflicts to report.

Introduction

Opioid abuse continues to be a major social, economic, and medical concern, with an annual global prevalence of 32.4 million users (World Drug Report, 2015). In the U.S., despite an almost unprecedented drive to thwart initiation of opioid abuse, develop new medications, and prevent opioid overdose, the number of heroin-related deaths has reached its highest level in a decade (CDC, 2015; World Drug Report, 2015). One factor that has been repeatedly implicated in both the initiation and continuation of drug abuse is behavioral impulsivity (Everitt et al., 2008; James & Taylor, 2007).

Impulsivity can be defined as a predisposition toward rapid unplanned reactions to internal and external stimuli without regard to the negative consequences (Moeller et al., 2001a; 2002). Clinical studies have shown that in comparison to controls, heroin-dependent subjects display deficits in reflection impulsivity (the tendency to gather and evaluate information before making a decision, Clark et al., 2006), response inhibition and temporal discounting (Kirby et al., 1999; Li et al., 2013; Madden et al., 1997). Within the context of opioid abuse, impulsive decision making equates to greater salience of immediate reinforcers (positive [i.e., euphoria] or negative [i.e., decrease in withdrawal symptoms, anxiety, or stress]), as opposed to adverse consequences that are typically delayed and/or probabilistic [i.e., transmission of blood-borne pathogens, and non-intentional overdose (Odum et al., 2000; Woelbert & Goebel, 2013)].

Though the relationship between impulsivity and opioid abuse is well-established, it remains unclear if the aforementioned deficits are a consequence of long-term drug exposure or predate drug taking and mediate the vulnerability to addiction. (Verdejo-García et al., 2008; Winstanley et al., 2010). Human clinical studies with alcohol, psychostimulants and marijuana have shown that acute drug administration increases impulsive performance on rapid-decision and continuous performance tasks (Reed et al., 2012; Dougherty et al., 2008; Dougherty et al., 2000; Fillmore & Weafer, 2012; Henges & Marcinksi, 2012; Mulvihill et al., 1997; Reynolds et al., 2006; Spronk et al., 2015; van Wel et al., 2013; Weafer & Fillmore, 2012).

The relationship between impulsive behavior and heroin administration has been studied much less within clinical samples. However, preclinical work has shown that rodents become more impulsive (increasing heroin choices over a potent nondrug alternative and preference for immediate, small rewards) with continued heroin self-administration (Lenoir et al., 2013; Schippers et al., 2012). Acute administration of the prototypical mu-opioid receptor agonist, morphine, has also been shown to impair inhibitory control and increase delayed discounting (Kieres et al., 2004; Pattij et al., 2009; Pitts & McKinney, 2005). Many of these drug effects can be blocked or attenuated through mu receptor antagonism, suggesting that the direct effects of the drug may contribute to greater impulsive behavior.

To the authors' knowledge, the effects of heroin administration on measures of behavioral impulsivity have not been assessed in a clinical sample. As such, assessing the relationship between these factors was the primary aim of this analysis. Previous clinical studies have

provided inconsistent evidence that chronic exposure to opioid drugs may be associated with impairments in impulsivity (Baldacchino et al., 2015). Accordingly, this study sought to determine whether various opioid use characteristics, such as duration of use and amount of daily use are associated with impulsivity.

Finally, we assessed changes in impulsivity in response to provocative drug cues. Cue-induced craving has been shown to increase impulsivity and may represent a pathway to relapse among those seeking to abstain from illicit drug use (Belin et al., 2008; Miedl et al., 2014; Potenza, 2008). To further investigate this relationship, we examined the association between measures of impulsivity, and participants' choice between heroin and a comparable alternative monetary reinforcer. The drug vs money task is intended to model the choice that drug users make on a daily basis. In the current study we use both a verbal, discrete-trial choice procedure (for direct drug vs money comparison and to minimize the delay between the operant and reinforcer) and a progressive-ratio task [(to provide a quantitative measure of drug reinforcement with broader applicability)(Jones et al., 2013)]. These procedures are discussed in detail in the Methods section. The present study represents a step towards a more comprehensive understanding of the relationship between opioid abuse and impulsivity. Although we may be limited in our ability to alter how impulsive traits predispose individuals to addiction; the ability to behaviorally or pharmacologically manipulate the acute effects of the drug on the addictive state has significant implications for treatment and recovery.

