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Effects of Experimental Unemployment, Employment and Punishment Analogs on Opioid Seeking and Consumption in Heroin-Dependent Volunteers

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Abstract

This study investigated the extent to which hydromorphone (HYD) choice and behavioral economic demand differed during experimental analogs of Unemployment (*Drug Only*: HYD and no money alternative), Employment (*Drug or Money*: HYD and $4 alternative), and Punishment (*Drug Only + Money Loss*: HYD only and $4 subtracted for each HYD choice), in the context of anticipated high vs. low post-session drug availability (HYD 24 mg vs. placebo). Eleven heroin-dependent, buprenorphine-stabilized (8-mg/day) volunteers first sampled two HYD doses (0 and 24 mg IM in randomized, counterbalanced order, labeled Drug A [session 1] and Drug B [session 2]). In each of the final six sessions, volunteers were given access to a 12-trial choice progressive ratio (PR) task and could work to receive HYD unit doses (2 mg each); cumulative dose units earned were administered in a bolus injection after the work session. Before the PR task, volunteers were told which HYD dose (Drug A or B) would be available 3 hr after the PR-contingent injection. Relative to Unemployment (*Drug Only*), Employment (*Drug or Money*) and Punishment (*Drug Only + Money Loss*) each significantly suppressed HYD seeking (e.g., breakpoints). Employment and Punishment also reduced HYD behavioral economic demand, but *via* different mechanisms: Employment increased HYD price-elasticity, whereas Punishment decreased HYD demand intensity. Adjusting for the initial level difference (i.e., normalized demand), Employment significantly decreased P_{max} (i.e., lower "essential value" of HYD) and O_{max} (maximum HYD responding) compared to Punishment or Unemployment. These effects were not significantly altered by post-session drug availability.

Keywords

Behavioral economic analysis; Heroin dependence; Employment; Unemployment; Punishment; Contingencies; Drug seeking

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1. Introduction

There has been spirited debate regarding two different approaches for reducing substance abuse: first, positive reinforcement of non-drug activities (e.g., employment, prosocial interaction) to forge a behavioral repertoire that competes with drug use; and second, punishment of drug use to dissuade this behavior. In practice, these approaches are not mutually exclusive: Contingency management treatment often uses a combination of positive reinforcement (e.g., vouchers for drug-free urine specimens) and negative punishment (e.g., resetting voucher value to low levels given urinalysis evidence of renewed drug use) to improve outcomes (Iguchi et al., 1988; Roll and Higgins, 2000; Schumacher et al., 2007; Chopra et al., 2009).

The controlled laboratory setting is useful for investigating mechanisms underlying these effects. It has been shown that drug self-administration (SA) can be attenuated in a magnitude-dependent manner using competing non-drug positive reinforcement, e.g., food with laboratory animals (Nader and Woolverton, 1991, 1992), and money with human subjects (Comer et al., 1998; Petry and Bickel, 1999; Heishman et al., 2000). In human studies of drug SA, providing a concurrent response-contingent economic alternative simulates employment. This is informative because, in the naturalistic setting, employment is associated with less substance use (Zanis et al., 2000; Kerrigan et al., 2004; Butzin et al., 2005; Silverman et al., 2005). Greenwald and Steinmiller (2009) showed that providing a $4 vs. $2 alternative could decrease opioid seeking behavior but only when no supplemental drug was available for consumption outside the choice session, suggesting that the individual's drug supply can moderate the impact of employment on drug seeking.

Bickel et al. (1995) examined effects of varying unit prices (UP = response requirement ÷ drug dose) to obtain cigarette puffs with vs. without opportunities to earn money (simulated employment) or, in separate sessions, to engage in recreational activities. Both non-drug reinforcers (money and recreation) attenuated cigarette use, due to lower cigarette demand intensity (i.e., consistently less consumption across all UPs) rather than increased elasticity of demand (i.e., progressively less consumption as UP increased). Data from these employment manipulations are consistent with observations that employment is associated with less substance abuse (e.g., Zarkin et al., 2002; Kidorf et al., 2004; Hser et al., 2006; Williamson et al., 2007). Bickel et al. (1995) note that the similar effects of employment and recreation indicate that money *per se* may not be the key factor that reduces drug consumption but, rather, the opportunity to engage in non-drug reinforced behavior.

