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ORIGINAL INVESTIGATION

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Sex differences in the acquisition of intravenously self-administered cocaine and heroin in rats

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Abstract *Rationale:* Despite numerous reports that male and female animals differ in behavioral responses to drugs, few studies have investigated sex differences in drug-reinforced behavior. *Objectives:* Acquisition of IV cocaine and heroin self-administration was compared in 20 female and 22 male Wistar rats. *Methods:* An autoshaping procedure was used to train rats to press a lever that resulted in either a 0.2 mg/kg infusion of cocaine or a 0.015 mg/kg infusion of heroin under a fixed-ratio 1 (FR 1) schedule. Daily sessions consisted of six 1-h autoshaping components followed by a 6-h self-administration component. During each autoshaping component, a retractable lever briefly (15 s) extended into the test chamber on a random interval schedule with a mean of either 90 s (cocaine groups) or 480 s (heroin groups) and either ten (cocaine groups) or five (heroin groups) computer-automated infusions were delivered each hour. During each 6-h self-administration component, the lever remained extended and each response on the lever resulted in an infusion of either cocaine (0.2 mg/kg) or heroin (0.015 mg/kg). The criterion for acquisition of cocaine self-administration was a mean of at least 100 infusions and the criterion for heroin self-administration was a mean of at least 20 infusions during the self-administration component over five consecutive sessions. *Results:* Female rats acquired both cocaine and heroin self-administration more rapidly than males. Acquisition of cocaine self-administration occurred in a greater percentage of female rats compared to males. Female rats self-administered more cocaine than males after acquisition criteria had been met. *Conclusions:* These findings indicate that female rats were more vulnerable than males to the acquisition of cocaine and heroin self-administration under the conditions of the present experiment.

Key words Acquisition · Cocaine · Heroin · Rat · Self-administration · Sex difference

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Introduction

Drug research involving both humans and animals has focused predominately on the study of males (Lex 1991; Carroll and Mattox 1997). However, it is now apparent that women and men differ on several characteristics of drug addiction. In general, more men than women abuse alcohol and drugs (except cigarettes, tranquilizers, and prescription medications; Hser et al. 1987; Lex 1991; Kosten et al. 1993; Ettorre et al. 1994; Dudish and Hatsukami 1996; Clemmey et al. 1997; Kandel et al. 1997). However, women initiate cocaine use sooner (Griffin et al. 1989; Lex 1991; Weiss et al. 1997), become more intoxicated after similar levels of alcohol intake (Lex 1991), have more emergency room visits following crack use (Dudish and Hatsukami 1996), and take less time to become addicted to cocaine, opioids, and alcohol after initial use than men (for review see Lex 1991). These differences may be due to innate biological gender differences, or to sociocultural factors. Animal models that mimic the different phases of the addiction process (acquisition, maintenance, withdrawal, relapse) might be useful for addressing the question of gender differences.

Such animal models are especially useful for investigating the acquisition phase of drug addiction, since it is not ethical to conduct experiments on the initiation of illicit drug use in drug naive humans. However, the acquisition phase is difficult to study because it is typically brief, and it is characterized by a sudden shift from low to high levels of intake (for review, see Carroll and Campbell 1999). Thus, the use of methods that slow the acquisition process, and decrease intersubject variability, are necessary to observe this transitory period. For example, acquisition has been investigated by using very low doses of drug per lever press response (Deminiere et al. 1989). A method that has been used in this laboratory is an automated autoshaping procedure (Brown and Jenkins 1968; Carroll and Lac 1993, 1997, 1998). This method was adapted to the study of acquisition of drug self-administration (Carroll and Lac 1993) because

previous work with food showed that the acquisition curve could be slowed by increasing the interval between lever retraction and presentation of food reinforcement (Messing et al. 1986). This method has the advantage of standardized acquisition criteria that are adjusted for dose and type of drug, and it offers a quantifiable measure of comparing differences between groups.

These acquisition methods have revealed several organismic and physiological factors that predict vulnerability to drug self-administration such as genetic strain (Grahame and Cunningham 1995; Kosten et al. 1997; Shoaib et al. 1997), corticosterone levels (Piazza et al. 1991), innate saccharin preference (Gahtan et al. 1996; Gosnell et al. 1998), dopamine release in the left medial prefrontal cortex (Glick et al. 1992, 1994), and behavioral reactivity to stressors and to acute injections of drugs (Deminiere et al. 1989; Piazza et al. 1989; Grimm and See 1997).