Methods

Participant Recruitment and Selection

Active heroin users who were not seeking treatment for their drug use were recruited using print and online advertisements within the New York City (NYC) metropolitan area. Following a brief telephone interview, potential participants who met preliminary study criteria were scheduled for several in-person screening visits at the New York State Psychiatric Institute (NYSPI). During screening visits, psychologists, nurses and physicians assessed participants' physical and mental health. Participants' health was also determined using: electrocardiogram (ECG), clinical laboratory tests (hematology, blood chemistry panel, liver and thyroid functioning urinalysis and syphilis serology), a clinical interview with a research psychologist, and a physical and psychiatric examination with a physician. At every screening visit, urine toxicology assessed for recent use of opioids, benzodiazepines, cocaine and marijuana. In order to be enrolled, participants needed to meet DSM-IV criteria for opioid dependence, be physically healthy, and be between the ages of 21 and 55 years. Participants who had chronic pain, were dependent on any psychoactive substance other than opioids, nicotine, or caffeine, or met criteria for any DSM-IV axis I diagnosis other than opioid dependence were excluded. The data for this manuscript were derived from participants randomized to the placebo group of a larger medication trial.

Procedures

Stabilization—For the duration of the $\approx$ 3-week study, participants resided on our secure inpatient unit, located on the 5th floor of the NYSPI. For the first 5–7 days following

admission, participants were stabilized on the maintenance drug, a daily 8mg sublingual (SL) dose of buprenorphine (BUP) + 2 mg of naloxone (NLX). The maintenance drug was taken each evening at 8 pm. This dosing regimen was chosen to ensure that the maintenance drug had the least impact on study measures (as BUP levels would be at their nadir during experimental testing sessions). During stabilization, participants were treated for emergent withdrawal symptoms with supplemental medications (clonazepam, clonidine, zolpidem). Self-reported and observer-rated withdrawal were assessed daily. Experimental testing did not begin until withdrawal symptoms were no longer present based on participants' reports and the clinical judgment of medical personnel. Table 1 shows the schedule of laboratory sessions.

Laboratory Testing—Following stabilization, participants began laboratory sessions, which took place from Monday-Friday. Participants completed three types of laboratory sessions over the course of two weeks. Monday through Thursday, participants were given five opportunities each day (at 10 am, 11 am, 12 pm, 1 pm, and 2 pm) to choose between a dose of drug (heroin or placebo) and \$10 using a simple “yes” or “no” verbal choice procedure. The same dose was tested in the procedure for the entire week (i.e., week 1 = active heroin, week 2 = placebo heroin (PCB)). The order of active heroin and placebo weeks was randomly assigned.

Active heroin was administered intravenously (IV: 10 mg) or intranasally (IN: 40 mg) depending on the participants' preferred route of street heroin use. Our previous work with heroin has shown that this 1-to-4 IV-to-IN ratio produces a similar magnitude of reinforcing, subjective, and physiological effects (Comer et al., 1999). Placebo consisted of a matching milliliter (ml) or milligram (mg) amount of dextrose solution or lactose powder, respectively (described in more detail in the Drugs section).

Friday or Day 5 laboratory sessions consisted of two parts. In the morning “sample” session (10 am) participants were administered an active dose of heroin followed by various assessments of: subjective effects, performance tasks, and impulsivity measures (discussed below). These data were collected at baseline and at various time points up to 90 minutes after drug administration. For safety, participants' vital signs were continuously monitored during all drug administration sessions (Table 2).

At approximately 2 pm, participants completed a drug “cue exposure” session. During the cue session, participants were shown a neutral stimulus (a water bottle) and asked to look at, hold and sniff it, and take a drink of the water inside. Participants were then asked to manipulate paraphernalia associated with intravenous or intranasal drug use. Intranasal users were instructed to watch as a research nurse opened a wallet, removed a \$1 bill, removed a packet of powder mimicking heroin, opened the packet and rolled the dollar bill. Participants were then given the packet and dollar bill to hold for approximately 30 seconds. Intravenous users were instructed to watch as a research nurse opened a packet of heroin, poured its contents onto a spoon, added a few drops of water to the spoon, lit a lighter under the spoon, added cotton to the spoon and drew the fluid into a syringe. Next, a tourniquet was placed on the participants' arm and the participant was instructed to look for a vein. The participant was then given the syringe to hold for approximately 30 seconds.