Controlled laboratory studies have also demonstrated the ability of punishment to reduce drug SA. Studies with laboratory animals have shown that cocaine SA is suppressed when its delivery is paired with positive punishers such as electric shock (Grove and Schuster, 1974; Johanson, 1977; Pelloux et al., 2007) and injection of histamine (Woolverton, 2003; Negus, 2005), or when cocaine is paired with negative punishers such as a variable interval time-out period (Nader and Morgan 2001). Similarly, opioid SA has been shown to decrease when opioid delivery is paired with electric shock (Panlilio et al., 2003, 2005). Studies with human subjects have shown that consumption of cigarettes (Powell and Azrin, 1968) and alcohol (Wilson et al., 1975) can be suppressed when response-contingent drug delivery is paired with electric shock.

Only one experiment has directly compared the efficacy of non-drug positive reinforcement *versus* punishment for reducing drug choice. Roll and Howard (2008) reported an effect of `economic valence' on cigarette smoking abstinence in volunteers who were randomly assigned to one of two 5-day interventions: money gain for abstinence *vs.* money loss for non-abstinence. Money gain was more effective than money loss for promoting 48-hr continuous abstinence

(90% vs. 44% of participants, respectively), although the money loss group also missed more outpatient visits. Further studies would be useful to determine whether positive reinforcement and punishment interventions differentially reduce drug responding across a wide range of unit prices, abused substances, and under limited-access (closed economy) *versus* open-economy conditions.

This study investigated in opioid-dependent individuals whether experimental employment and punishment differentially reduce hydromorphone (HYD)-seeking behavior relative to experimental unemployment, where drug seeking should be at high levels (Bray et al., 2000; MacDonald and Pudney, 2000; Khan et al., 2002; Khlat et al., 2004; Merline et al., 2004; Mossakowski, 2008). In the Unemployment analog, there was no money alternative; participants could respond to earn HYD unit doses or not respond at all. In the Employment analog, participants could respond to earn units of money or HYD doses. The Punishment analog resembled the Unemployment condition in that there was no money alternative but responding for each unit HYD dose resulted in losing money. The hypothesis was that, relative to Unemployment, both Employment and Punishment conditions would decrease HYD seeking and consumption. Based on the `economic valence' results of Roll and Howard (2008), it was also hypothesized that Employment might decrease HYD seeking more than Punishment.

2. Methods

2.1. Participant recruiting and selection

The Wayne State University Institutional Review Board approved all procedures. This study was conducted according to the Declaration of Helsinki and registered as NIH clinical trial NCT00608504 (http://clinicaltrials.gov/ct2/show/NCT00608504). Heroin-dependent males and females, ages 18 to 55 years, and not seeking substance abuse treatment were recruited by advertisements and word-of-mouth. Volunteers provided a medical history, blood and urine samples, and received an electrocardiogram, tuberculin screening and physical exam. Those selected reported no chronic health problems and were not taking prescribed medications. A clinician administered a semi-structured interview (SCID-IV; First et al., 1996). Volunteers were excluded if they met DSM-IV diagnostic criteria for a current Axis I disorder (except Opioid and Nicotine Dependence) or were cognitively impaired (IQ < 80) based on the Shipley Institute of Living Scale (Zachary, 1991). As in our previous studies, individuals were excluded who scored more than 15 on the 10-item Injection and Blood Withdrawal Phobia subscale of the Medical Fear Survey (Kleinknecht et al., 1999).

During screening, volunteers had to provide a urine sample positive for opioids (> 300 ng/ml) and negative for methadone, benzodiazepines (< 300 ng/ml) and barbiturates (200 ng/ml). Urine samples testing cocaine-positive (> 300 ng/ml) and THC-positive (> 50 ng/ml) were allowed at screening but subjects meeting diagnostic criteria for Cocaine or Cannabis Use Disorders were excluded. Volunteers also had to provide alcohol-free breath samples (< .002%). After procedures were fully explained, all volunteers provided written informed consent.

2.2. Study Design

Study design and methods were similar to two related protocols (Greenwald and Hursh, 2006; Greenwald and Steinmiller, 2009). This experiment had two parts. In part 1 (sampling), each participant was exposed to HYD 24 mg (HYD) and saline (SAL) in randomized order, counterbalanced across subjects. Individuals who reported greater subjective effects to HYD than SAL, and had no adverse effects, could continue. In part 2 (choice), a within-subject randomized crossover design was used to test the effects of Economic Contingency Condition (3 levels: Unemployment, Employment, Punishment) and post-session drug availability (2

levels: SAL, HYD) on HYD seeking and consumption. Within each of the final 6 test sessions, response requirements in the progressive ratio (PR) schedule generated an exponentially increasing range of 12 unit prices (UP = fixed ratio [FR] ÷ HYD unit dose [2 mg per trial], from 62.5 to 6250; same as Greenwald and Steinmiller, 2009).