An additional factor that may predict vulnerability to drug self-administration is sex. Results from studies that have investigated maintenance levels of psychostimulant self-administration reveal that female rodents self-administer significantly more caffeine (Heppner et al. 1986) and cocaine (Hill and Powell 1976; Morse et al. 1993) than do males, and females are more sensitive than males to the reinforcing effects of cocaine (Roberts et al. 1989). Additionally, previous research has shown that female rats display a more intense behavioral response to environmental stressors (Burke and Broadhurst 1966), and a greater locomotor response to psychostimulant drugs (Schneider and Norton 1979). In males, these characteristics have been shown to be positively correlated with an increased rate of acquisition to psychostimulant self-administration (Piazza et al. 1989). However, to our knowledge, only one study has investigated sex differences in acquisition of psychostimulant drug self-administration (Haney et al. 1995). In this study, a high dose of cocaine was used, and all animals acquired self-administration rapidly.

Sex differences have also been reported for other drug classes. For example, drug-experienced female rodents self-administer more morphine (Alexander et al. 1978), fentanyl (Klein et al. 1997), and alcohol (Lancaster and Spiegel 1992) than male rodents. Additionally, female vervet monkeys showed a higher frequency of alcohol intake than males (Juarez et al. 1993). In contrast, Stewart et al. (1996) reported that female and male rats did not differ in either the acquisition or the maintenance of heroin self-administration. The purpose of the present experiment was to compare the rate of acquisition of cocaine and heroin self-administration in female and male rats. Low doses of cocaine and heroin were selected and compared in female and male rats to extend previous work to lower doses and other drug classes (opioids). Since it was postulated that female rats would acquire drug self-administration more quickly than males, drug doses and feeding conditions were based on previous work that produced relatively slow rates of acquisition in males (Carroll and Lac 1993, 1998).

Materials and methods

Animals

Twenty female and 22 male, drug naive, sexually mature Wistar (Harlan Sprague Dawley, Madison, Wisc., USA) rats were used as subjects. Female and male rats were matched for age, and they weighed a mean of 285.0±6.16 g (female) and 396.5±8.15 g (male) at the start of the experiment. Rats were individually housed in hanging stainless steel home cages with free access to food and water for a minimum of 5 days after arrival in the laboratory. Subsequently, each rat was implanted with a chronic, indwelling catheter into the right jugular vein following methods that have been described previously (Weeks 1972; Carroll and Boe 1982). After cannulation, the rats were placed in individual operant test chambers where they remained for the duration of the experiment. Rats had free access to Purina Laboratory Chow (Purina Mills, Minneapolis, Minn., USA) and water. Food and water were changed daily at 8:00 a.m. and intake of each was recorded.

Apparatus

Operant test chambers were octagonal in shape with alternating stainless steel and Plexiglas walls. Stainless steel walls contained a drinking spout, a food jar, a standard response lever, and a retractable lever (Coulbourn Instruments, Lehigh Valley, Pa., USA). Three colored stimulus lights were located above each lever, and a house light (4.76 W) that was constantly illuminated was located at the top of the chamber. A sound-attenuating wooden box containing an exhaust fan for ventilation enclosed each operant chamber. An infusion pump (RHSYH, Fluid Metering, Oyster Bay, N.Y., USA) and a 500-ml aspirator bottle containing a solution of cocaine or heroin were mounted outside each chamber. Details of the infusion system and chambers have been described previously (Carroll and Boe 1982). Programming and data collection were controlled by an IBM-compatible computer with Med-PC interface (Med Associates, St Albans, Vt., USA) that was located in an adjacent room.

Drugs

Cocaine HCl and heroin (3,6-diacetylmorphine) HCl were provided by the National Institute on Drug Abuse (Research Triangle Institute, Research Triangle Park, N.C., USA). Drugs were mixed in sterile saline solutions and dose was determined by infusion duration which was 1 s/100 g body weight. Cocaine and heroin doses (0.2 and 0.015 mg/kg per infusion, respectively) were held constant. Rate of infusion was also held constant, rather than infusion duration, in accordance with previous work that has shown that the speed at which the drug is delivered determines its reinforcing efficacy (Kato et al. 1987). The mean infusion duration was 2.9 s for females and 4.0 s for males. Drug solutions were made weekly and refrigerated, but they were added to the aspirator bottles at room temperature.