Following the cue exposure session, participants completed a progressive ratio self-administration task to receive portions of the dose of drug or money they had sampled earlier in the day (0 to 100%, in increments of 10%). Participants were told that they could work for all or part of the sampled dose or the sampled money amount by choosing the drug or money option each time a choice was available. The alternative money value (\$20) was chosen based on previous studies conducted in our laboratory (Comer et al., 1997). Drug and money were available at each choice trial. For example, at each opportunity intranasal users could respond for 4 mg (10% of the total dose of 40 mg) or \$2 (10% of \$20).

Completion of the ratio requirement for each choice trial was accompanied by a visual stimulus on the computer screen. After a choice was made for one option, by clicking on its visual representation on the computer screen, responding for the other option was not possible until the ratio was completed and another trial was initiated. Responses to complete the ratio requirement consisted of finger presses on a computer mouse. The response requirement for each of the two options increased independently such that the initial ratio requirement for each option was 50 responses; the ratio increased progressively each time the option was selected (50, 100, 200, 400, 800, 1200, 1600, 2000, 2400, and 2800). At the end of the self-administration task (approximately 4 pm), the participant received whatever he or she had chosen: money (added to their study payment) and/or the IV or IN test drug.

Tasks and Measures—Behavioral impulsivity was measured using the Immediate Memory Task (IMT), Delayed Memory Task (DMT), and GoStop paradigms. Impulsivity measures were collected 45 min prior to heroin administration or cue exposure (referred to as “baseline”) and ~65 min after. The present study included only data from the Friday/Day 5 sessions. A brief description of each task can be found below.

- The IMT/DMT is a task designed to measure response initiation (Dougherty et al., 2002; 2003a). In the IMT, a series of five-digit numbers are presented on a computer screen. Participants are instructed to look for repeating patterns of numbers such that if the five-digit number presented is identical to the five-digit number that preceded it, they respond with their mouse. Each five-digit number appears for 500-msec and is followed by a 500-msec inter-trial interval. During the DMT, participants are again instructed to respond to repeating number patterns, but must remember number patterns while presented with a distracter stimulus (the number 12345, repeated three times in a row). Participants therefore need to remember the number patterns presented before and after the distracter stimulus, and if identical, respond using their mouse. The IMT/DMT consists of two five-minute blocks of IMT followed by two five-minute blocks of DMT, with a 30-second rest period between each block. The dependent measure for the IMT/DMT is the IMT and DMT ratio, which is determined by the proportion of commission errors to correct detections.
- The GoStop task is designed to measure response inhibition (Dougherty et al., 2003b; 2005). As in the IMT/DMT, participants are presented with five-digit numbers and instructed to respond when a five-digit number is

presented twice in a row. However, in the GoStop task, half of all trials feature a target-stop trial where the second presentation of a number changes from black to red at 30, 150, 250 and 250 milliseconds after presentation. Participants are instructed *not* to respond to identical numbers that turn to red. The primary dependent measure of the GoStop task is the 150-msec GoStop ratio, which is determined by the number of failed response inhibitions relative to the number of responses to go trials.

Drugs—Naloxone HCL solution was used to confirm physiological opioid dependence during screening and was obtained from System Limited Amphastar (South El Monte, CA, USA). Intramuscular naloxone was administered in doses between 0.2 and 0.8 mg. Buprenorphine/naloxone tablets for SL administration were obtained from Reckitt Benckiser Pharmaceuticals Inc. (Richmond, VA, USA).

Heroin HCl powder was obtained from RTI International (Research Park Triangle, NC, USA) through the Research Triangle Institute. Placebo IN heroin doses consisted of lactose monohydrate powder, purchased from Spectrum Chemicals (Gardena, CA, USA). For intravenous users placebo consisted of sterile 5% dextrose solution. All IN doses were insufflated through a plastic straw within 5–10 seconds, and IV doses were injected through a catheter by a research physician within 30 seconds. All test drugs were prepared and blinded by the New York State Psychiatric Institute Pharmacy and were administered by a physician.

Statistical Analyses

Continuous and categorical demographics variables were summarized descriptively. Two-way repeated-measures analysis of variance (ANOVA) was used to analyze the GoStop task at the time points at which errors are most likely to begin to occur (150, 250, and 350 secs; Dougherty et al., 2003b; 2005) and following acute conditions on Fridays (**Baseline**, following the acute heroin dose (**Heroin**) and drug cue exposure (**Cue**)), and conditions of placebo self-administration the preceding 4 days (**PCB week**), and heroin self-administration the preceding 4 days (**Heroin week**). Similarly, repeated-measures ANOVA was used to compare IMT and DMT scores at baseline (Baseline) and following the intervention under investigation (e.g., Heroin, Cue). For all ANOVAs, Planned comparisons (t-tests) were used to specify which two comparator groups (emboldened in the previous sentence) were significantly different.

