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Impact of inpatient research participation on subsequent heroin use patterns: Implications for ethics and public health

P. Roux[1,2], **C. Tindall**[1], **L. Fugon**[2], **J. Murray**[1], **S.K. Vosburg**[1], **P. Saccone**[1], **M.A. Sullivan**[1], **J.M. Manubay**[1], **Z.D. Cooper**[1], **J.D. Jones**[1], **R.W. Foltin**[1], and **S.D. Comer**[1]

[1]Substance Use Research Center, NYSPI, Columbia University, New York, USA

[2]INSERM, U912 (SE4S), Marseille, France

Abstract

Aims—Research on drug dependence often involves the administration of drugs of abuse to experienced drug users under controlled laboratory conditions. The primary objective of this study was to assess whether participation in such research alters the frequency of heroin use by non-treatment seeking opioid-dependent volunteers after study completion.

Design—Data were examined from four inpatient studies involving controlled opioid administration.

Setting—Substance Use Research Center at Columbia University, New York State Psychiatric Institute.

Participants—Sixty-nine heroin dependent volunteers.

Measurements—Participants' self-reported heroin use prior to and one month after study participation was compared using a Wilcoxon test. Because a number of participants reported that they had stopped using heroin, a logistic regression was used to identify correlates of heroin cessation one month after study completion.

Findings—One hundred one participants entered laboratory studies and 69 completed them. Self-reported heroin use significantly decreased one month after study participation [1.7 (+/− 2) bags per day] compared to baseline [6.8 (+/− 4.2) bags per day], $p < 0.001$ among the 69 completers. In addition, 42% of the completers were heroin abstinent one month after study completion. Being African American, having a history of opioid dependence treatment, reporting heavier heroin use at baseline, and a longer history of heroin use were correlated with cessation of heroin use.

Conclusions—These findings demonstrate that participation in opioid administration studies does not increase subsequent heroin use and for some individuals leads to accessing opioid dependence treatment and cessation of heroin use in the short term.

Keywords

self-administration; experimental study; heroin; drug use

Correspondence: Dr Sandra D. Comer, Department of Psychiatry, Columbia University and the New York State Psychiatric Institute, 1051 Riverside Drive, Unit 120, New York, NY 10032, USA. sdc10@columbia.edu.

Declaration of interest

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Introduction

Human laboratory studies investigating drug dependence have been conducted since the middle of the 20th century (1). In an effort to understand the causes and effects of drug taking behavior, various methods have been developed for both laboratory animals and humans (2). These studies are conducted to better understand the relative abuse liability of existing drugs and the factors that affect the likelihood of abuse (3). One method of assessing the abuse liability of drugs is to examine drug self-administration under controlled laboratory conditions. With this methodology, the drug of abuse is provided as a reinforcer contingent upon an operant behavior. For example, participants are given the opportunity to self-administer a previously sampled dose of drug by making responses on a manipulandum (e.g., computer mouse, joystick, lever, etc.). The relative abuse liability of a drug can be determined by asking the participant to choose between receiving the previously sampled drug and another drug or non-drug (i.e., money) reinforcer. In addition to assessing the reinforcing effects of the drug, other variables also can be evaluated such as subjective (e.g., drug "liking") and objective (e.g., physiological) effects. The results of these studies allow us to better understand pharmacological or non-pharmacological factors that influence addictive behaviors in drug abusing individuals (2).

Despite the fact that experimental studies based on administration of drugs of abuse have led to improvements in the understanding of drug dependence, many questions remain about the impact of such experimentation on subsequent drug use patterns in individual drug abusers (4). Previous studies have shown that administration of drugs of abuse to drug abusing volunteers does not lead to increased drug use after study participation (5, 6, 8, 9, 10) and does not alter subsequent psychosocial functioning (7). The objective of the present study was to assess the extent to which participation in an experimental study investigating the reinforcing and/or subjective effects of opioids changed the frequency of heroin use by opioid-dependent research participants after study completion and the likelihood of accessing treatment for heroin dependence. Correlates of heroin cessation after study completion were also identified to better understand variables that affected changes in patterns of drug use.