Procedure

Two groups of ten female rats (cocaine and heroin), one group of ten male rats (cocaine), and one group of 12 male rats (heroin) were tested. After 5 days of recovery from surgery, the autoshaping sessions began. The autoshaping program that was used has been previously reported (Carroll and Lac 1993). Autoshaping sessions began at 9:00 a.m., 7 days per week and consisted of six 1-h autoshaping components followed by a 6-h self-administration component. At the beginning of each 1-h autoshaping component, the retractable lever extended into the operant chamber on a random interval schedule with a mean of 90 s for cocaine groups and 480 s for heroin groups, and the three stimulus lights above each lever were illuminated. The inactive (activity) lever was extended into the chamber throughout the experiment. The active lever was retracted when the animal depressed the lever, or after 15 s, whichever came first. An infusion of cocaine (0.2 mg/kg), or heroin (0.015 mg/kg) was delivered 1 s after each lever retrac-

tion. After either ten infusions (cocaine groups) or five infusions (heroin groups) were delivered, stimulus lights were extinguished, the drug lever was retracted, and responses were recorded but not reinforced. Each autoshaping component lasted approximately 13–15 min for cocaine groups and 30–35 min for heroin groups. Following the last autoshaping component, the 6-h self-administration component began. At the beginning of this period, the retractable lever extended into the operant chamber and stimulus lights above the activity lever were illuminated. Each lever press resulted in an infusion of either cocaine (0.2 mg/kg), or heroin (0.015 mg/kg), and the stimulus lights above the drug lever were illuminated, but the lever remained extended. A time-out occurred at the end of the 6-h self-administration component and all stimulus lights turned off until the next day when the autoshaping session began. Approximately every 7 days, the patency of the catheter was tested by delivering 0.15 ml sodium methohexital (5.0 mg/kg IV) through the cannula and flushing it with 0.30 ml saline. Patency was assumed if loss of muscle tone was observed within 5 s. If a catheter was not patent, a new one was implanted into the left jugular vein, and testing resumed 3 days after the animal recovered from surgery.

The criterion for acquisition of cocaine self-administration was a mean of 100 or more infusions and the criterion for acquisition of heroin self-administration was a mean of 20 or more infusions during the self-administration component over five consecutive sessions. These acquisition criteria were based on previous work conducted in this laboratory on acquisition of cocaine self-administration (Carroll and Lac 1993, 1997, 1998), and on intake patterns observed in a pilot study on acquisition of heroin self-administration. For both groups, if the acquisition criteria were not met within 30 sessions, the experiment was terminated. The cocaine dose (0.2 mg/kg) selected was based on previous research that showed that approximately 50% of male, food satiated rats acquired 0.2 mg/kg cocaine self-administration in 11 days or more (Carroll and Lac 1993, 1998). The heroin dose was chosen because pilot data from this laboratory showed that both female and male food-satiated rats rapidly acquired self-administration of a higher dose (0.03 mg/kg per infusion), suggesting that a lower dose was needed to avoid a ceiling effect. To obtain information regarding the estrous cycle of female rats self-administering IV drugs, several rats in the present experiment were tested for whether or not the estrous cycle was functioning. Although this was done randomly in only a few rats, and the data are not presented, results indicated that the rats were cycling. The testing procedure which required brief vaginal swabbing did not interfere with the experimental protocol. Phase of estrous cycle and drug self-administration patterns are the focus of an ongoing study.

Data analysis

Dependent measures were the number of days to meet the acquisition criterion, the percentage of rats per group to meet acquisition criterion, drug intake during the last five self-administration sessions of the acquisition period, and food and water intake. Separate one-tailed *t*-tests were used for all predicted a priori comparisons, and separate two-tailed *t*-tests were used for all other a priori comparisons. The Kaplan-Meier survival analysis (StatView; Abacus Concepts Inc., Berkeley, Calif., USA) and the Breslow-Gehan-Wilcoxon rank statistic were used to compare statistically the rate of acquisition and percentage of female and male rats acquiring cocaine and heroin self-administration. A P value ≤ 0.05 indicated significant differences. Rats that did not meet the acquisition criteria within 30 days were excluded from all analyses except food and water comparisons.