For the sake of clarity and brevity, the results of the omnibus F-tests (ANOVA) have been omitted and only the final planned comparisons are reported in the results section. Within-samples t-tests were used to compare IMT and DMT outcome measures following week-long placebo (Placebo week) and heroin access (Heroin week). Levin's and Mauchly's tests were used to ensure that parametric tests could be employed.

Pearson's correlational test was used to measure the strength of the association between impulsivity and percentage of heroin relative to money choices and between all impulsivity measures and quantitative heroin use features. In order to determine whether the results differed between individuals who received IN heroin versus IV heroin, independent-samples

t-tests compared these measures between these two groups. Because no significant differences were found, the data presented below were collapsed across this condition.

For all analyses the significance level of α was set at <0.05 . Because of the exploratory nature of the study along with being a secondary data analysis, an α of 0.05–0.10 considered as approaching statistical significance or as a “trend.” All data analyses were performed using SPSS version 18 (SPSS, 2009) and SuperANOVA (Gagnon et al., 1990).

Results

Sample Characteristics

Sixteen participants completed testing and were included in the present analysis. The mean age of participants was 44.3 years and 88% were male. Five participants self-identified as African-American, 5 as Caucasian, and 6 as Latino. All participants reported daily heroin use, with a mean use of 6.9 bags per day. Nine participants reported that their primary route of use was intravenous and 7 reported their primary route of use as intranasal. For more extensive participant demographic information see Table 3.

Immediate Memory Task

When the IMT ratio was assessed following 4 days of heroin or placebo access (baseline measurements from the Friday/Day 5 session of each week), analysis revealed a trend for access to active heroin to increase the IMT ratio [$t(15) = -1.37$, $p = 0.09$, $\eta^2 = 0.11$; Figure 1, Left Panel]. Alternatively, measurements taken 60 minutes after acute dosing on Friday/Day 5, showed no effect of heroin on task performance. Presentation of drug cues resulted in an increase in IMT ratio trending towards statistical significance [$t(15) = -1.40$, $p = 0.09$, $\eta^2 = 0.12$; Figure 1, Right Panel]. This effect was only observed following PCB self-administration the preceding four days.

Delayed Memory Task

As with the IMT, we observed a trend where four preceding days of heroin availability increased DMT ratio to an extent that approached significance [$t(15) = -1.36$, $p = .09$; $\eta^2 = 0.10$; Figure 2, Left Panel]. Again, the acute heroin dose had no effect, while presentation of drug cues significantly increased DMT ratio [$t(15) = -1.79$, $p < 0.05$, $\eta^2 = 0.18$; Figure 2, Right Panel]. This effect was only observed following PCB self-administration.

GoStop Task

ANOVA revealed a significant effect of Time on the GoStop ratio, wherein longer delays significantly increased impulsive responding ($p < .05$). Planned comparisons of the influence of prior heroin or placebo access revealed no effect (Figure 3, Left Panel). However, with a 250s delay, the effect of drug cues to increase GoStop ratio approached statistical significance [$t(15) = -1.39$, $p = 0.08$; $\eta^2 = .12$; Figure 3, Right Panel]. This effect was only observed following PCB self-administration.

Impulsivity and Drug Self-Administration

During Days 1–4 active heroin was significantly self-administered above placebo ($p < .05$). The PR breakpoint for heroin (from Day 5) was greater following PCB heroin access the preceding week (Mean = 2050.0, SE = 558.5) compared to active heroin (Mean = 1037.5, SE = 471.4) ($p < .05$; Figure 4). The money breakpoint was similar between the groups (PCB: Mean = 3881.3, SE = 1352.3; Heroin: Mean = 3776.6, SE = 1358.5).