Methods

Data collection

Information about participants in four experimental inpatient studies investigating the effects of opioids in non-treatment seeking, opioid-dependent volunteers conducted between 2006 and 2010 at the Substance Use Research Center of the New York State Psychiatric Institute were used in this analysis. For each study, the design, objectives and other study-related contingencies are described in Table 1 (11, 12).

Screening

After completing an initial telephone interview, eligible participants came into the laboratory to provide consent to receive additional screening, which included completing detailed medical history and drug use questionnaires, interviews with a psychologist and psychiatrist, and a medical evaluation conducted by a physician. Urine drug toxicologies (using urine quick tests) also were performed several times during screening to test for opioids, benzoylecgonine (cocaine metabolite), benzodiazepines, cannabinoids, and amphetamines. A naloxone challenge test or visual observation of opioid withdrawal symptoms was carried out on all potential participants to confirm current dependence on opioids. Participants who were requesting drug treatment, had a current major Axis I psychopathology other than opioid dependence (i.e., schizophrenia or major depression), or

met DSM IV criteria for dependence on drugs other than opioids, nicotine, or caffeine were excluded from the study. Individuals on parole or probation, or with histories of significant violent behavior also were excluded.

Before admission, all participants signed consent forms that described the risks and benefits of participation and explained the overall aims of the study. For these studies, the common inclusion criteria required participants to be healthy volunteers, users of heroin, and not seeking treatment for their heroin dependence. Because the 4 studies differed in length and therefore overall remuneration (participants received more money for participating in the longer studies), a 4-category variable entitled "Study protocol" was entered into the statistical model, comparing protocol #5725, #5182 and #5518 to protocol #4857, which was used as a reference.

One-month follow-up visit

During the one-month follow-up visit, participants met with a trained interviewer. During the visit, information regarding heroin use was solicited with identical questions that had been employed at baseline. Information about treatment status for heroin dependence was also collected, e.g, detoxification program or opioid-maintenance treatment.

Statistical analyses

We selected participants who completed the study and were administered the one-month follow-up questionnaire. To better understand the non-completer population and examine any potential negative consequences of study participation on their heroin use, we described this population in the Results.

For the primary analysis, the average number of self-reported heroin bags used per day before entering the study and after study completion at the one-month follow-up visit were compared. One street bag of heroin in New York City contains approximately 25 mg of pure heroin and costs $10 (13–15). Statistical analyses consisted of Wilcoxon signed-rank tests. Single logistic regression analyses were performed to identify factors associated with heroin cessation (heroin use = 0 bag per day at the one month follow-up). To avoid situations where strong confounds could hide important predictors of heroin cessation, a liberal p-value of <0.20 was defined in the univariate analyses to select eligible factors for a multivariate model. Afterwards, terms that were significant at the $p<0.20$ level were entered into the multivariate model, and a stepwise backward selection procedure was used, in which only terms that were significant at the $p<0.05$ level were retained.

Because the inverse phenomenon (an increase in heroin use) may be a concern for drug users enrolled in inpatient studies, a similar analysis was performed to study the correlates of increased heroin use to better identify individuals for whom study participation may be detrimental. Given the small sample size of participants who increased their heroin use after having ended the study, we performed a logistic regression model for rare events using the RELOGIT package in STATA (StataCorp LP, College Station, TX, USA) to identify factors associated with increased heroin use after study completion. Due to small sample and outcome imbalance, we presented only exploratory variables with a p-value<0.20 within the bivariate analysis.

Results

Sample characteristics

As summarized in Table 2, 101 participants enrolled in the studies and 69 completed them. No significant difference in baseline characteristics was observed between those who

completed the studies (n=69) and those who did not (n=32) except that completers were more likely to use less heroin at baseline (p=0.05). Of the 69 participants who completed the studies, 13% were female and the median age was 38 years [35 – 42]. More than half (55%) of the completers reported a lifetime history of treatment for heroin dependence either with opioid maintenance treatment or detoxification. At baseline, 65% of completers reported being intravenous heroin users and the remaining 45% were intranasal heroin users.