Results

In Fig. 1, data are presented as an inverse survival function (Cox and Oakes 1984) to illustrate rates of acquisition and the percent of rats meeting the acquisition criteria in each

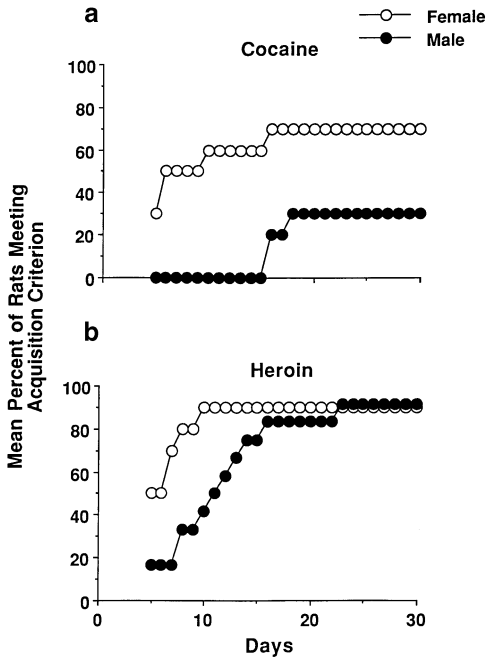

Fig. 1a, b The percentage of female (*open circles*) and male (*solid circles*) rats to meet the cocaine (**a**) and heroin (**b**) acquisition criteria within the 30-day limit. Data are presented as a function of day during the autoshaping testing period

group. For cocaine self-administration, female rats acquired drug self-administration at a faster rate than male rats, and a greater percentage met the acquisition criterion. Female rats that met the acquisition criterion did so in significantly fewer days than male rats that met the acquisition criterion (t=–10.74, df=6,2, P<0.05). Specifically, female rats acquired in a mean of 7.57 (±1.56) days, whereas male rats acquired cocaine self-administration in a mean of 16.67 (±0.67) days. As with cocaine self-administration, female rats acquired heroin self-administration in significantly fewer days compared to male rats (t=–5.97, df=8,10 P<0.05). Female rats met the acquisition criterion in a mean of 8.7 (±2.43) days, compared to a mean of 13.0 (±2.12) days for the male rats. Of the female rats self-administering cocaine, 70% met the acquisition criterion within the 30-day maximum compared to only 30% of males. For heroin self-administration, the percentage of female rats meeting the heroin acquisition criterion was 90% compared with 91.7% of the male rats within the 30-day maximum. Survival analyses were used to test for differences in rates of acquisition between female and male rats for both drug groups. The results, which produced the Breslow-Gehan-Wilcoxon rank statistic revealed significant differences between females and males for both cocaine and heroin self-administration (c^2=6.052, df=1, P<0.05; c^2=4.975, df=1, P<0.05, respectively). However, although females acquired heroin self-administration at a faster rate than male rats, by day 23 female and male rats did not differ. Thus, female rats acquired drug self-administration at a significantly faster rate than male rats, and more females than males acquired cocaine self-administration.

Figure 2 shows mean number of cocaine and heroin infusions during the self-administration component for

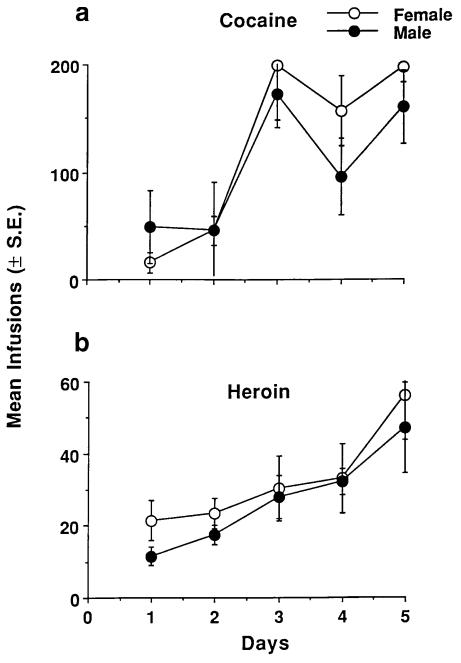

Fig. 2a, b Mean (±SE) number of cocaine (**a**) and heroin (**b**) infusions per day for female (*open circles*) and male (*solid circles*) rats. Data represent means for each day during the 5-day criterion period for the seven female rats and three male rats that met the cocaine acquisition criterion and for the nine female and 11 male rats that met the heroin acquisition criterion