Correlational analyses revealed no significant association between self-reported assessments “urge” and “desire” for heroin, and any of the study’s dependent measures. Similarly, we found no significant association between measures of impulsivity under any conditions and percent of heroin choices (PCB Week: 38%, Heroin Week: 36%) in the self-administration session that same day (Day 5/Friday). Baseline impulsivity scores and impulsivity scores following heroin administration was also not significantly associated with either years of heroin use, or amount of daily heroin use (bags/day) for any of the three measures. IMD and DMT impulsivity measures following cue exposure were significantly associated with the number of bags per day that participants reported using prior to study enrollment [IMT: $R^2(15) = 0.25$, $p < .05$; DMT: $R^2(15) = 0.37$, $p < .05$ GoStop: $R^2(15) = 0.002$, $p = \text{NS}$] (Figure 5).

Discussion

Although previous studies have demonstrated that impulsivity is a common feature among heroin users, clinical investigations have not gone beyond case vs control comparisons (Dissabandara et al., 2014; Vassileva et al., 2007; Zeng et al., 2013). The present clinical study is the first to assess the direct effects of acute and repeated heroin administration on measures of impulsivity under controlled laboratory settings. Although a moderate, acute dose of heroin was found to have a negligible effect on measures of impulsivity, we discovered trends suggesting that continued access to heroin increased response initiation impulsivity. While some studies in this area suggested that opioid use was less likely to impair cognitive control (vs other drugs like cocaine), other research has found that chronic heroin use may lead to deficits in inhibition and impulse control (Guerra et al., 1987; Fishbein et al., 2007; Lee & Pau, 2002; Rounsaville et al., 1982). The current data support the later line of research.

In addition to the direct effects of heroin on measures of impulsivity, we were able to assess the influence of provocative drug paraphernalia specific to the participants’ preferred route of use. We found that exposure to drug cues increased impulsivity across both of the dimensions tested (response initiation and response inhibition). This result was only observed following a week of placebo self-administration suggesting that the influence of drug cues is more robust during periods of abstinence. These behavioral data corroborate fMRI studies showing greater brain reactivity to heroin cues following acute abstinence (Lou et al., 2012; Li et al., 2012). This finding also substantiates the literature on alcohol, nicotine and psychostimulants, which have all found a significant positive relationship between impulsivity and drug cues/craving (Bourque et al., 2013; Doran et al., 2007; Moeller et al., 2001b; Papachristou et al., 2012; 2013).

The combined findings of the influence of repeated heroin use and drug cues may help us better understand how impulsivity moderates the persistence of opioid abuse. Impulsivity has been shown to be a significant predictor of treatment outcome (Moeller et al., 2001b). Repeated heroin use may increase impulsivity, making abstinence initiation more difficult. And once achieved, exposure to drug cues may undermine abstinence leading to lapses in sobriety and relapse to drug use.

Interestingly, this study did not find a relationship between impulsivity measured prior to experimental intervention, following acute heroin administration, or after drug cues, and the participants' choice behavior between heroin and money. This finding suggests that minor variations in impulsive state (as opposed to greater impulsivity as a trait), may not directly affect drug seeking, particularly among such experienced heroin users. Users with a longer duration of opioid abuse often report that opioid use is motivated by negative reinforcement (e.g., avoiding withdrawal) as opposed to positive reinforcement (e.g., the euphoria produced by the drug), which may have motivated initial drug use (Bozarth, 1994; Wise & Koob, 2014). Therefore, the nature of the relationship between impulsivity and clinical assessments of drug taking may vary within a sample that has recently initiated opioid abuse.

That none of our measures of impulsivity were associated with participants' choice behavior may also suggest that impulsivity alone is not sufficient to lead to significant changes in drug seeking. However, the parametric conditions of this study may have contributed to this finding. Participants were maintained on buprenorphine; a partial opioid agonist that blocks the reinforcing effects of heroin and decrease its self-administration (Comer et al., 2005), an effect well known among heroin users. It is likely that the choice behavior itself and the influence of impulsivity would have varied under different opioid maintenance conditions.

In order to investigate the etiological relationship between impulsivity and heroin abuse, we also assessed the strength of association between features of the participants' heroin abuse (duration and daily use) and impulsivity. To this effect we found no correlation between the number of years participants had used heroin and our impulsivity measures. We did find a significant positive association between participants' daily amount of heroin use and cue-induced deficits in response initiation. This finding agrees with other studies reporting greater impulsivity among heavier users of other drugs (Reed et al., 2012; O'Boyle & Barratt, 1993; Papachristou et al., 2012; Walsh et al., 2010).

Although this investigation presents some novel and interesting findings, a number of limitations must be noted. First, only two measures of impulsivity were tested. Impulsivity is a multi-dimensional construct, which can be measured in many different ways (Acheson et al., 2006; Dougherty et al., 2005). As such, our limited number of measures may have only captured a small aspect of the influence of this trait.