Description of changes in heroin use patterns at the one-month follow-up

Among the 69 participants who completed the studies, self-reported heroin use decreased from an average of 6.8 (+/− 4.2) bags per day at baseline to 1.7 (+/− 2.0) bags per day at the one-month follow-up visit ($z = -7.0$; $p < 0.001$). At the one-month follow-up visit, 42% of the participants (n=29) reported having stopped using heroin. The remaining 58% of participants (n=40) were not abstinent after study completion, yet, the number of bags of heroin used decreased by nearly 50 percent from 5.9 (+/−2.7) bags per day at baseline to 2.9 (+/− 1.8) bags per day at the one-month follow-up visit ($z = -5.$; $p < 0.001$). Interestingly, at the one month follow-up, percentage of initiation of treatment for heroin dependence was high: 21% of participants began opioid maintenance treatment (buprenorphine or methadone), 6% became enrolled in a detoxification program, 25% were referred to treatment, and 48% remained without treatment for heroin dependence. Among the 69 completers we found that 4 (6%) of the participants increased their heroin use from 3.5 (+/− 1.3) bags per day prior to enrollment to 4.8 (+/− 1.5) bags per day after study completion.

Description of non-completers

Among the 32 participants who did not complete the study, 19 did not receive any drug of abuse. In other words, they dropped out a few days after their admission, before starting the laboratory sessions. Thus, they were not exposed to drug administration. An additional participant was discontinued from the study by medical staff because he developed dermatitis during the study and was referred to outpatient care. The remaining 12 non-completers were discharged during the early stages of the study because of behavioral issues (e.g., aggression toward staff members, smoking on the unit) and we do not have data about their heroin use subsequent to their discharge. Two of these 12 non-completers decided to initiate treatment for their drug use.

Predictors of heroin cessation after study completion

Table 2 presents the results of the bivariate and multivariate analyses performed to identify the correlates of heroin cessation. In the bivariate analysis, it is interesting to note that protocol #5725, which has the shortest length of participation (3 weeks), was associated with less heroin cessation compared to protocol #4857 with a length of 6 to 8 weeks. However, this variable was no longer statistically significant when entered in the final model. After the multivariate analysis, which consisted of adjusting for all the variables in the same model, the full model revealed that the predictors of heroin cessation were being African American, having a lifetime history of treatment for heroin dependence, using heroin for a shorter period of time, and using large amounts of heroin at baseline (number of bags of heroin per day).

Exploratory analysis of factors associated with increased heroin use one month after study completion

We found that individuals who self-reported higher cannabis use (OR[95%CI]=1.09[1–1.20]; p=0.06), cocaine use (OR[95%CI]=1.11[0.96–1.27]; p=0.17) or alcohol use (OR[95%CI]=1.04 [0.98–1.11]; p=0.16) (per one unit increase monthly) may be more likely

to report increased heroin use one month after the end of the study compared to their baseline heroin use.

Conclusions

To our knowledge this is the first study to demonstrate that participating in an opioid administration study does not harm heroin users, and instead may make it more likely for users to seek treatment and to reduce their heroin use. The descriptive analysis showed that almost half of the participants completely stopped using heroin within 1 month of study completion. This finding was particularly interesting because participants left the hospital with monetary compensation for completing the study and one might expect that drug use would increase after discharge. The decrease in heroin use that was found may be due to the fact that participants were referred to treatment for heroin dependence immediately following a fairly prolonged inpatient stay, where they had continuous access to psychiatric care. Moreover, participants typically received less drug in the hospital than they normally used on the street (i.e., their level of opioid dependence was reduced). It could therefore be hypothesized that residing in a controlled inpatient facility may have a positive impact on participants who are not seeking treatment for their drug use, even though drug is administered during the inpatient stay. One part of the explanation may be that attitudes towards treatment may shift slightly during participation because subjects are reminded repeatedly throughout their inpatient stay that they can discontinue study participation at any time and seek treatment. This interpretation is endorsed by the correlation between study protocol and heroin cessation found in the bivariate analysis, which suggests that longer study durations may have a greater positive impact on heroin use.