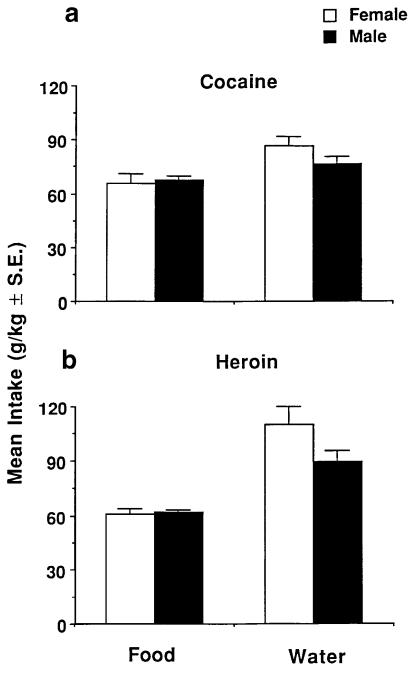

Fig. 3a, b Mean (±SE) food and water intake in g/kg for female (*open bars*) and male (*solid bars*) rats in the cocaine (**a**) and heroin (**b**) groups. Data represent mean intake over the acquisition testing period and each bar represents a mean of ten rats, except for male rats in the heroin group (n=12)

the last 5 days of acquisition for male and female rats. For cocaine self-administration, acquisition was characterized initially by low levels of intake (days 1 and 2), followed by a peak in intake (day 3), and then levels stabilized (days 4 and 5). This sudden transition from low to high levels of intake was not typically observed with heroin acquisition; rather, the number of infusions gradually increased over the 5-day acquisition period. For both cocaine and heroin self-administration, mean drug intake was slightly greater in female rats compared to male rats; however, the difference in mean intake over the 5-day period was significant only for cocaine self-administration (t=5.549, df=7,3, P<0.05). Responses on the activity lever were very low throughout the experiment, and there were no significant differences between female and male rats for either drug groups (data not shown). Thus, patterns of intake during the acquisition period differed between cocaine and heroin, and female rats self-administered more cocaine compared to male rats.

Figure 3 shows food and water intake (g/kg) for cocaine and heroin groups. Similar levels of food intake were observed between drug groups and between female and male rats when adjusted for body weight. Water intake was slightly greater in female rats for both cocaine and heroin groups, but this difference was not statistically significant. Thus, female and male rats did not differ in their relative intake of food and water.

Discussion

This investigation was designed to characterize sex differences in the acquisition of IV cocaine and heroin self-administration. The results demonstrate that 1) female rats acquired both cocaine and heroin self-administration more rapidly than did males, 2) acquisition of cocaine self-administration occurred in a greater percentage of female rats compared to males, and 3) female rats self-administered more cocaine than did males. Furthermore, the differences observed in acquisition of drug self-administration can not be attributed to either 1) differences in food and water intake as female and male rats consumed similar levels of both or 2) differences in nonspecific activity as responses on the inactive drug lever were negligible for both male and female rats.

A greater percentage of female rats acquired cocaine self-administration, and female rats acquired at a faster rate than male rats. These results were expected based on previous research that has shown that female rats are more sensitive to both the behavioral effects (e.g. Schneider and Norton 1979) and the reinforcing effects of psychostimulants (Roberts et al. 1989). Thus, the present results extend previous findings on sex differences to include acquisition of cocaine self-administration in drug naive animals.