As previously mentioned, these data were taken from participants randomized to the placebo condition of a larger trial of an experimental medication. As such, the power to detect significant differences was significantly reduced resulting in heavy reliance on findings that only approached statistical significance. However, despite being underpowered, the observed

effect sizes were all medium-large (0.10 – 0.17; Cohen, 1988), adding validity to the observed influence of these independent variables.

Additionally, the design of the larger trial from which these data were taken was not intended to directly assess the variables discussed in this manuscript. As such, these findings warrant replication utilizing a procedure that examines the effects of drug cues independently of self-administration or controls for the potential carry-over effects among the experimental conditions. Future research should also employ an acute placebo drug condition to better discriminate the effects of heroin administration and cue presentation on impulsivity.

An additional limitation of the study is that the design was intended to test the effects of repeated heroin access/availability. This 4-day duration may not have been sufficient to model repeated heroin use. That the current analyses found trending results with such a relatively short duration indicate that follow-up research with longer exposure to heroin is warranted. Similarly, impulsivity was only measured at a single time point following the intervention (60 min). Thus, we may have missed the time at which impulsive behavior peaked. Most other investigations measure impulsivity repeatedly after drug administration, with some studies showing peak effects after 2 hr (Reed et al., 2012). Finally, this study could not measure or control for differential trait impulsivity, which may have existed prior to initiation of drug abuse. Despite its limitations, the current study represents a step towards a more comprehensive understanding of the relationship between impulsivity and heroin use.

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Figure 1.
Immediate Memory Task

Figure 2.
Delayed Memory Task

Figure 3.
Gostop Task

Figure 4.
Drug Self-Administration

Figure 5.
Heroin use and Impulsivity

Table 1

Representative Study Design

Week 1		Week 2					Week 3				
Bup/Nx Stabilization	5-6 Days	M	T	W	Th	F	Sa-Su				
		Heroin Verbal Choice				Heroin PR Choice and Cue Sessions				Placebo Verbal Choice	
										Heroin PR Choice and Cue Sessions	

Table 2**Day 5 Session Schedule**

	-45	0	5	15	30	45	60	90	End	-13	*-5	0	60	70	120	End
Physiological Monitoring																
Blood Pressure																
Heart Rate																
Oxygen Saturation																
Assessments																
Pupil Diameter																
Task Battery																
IMT/DMT																
GO/STOP																
Cue Exposure Task										Neutral	Drug					
Drug Administration																
Drug Self-Administration																

TABLE 3

Sample Characteristics

Demographics	Mean (% or SD)
Age	44.5 (26–57)
Sex*	
Male	14 (88)
Female	2 (12)
Ethnic/Racial Category	
African American	5 (31)
Caucasian	5 (31)
Hispanic	6 (38)
Education Level	
Some high school	2 (13)
High school diploma or equivalent (GED)	11 (69)
Some college	2 (13)
Bachelor's degree or above	1 (6)
Daily Heroin Use (bags per day)	6.89(2.98)
Years of use	18.20 (9.82)
Route of administration preference	
Intranasal	7 (44)
Intravenous	9 (56)
Current Cocaine Use (yes)	9 (56)
Frequency of use	
Once every few months	1 (11)
Once per month	--
Twice per month	2 (22)
Once per week	2 (22)
Two-three times per week	3 (33)
Four-six times per week	1 (11)
Daily	--
Current Benzodiazepine Use (yes)	4 (25)

Demographics	Mean (% or SD)
Frequency of use	
Once every few months	--
Once per month	--
Twice per month	1 (25)
Once per week	--
Two-three times per week	2 (50)
Four-six times per week	1 (25)
Daily	--
Current Marijuana Use (yes)	3 (19)
Frequency of use	
Once every few months	--
Once per month	--
Twice per month	1 (33)
Once per week	--
Two-three times per week	--
Four-six times per week	--
Daily	2 (67)
Current Alcohol Use (yes)	11 (69)
Frequency of use	
Once every few months	1 (9)
Once per month	2 (18)
Twice per month	3 (27)
Once per week	1 (9)
Two-three times per week	3 (27)
Four-six times per week	1 (9)
Daily	--
Drinks per episode	2.00 (1.70)
Current Nicotine Use (yes)	13 (81)
Cigarettes per day	13.10 (11.34)