To better understand the factors that may contribute to cessation of heroin use after study completion, logistic regression analyses were conducted. These results deserve attention. First, although participants who reported greater heroin use at baseline are less likely to complete the study, when they do end it they are more likely to stop using heroin after study completion. This result is consistent with many findings in the literature demonstrating a higher level of motivation and readiness to change in drug or alcohol dependent persons who have more problems associated with their drug use (16, 17), which one might expect for those who use greater amounts of heroin. Second, participants who reported a lifetime history of treatment for heroin dependence had better outcomes in terms of heroin cessation. This characteristic in the sample could be a sign of openness toward drug abuse treatment, which is known to influence drug users' subsequent engagement in treatment for their drug dependence (18). Prior research has shown that motivational status is an important determinant of access to treatment for heroin dependence and for treatment success (19). However, frequent relapses, or expensive or inadequate care may have led even motivated users to withdraw from previous treatment programs.

African-Americans were more likely to stop using heroin at the end of the study. These findings highlight that racial and ethnic factors are associated with different needs for drug abuse treatment modalities (20). In addition, some data suggest that minorities, such as African-American drug users, have more difficulty accessing and maintaining treatment for heroin dependence (21). It may be that the currently described context in which drugs of abuse are administered in laboratory studies is perceived to be less judgmental, which encourages participants to seek benefits from treatment services (22).

With regard to accessing treatment, an interesting parallel could be made between inpatient experimental studies involving drug administration and supervised injecting facilities, where medical follow-up and nursing care are provided (23). For instance, the opening of a supervised injecting facility in Vancouver was associated independently with a 30% increase

in detoxification service use, and this behavior was associated with increased long-term engagement in heroin dependence treatment (24). In addition, the Sydney Medically Supervised Injecting Centre has been reported to serve as a referral gateway to drug treatment for injection drug users (25). In that study, 16% of clients who received written referrals had confirmed initiation of opioid substitution therapy. Moreover, as was found in the current study, their results also showed that heavier heroin users were more likely to initiate treatment. And finally, the finding that participants with a longer history of heroin use were less likely to stop using heroin after study completion corroborates the findings of Rosen et al. (2011) showing that older heroin users, who are presumably those with a longer history of use, are less likely to seek treatment (26). Specifically, those who use heroin for longer periods of time are more likely to be in denial and thus less motivated to change their drug using behaviors (27). The fact that those participants who report greater cannabis, cocaine, or alcohol use actually may be at risk of increasing their heroin use after study completion is of concern. While our findings may have implications for the risk/benefit analysis of study participation for longer-term heroin users, the results should be viewed with caution because of the small sample size in our study. Future research should explore this issue more fully.

Overall, our findings suggest that participation in inpatient studies may provide non-treatment-seeking heroin users an opportunity to build trust in the medical system. In addition, through study participation, heroin users may become aware of a variety of resources that are available to them, including different social service and treatment options. Although heroin users experience many barriers to accessing care (28), results of interviews with drug users suggest that access to care may be increased by improved staff relations (22). The present findings support this latter assertion.

Some limitations of the present study should be acknowledged. First, the motivation to seek treatment for drug abuse typically waxes and wanes over time within individual users. Even though the participants who completed these studies reported a lack of interest in treatment during screening, it is possible that they were interested in deferring treatment until after they could earn some money for study participation. A second limitation was that information about heroin use beyond the one-month follow-up visit was not collected, and no urinary toxicology was performed to confirm self-reported abstinence. Ideally, the abstinence status of the participants would have been confirmed with urine drug toxicologies, as well as further interviews performed several months after the study. However, as in most studies in this field, most of our knowledge about patterns of drug use and injection behavior is based on self-reported information. The validity and reliability of self-reports of active drug use have been established in many studies utilizing similar methods for collecting information about addictive behaviors (29), as well as in a previous study in which substantial agreement between self-reported heroin use and morphine detection in urine was documented (30).

Overall, these results suggest that experimental studies involving opioid administration to non-treatment seeking heroin dependent individuals were associated with few ethical concerns regarding subsequent heroin use. In fact, such research participation appeared to provide an opportunity for many of the heroin users to decrease their heroin use or even to initiate treatment for their heroin dependence. In the overall context of difficult access to opioid dependence treatment, participation in laboratory studies might serve as an entry point to improve access to care for drug users and at the same time to improve our knowledge of drug abuse and addiction.

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Table 1

Description of studies conducted in the Opioid Laboratory of the Substance Abuse Research Center at Columbia University.