The finding that only 30% of male rats acquired cocaine self-administration under the conditions of the present experiment is lower than that found in previous research on acquisition of cocaine self-administration (Carroll and Lac 1993, 1998). For example, Carroll

and Lac (1998) investigated acquisition of cocaine (0.2 mg/kg) self-administration in male rats that received unlimited amounts of ground chow using the same auto-shaping procedure. Under these conditions, 76.92% of the male rats acquired cocaine self-administration. Two differences between the present experiment and the previous experiment may explain this discrepancy. First, at the start of the present experiment the rats were approximately 90–100 days compared to 125–190 days old in the previous study. However, differences in age seems an unlikely explanation for the discrepancy, as previous research with vervet monkeys showed that juvenile monkeys initiated oral alcohol self-administration sooner than adult monkeys (Juarez et al. 1993). A second difference between the present experiment and the previous one is level of food intake. In the previous study, male rats consumed a mean of 20.5 g of food compared to a mean of 27.8 g in the present study. Several studies have demonstrated that acquisition of drug self-administration is inversely related to food intake (DeVry et al. 1989; Carroll and Lac 1993, 1998; Donny et al. 1998). Moreover, feeding condition has been shown to have a powerful effect on drug self-administration that can after behavior in each phase of the addiction process (Carroll 1997). Thus, differences in the percentage of male rats acquiring cocaine self-administration in the present experiment as compared to that of the previous experiment, are most likely due to differences in food intake. It should be noted, however, that the differential rate of acquisition between female and male rats in the present experiment cannot be attributed to food intake as female and male rats consumed similar levels on a g/kg basis.

The finding that female rats acquired heroin self-administration at a faster rate than males, is not supported by findings reported by Stewart et al. (1996). In their study, acquisition of heroin self-administration was compared in male and female rats using four doses of heroin (approximately 0.006, 0.013, 0.025, and 0.050 mg/kg per infusion) presented in ascending order. There were four 3-h sessions per day, and each dose was available for 3 days. Although acquisition criteria were not specified, mean number of infusions at each dose, each day, were used to compare males to females. They found that male and female rats did not differ in either the acquisition of low doses or in intake as dose was increased. Furthermore, all animals (except one male, and two female rats) acquired heroin self-administration rapidly, and they all had stabilized on heroin within 7 days (at the 0.025 mg/kg dose). In contrast, in the present study, the mean number of days to acquire heroin self-administration was 8.7 (±2.43) for females and 13.0 (±2.12) for males, a significant difference; however, these differences disappeared once the acquisition criteria were met (e.g. no significant differences in total intake). The present results suggest that differences between female and male rats in the acquisition of heroin self-administration may be restricted to rates of acquisition, and they were revealed only under the auto-shaping conditions that slowed acquisition.

Female rats in the present study self-administered more cocaine than male rats. These results are consistent with other studies that have reported a significant sex difference with female mice self-administering slightly greater levels of cocaine than male mice (Hill and Powell 1976; Morse et al. 1993). However, two previous studies have reported no difference between female and male rats in total intake (Roberts et al. 1989; Haney et al. 1995). In contrast to findings that female rodents self-administer more morphine (Alexander et al. 1978) and fentanyl (Klein et al. 1997) than male rodents, no significant difference between males and females in heroin intake was observed in the present experiment. In the previous study investigating morphine self-administration (Alexander et al. 1978), rats had experience self-administering morphine for 68 days before intake data between males and females were compared due to low levels of intake during earlier sessions. Thus, differences in intake may develop over time such that differences in opioid intake may not be apparent during the acquisition phase. In contrast, differences between females and males in fentanyl self-administration were observed by day 3 of initial self-administration, suggesting that tolerance may develop more rapidly in female rodents compared to males (Klein et al. 1997). Future research is needed to address this question.

In conclusion, the results of this investigation revealed that although female and male rats consumed similar levels of food and water, female rats were more vulnerable to the acquisition of both IV cocaine and heroin self-administration under the conditions of the present experiment. Additionally, female rats self-administered more cocaine than did males when self-administration behavior had stabilized. This experiment was designed to characterize sex differences in acquisition of drug self-administration. However, the present data do not provide information on the mechanisms underlying the observed differences. Previous research suggests that gonadal hormones, particularly ovarian hormones, may be an important factor in producing sex differences in both behavioral responses to drugs (e.g. Becker et al. 1982) and in drug use (e.g. Roberts et al. 1989)). Future research is underway to investigate the effect of gonadal hormones on acquisition of drug self-administration, as well as their effects in maintenance, and relapse to drug self-administration.

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