The Unemployment analog provided only response-contingent HYD (2 mg/trial) but no money alternative (*Drug Only*). The Employment analog provided subjects the option to respond to earn $4 per trial with HYD 2 mg/trial concurrently available as the other option, for a maximum of $48 or 24 mg across choice trials per session (*Drug or Money*). The Punishment analog also lacked a money-earning option and, for each drug choice (HYD 2 mg/trial), participants lost $4, i.e., maximum $48 loss (*Drug Only + Money Loss*). Amounts lost in the *Drug Only + Money Loss* condition were subtracted from participants' base pay (see section 2.6).

2.3. Settings and Protocol Timeline

Participants were initially outpatients during stabilization on buprenorphine (BUP) 8 mg/day for at least 10 days; extensions of this period were due to participant and staff scheduling constraints. Actual (mean ± 1 SD) duration of BUP stabilization was 16.5 ± 5.5 days (range, 12 to 28). Participants were typically admitted on a Tuesday, and testing occurred on consecutive weekdays. Residential living combined with staff observation and daily urine testing ensured abstinence from unsanctioned drug use during the study procedures. On test session days, participants were escorted from the inpatient unit to the laboratory, and returned to the inpatient unit after each session. During non-experimental periods (evenings and weekends), volunteers could engage in recreational activities available on the unit, e.g., reading, listening to music, riding an exercise bicycle, watching television or movies, arts and crafts, and making telephone calls.

2.4. Procedures

2.4.1. Sampling sessions—Hydromorphone sampling occurred on the first two weekdays (11:30 am – 3:00 pm) of the inpatient stay. The injections administered in the first and second sessions were identified as “Drug A” and “Drug B”, respectively. Participants were asked to attend to the effects produced by each dose because, in later sessions, they would be able to choose to take these drugs. Whether SAL or HYD served as Drug A or Drug B was randomized and counterbalanced across subjects. Subjective drug effects and vital signs were measured −0.5, +0.5, 1.0, 1.5, 2.0, 2.5 and 3.0 hr relative to drug administration.

2.4.2. Choice sessions—The six drug/money choice sessions were conducted from 8:30 am – 5:30 pm on subsequent weekdays. The timeline for each choice session and the PR schedule are identical to our recent study (see Figure 1 in Greenwald and Steinmiller, 2009). In each choice session, only units of the participant's active HYD dose (Drug A or B) were available. At 8:50 am, the volunteer was instructed in one of the following three ways: “This morning from 9:00 am to noon, you will be able to work on 12 trials for …”

> [*Drug Only condition*] “…1/12th of Drug ___ (A or B [*active dose*]) per trial only; today money will not be available. You can work for all or part of the drug, or you do not have to respond at all. On each trial, you will only see the word `Drug' on the computer screen. Once you complete a single key press on the option, you will be committed to that choice. Once you complete responding for that trial, you are again free to choose drug or not. If you respond for drug, you will earn 1/12th of the total drug for every trial that you complete.”
>
> [*Drug Only + Money Loss condition*] “…1/12th of Drug ___ (A or B [*active dose*]) per trial only; today money will not be available. You can work for all or part of the drug, or you do not have to respond at all. On each trial, you will only see the word

> `Drug' on the computer screen. Once you complete a single key press on the option, you will be committed to that choice. Once you complete responding for that trial, you are again free to choose drug or not. If you respond for drug, you will earn $1/12^{th}$ of the total drug for every trial that you complete. Furthermore, every time you choose drug today, you will lose $4 from your study earnings."
>
> [*Drug or Money condition*] "…$1/12^{th}$ of Drug ___ (A or B [*active dose*]) or $4 per trial. You can work for all or part of the drug, all or part of the money, or you do not have to respond at all. On each trial, you will see the words `Drug' and `Money' on the computer screen. Once you complete a single key press on the option, you will be committed to that choice and a box will appear on the screen surrounding whatever option you have chosen for that trial. However, once you complete responding for that trial, you are again free to choose drug or money for the next trial. If you respond for money, you will earn $4 per trial that you complete. If you respond for drug, you will earn $1/12^{th}$ of the total drug per trial that you complete. If you choose neither, then you will not earn any money or any drug for that trial."