Study protocol	# 4857	# 5182	# 5518	# 5725
Length	8 weeks	2.5 weeks	8–9 weeks	3 weeks
Total number of participants	26	19	15	41
Number of completers	15	12	12	30
Payment ($)	2800–3500	1010–1130	3300–3900	1175
Objectives	Examination of the reinforcing effects of oral prescription opioids in buprenorphine-maintained participants.	Relationship between infusion duration and reinforcing effects of intravenous oxycodone in buprenorphine-maintained individuals.	Reinforcing effects of intravenous buprenorphine versus bup/naloxone in bup-maintained intravenous drug users maintained on different doses of sublingual buprenorphine.	Evaluation of ibudilast, a glial activation inhibitor, in heroin abusers under conditions of morphine maintenance and withdrawal.
Drugs of exposure	Oxycodone Morphine	Oxycodone Buprenorphine	Buprenorphine Bup/naloxone Heroin	Oxycodone Morphine AV411
Procedures	Drug versus money choice Drug versus drug choice	Drug versus money choice	Drug versus money choice	Drug administration
Measurements	Subjective effects Reinforcing effects Performance effects Physiological effects	Subjective effects Reinforcing effects Performance effects Physiological effects	Subjective effects Reinforcing effects Performance effects Physiological effects	Withdrawal symptoms Subjective effects Performance effects Physiological effects Analgesic effects
Publications	These data also include participants who completed a pilot phase of the study; Manuscript in preparation.	Comer et al., 2009 [9]	Comer et al., 2010 [10]	Manuscript in preparation.

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Table 2

Factors associated with heroin cessation at the one-month follow-up visit; Bivariate and multivariate analysis based on a logistic regression model (n=69)

		Bivariate analysis		Multivariate analysis	
	Number of participants (%) or median [IQR]	**OR (95%CI)**	**p-value**	**aOR (95%CI)**	**p-value**
Study protocol[a]					
#4857	15 (22)	1			
#5182	12 (17)	0.88 (0.19 – 4)	0.86		
#5518	12 (17)	1.23 (0.26 – 5.67)	0.80		
#5725	30 (43)	0.32 (0.09 –1.17)	0.08		
Age	38 [35 – 42]	0.98 (0.88 –1.08)	0.65		
Gender					
Male	60 (87)	1			
Female	9 (13)	1.88 (0.46 – 7.70)	0.38		
Years of education[b]	12 [11 – 13]	1.03 (0.87 –1.22)	0.75		
Race					
Caucasian or Hispanic *	**50 (72)**	**1**			
African American	**19 (28)**	**2.44 (0.83 – 7.19)**	**0.10**	**3.90 (1.04–14.66)**	**0.04**
Employment					
No	57 (83)	1			
Yes	12 (17)	1.48 (0.42 –5.16)	0.54		
History of treatment[c]					
No	**29 (42)**	**1**			
Yes	**38 (55)**	**3.88 (1.34 – 11.25)**	**0.01**	**5.03 (1.49–17.03)**	**0.01**
Years of heroin use[d]	**12 [8 – 16]**	**0.94(0.88 – 1.02)**	**0.14**	**0.90 (0.82–0.98)**	**0.02**
Route of administration					
Intravenous	45 (65)	1			

		Bivariate analysis		Multivariate analysis	
	Number of participants (%) or median [IQR]	**OR (95%CI)**	**p-value**	**aOR (95%CI)**	**p-value**
Intranasal	24 (35)	0.57 (0.20–1.60)	0.29		
Heroin bags per day (M0)[e]	**6 [4 –8]**	**1.15 (0.99 –1.34)**	**0.07**	**1.19 (1.03–1.36)**	**0.02**
Polydrug use[f]					
No	36 (52)	1			
Yes	31 (45)	1.01 (0.38 – 2.68)	0.98		
Cocaine use[g]	**1 [0 – 2]**	**1.12 (0.96 –1.32)**	**0.14**		

[a] see Table 1

IQR = Inter-Quartile Range

aOR = adjusted Odds Ratio

[b] for each grade year increase

[c] for heroin dependence (opioid maintenance treatment or detoxification program) during lifetime

[d] per one year increase

[e] at the consent visit before entering the study (baseline visit)

[f] use of more than 2 drugs during the previous month

[g] number of days per month

[*] no significant difference between Caucasian and Hispanic was found