Then the volunteer was informed, "This afternoon, Drug __ (A or B) will be available. If you choose to take the drug, it will be administered at 3:15 pm." Volunteers were also told they would still receive a placebo injection if they chose no drug during PR sessions. Individuals with injection phobia were excluded, but this extra step reduced the possibility that participants would simply avoid injections. Screening procedures, instructions, control procedures and periodic assessments of subjective effects confirmed that participants were not injection-avoidant (i.e. did not respond for money to decrease injection frequency), and did not report aversive subjective effects of injections.

During the choice PR task, a sign posted above the computer reinforced the instructions read to them. The monitor screen also differed across experimental conditions. In the *Drug or Money* condition, two adjacent colored boxes at the top of the computer monitor were labeled Money (green) and Drug (red); the subject clicked the mouse button inside the available box to register responses. Across the middle of the computer monitor, adjacent boxes indicated the number of units (range, 0 to 12) earned for money (if available) and drug. In the *Drug Only* and *Drug Only + Money Loss* conditions, the only stimuli visible were the Drug box and its units earned. In all conditions, a counter at the bottom of the computer monitor displayed the time (sec) remaining in the 3-hr session. Immediately after the participant completed each choice, a tone indicated that the unit of drug or money had been earned. A different display appeared for 10 sec (inter-trial interval), during which responding had no consequences and a separate timer counted down. After this time-out period, the original display re-appeared to begin the next choice opportunity.

Few alternative activities were permitted during the 3-hr choice PR task. Participants could not read, smoke cigarettes, eat, watch television, and could not unseat themselves (except bathroom breaks) until time expired. Participants could drink water but not other beverages. After the choice task, the amount of HYD (total unit doses) earned was delivered in a bolus injection. The participant signed his/her subject identification code to provide a receipt of drug and money earnings.

Three hours after receiving the PR-contingent HYD dose (3:00 pm), the research assistant asked the participant whether s/he wanted to receive the additional SAL or HYD injection (i.e., all-or-none) and, if so, a nurse or physician administered the injection. The participant only had to provide a yes/no verbal response to receive the dose.

2.5. Drug Administration

All drugs were administered under double-blind conditions. Drug administration differed based on study phase: (1) outpatient BUP stabilization, (2) inpatient experimental testing, and (3) outpatient dose tapering. During the study, participants received BUP 8-mg tablets (phases 1 and 2) or combinations of 2-mg tablets (phase 3) and matching placebo tablets (mono product, Subutex™; Reckitt-Benckiser, Hull, UK; supplied by Research Triangle Institute, Research Triangle Park, NC, USA). BUP tablets were held sublingually until dissolved, as supervised by a research assistant.

During phase 1 (Monday–Friday), participants attended the laboratory to receive their daily dose of 8 mg; on Saturday, they received a double dose (16 mg) and did not attend the laboratory on Sunday. There were no contingencies associated with opioid use during the lead-in period. During phase 2, participants received daily BUP doses (8 mg) at 8:00 pm. Importantly, BUP dosing itself provides an open (albeit constant) economy for all opioids beyond HYD availability in this laboratory model. For this reason, post-session availability of HYD is parsimoniously not referred to here as an open economy. During phase 3, participants attended the laboratory Monday–Saturday and received BUP 4 mg/day during week one, 2 mg/day during week two, and 0 mg/day during week three.

Doses of HYD (Dilaudid-HP™ in 10 mg/ml ampoules; purchased from the hospital pharmacy) were administered as IM injections (constant volume = 2.4 ml). Doses administered were 0 mg (2.4 ml physiological saline [SAL]) or 24 mg or, after choice PR performance, the response-contingent dose (variable, from 0 to 24 mg).

2.6. Income

Participants were paid (by check) a fixed wage of $40 per night for living on the inpatient unit (to compensate for outpatient opportunity costs); this money was paid in 3 weekly installments during the BUP dose tapering period. Participants were paid an additional $30 for each drug sampling session (for intensive measurement of responses to these doses and to facilitate retention early in the study). Money amounts that could be earned in the *Drug or Money* condition ($4 per choice, up to $48 per session) or lost in the *Drug Only + Money Loss* condition ($4 per drug choice, up to −$48 per session) are a behavioral-economic factor relative to this income level, and the *Drug or Money* condition is a partial replication of our recent study (Greenwald and Steinmiller, 2009). The maximum money loss was roughly equated with the daily wage rate to be an effective deterrent to drug choice. Actual (mean ± SD) money lost on *Drug Only + Money Loss* days (across subjects and post-session supplement days) was $18.91 ± $18.85 (median = $24; mode = $0; range, $0 – $44). During choice sessions, participants did not earn any fixed payment, i.e., the only money earned was obtained by responding on the PR task in the *Drug or Money* sessions. Earnings from those two choice sessions were combined (along with one-half of the inpatient night money) in a single paycheck on the day of discharge from the inpatient unit. Total compensation for participants who completed this study averaged $591 ± $50 (range, $499 to $676).

2.7. Measures

2.7.1. Urine drug testing—Urine samples were obtained during screening and Mon-Wed-Fri during outpatient BUP stabilization (phase 1) and dose tapering (phase 3), and the morning of each inpatient day (phase 2). Collection cups with a temperature-sensitive strip combined with a multi-drug dipstick immunoassay card were used for qualitative urine toxicology. The research assistant first verified that urine temperature was in the valid range (92–96 degrees F). After exposing the test-strip of the dipstick card to the sample, results were for the presence of opioids, cocaine metabolites, benzodiazepines (cutoffs for positive = 300 ng/ml),

barbiturates (cutoff for positive = 200 ng/ml), and THC metabolites (cutoff for positive = 50 ng/ml).

2.7.2. Subjective effects and vital signs—Throughout each drug sampling and choice session, vital signs (respiration rate, oxygen saturation, heart rate, and systolic and diastolic blood pressure) and subjective drug effects questionnaires were completed. Heroin craving was assessed with a 10-item Brief Form (S.T. Tiffany, personal communication, 11/23/99) of the Heroin Craving Questionnaire (Schuster et al., 1995). Seven visual analog scale (VAS, 0–100) ratings were obtained: Any Drug Effect, Good Drug Effect, Bad Drug Effect, High, Like the Drug Effect, Stimulated, and Sedated. Opioid agonist and withdrawal symptoms were assessed using a 32-item Opioid Symptom Questionnaire (Schuster et al., 1995), with 16 Agonist scale items and 16 Withdrawal scale items. Each item was scored on a scale from 0 (not at all) to 4 (extremely), yielding total scores ranging from 0 to 64.

2.7.3. Drug reinforcement—During sampling sessions, a modified Multiple Choice Procedure (Griffiths et al., 1993) was used. Three hours after each HYD dose, the participant used a questionnaire to make independent choices between that day's drug dose (Drug A or B) and 44 money amounts from $0.25 to $25.00. The amount at which the participant switched from choosing drug to money was a proxy measure of the reinforcing value of each dose. This hypothetical reinforcement measure was used to probe whether participants were sensitive to drug dose and would likely be responsive under the more labor-intensive conditions of the choice PR procedure.

During choice sessions, a PR procedure was used. Across trials in each session, the response requirement on each option (i.e., for drug and, in the *Drug or Money* condition, for money) increased independently. Participants were not forced to respond for drug (or money, when available), i.e., they did not have to respond at all, and could rest. Thus, choosing one alternative would not necessarily mean avoidance of the other option.

Several measures of HYD relative reinforcing efficacy were analyzed in each experimental condition: (1) PR breakpoint (highest FR completed); (2) cumulative drug responding, which included all FRs completed plus any non-completed responding for HYD when the 3-hr test session terminated; and (3) total HYD dose (mg) consumed per condition, which included both the HYD supplement dose and the response-contingent HYD dose. Breakpoint and cumulative responding were $\log_{10}$-transformed for ANOVAs, but untransformed data are presented for clarity in Table 2. When subjects did not choose drug at all (i.e., in which case breakpoint and cumulative responding both equaled zero), $\log_{10}$ data were assigned a value of 0.1 for ANOVAs.

2.8. Data Analyses

2.8.1. Sampling—Subjective effects and vital signs measures from sampling sessions were analyzed using two-way HYD Dose (0 and 24 mg) × Time (−0.5, +0.5, 1.0, 1.5, 2.0, 2.5 and 3.0 hr relative to drug administration) repeated measures Analyses of Variance (ANOVAs). Huynh-Feldt adjusted *P* values were used for sphericity violations. The minimum level of significance was set at $P < .05$.

2.8.2. Choice—ANOVAs were used to examine the effects of contingency condition (Employment, Unemployment and Punishment) and post-session drug availability (0 and 24 mg) on several measures of HYD responding. Whether or not the post-session drug dose was consumed in each experimental condition was another dependent measure (i.e., proportion of the sample taking the available dose in each condition), and was analyzed using a binomial test.

Behavioral economic analysis: Drug unit prices (UPs) were defined as the FR requirements of the PR schedule (125, 225, 365, 590, 950, 1500, 2300, 3415, 4915, 6875, 9375 and 12500) divided by the HYD unit dose (2 mg). Demand curve analyses were only conducted on the group data. When binary-coded (0/1) drug choices for each individual are averaged across volunteers at each UP in each condition, the percentage of the group that chooses drug at each UP ("group-percent choice") can be analyzed under the assumptions of behavioral economics. Using the software GraphPad Prism® v.4 (San Diego, CA, USA), a demand curve on UP was fit to the $\log_{10}$–transformed group-percent choice, using the exponential regression equation: $Y = \log(L) * \exp(-A*X)$

In this equation, parameter Y was group-percent choice; parameter L (level of drug choice at the lowest UP) was set to 100% to solve for normalized demand; parameter X was the unit price; and parameter A (i.e., rate of change in slope, or elasticity) was allowed to vary. This equation is a simplified revision of the normalized demand equation (Hursh and Winger, 1995). To evaluate effects of economic contingency condition and post-session drug supply, ANOVA (in GraphPad Prism®) tested whether parameter A of the group-percent choice curves for each factor was explained by a single model (accept null hypothesis) or not (reject null hypothesis) based on goodness-of-fit criteria, i.e., sums of squares of the vertical distances of the data points from the curve.

The response output curve was constructed in a similar manner as the demand function. At each UP, the average number of responses by the group was calculated. This metric corresponds to behavior "spent" on drug at a given UP by this "market" (group). For illustration (Figure 3), second-order polynomial curves ($Y = A + BX + CX^2$) were fit to these data, which are usually bitonic (where X is unit price and Y is average responding).

The unit price at which the maximum response output occurs is called P_{max}, and the maximum of responding at P_{max} is called O_{max}. These two measures were identified in each experimental condition. P_{max} was calculated based on the results of the curve fit to the percent choice data using the exponential demand equation, above. Maximal responding coincides with the location on the demand curve where the slope in log-log space equals −1, also referred to as `unit elasticity'. When parameter $L = 100$, the price at unit elasticity (P_{max}) is closely approximated by the expression: $P_{max} = 0.29 / A$, where A is the slope parameter from the exponential equation. O_{max} was calculated based on the maximum group-average responding.

3. Results

3.1. Participant Characteristics

A total of 68 individuals (33 male and 4 female African Americans, 24 male and 4 female whites, 2 female Hispanic, and 1 Native American male), attended the first screening visit. Fifty were excluded for not completing screening ($n = 7$), medical problem ($n = 25$), psychiatric or substance use disorders other than opioid dependence ($n = 15$), and other reasons ($n = 3$). Of the 18 volunteers who enrolled, 2 discontinued before inpatient admission. Sixteen participants completed at least the first sampling session; of these, one dropped out due to complaints of opioid withdrawal (after session 1), three were excluded because their subjective drug effects did not differentiate SAL and HYD (after session 2), and one no longer wished to receive the IM injections (after session 3).

The 11 study completers were 7 African American and 3 white males, and 1 African American female. These individuals were (mean ± SD) 38.5 ± 11.4 years old (range, 22 to 52), had 12.8 ± 1.6 years of education (range, 11 to 16), and used heroin regularly for 15.5 ± 11.4 years (range, 4 to 34). Primary route of heroin use was intravenous for 4 volunteers and intranasal for 7 volunteers. Based on a semi-structured interview during screening (cf. Roddy and

Greenwald, 2009), participants reported median total past 30-day income of $1,330 (range, $615–$3,230); spending 68% of this income on heroin (median expenditure of $224 per week); consuming a median of 4 bags of heroin/day (range, 1–10) at a median cost of $10/bag (range, $5–$15); and their estimated purity of the heroin they regularly bought was 50% (range, 2%–80%). These individuals reported a median round trip heroin purchase time of 25 min (range, 5–120 min); a median of 10 purchases per week (range, 3–28); a median unit purchase amount per episode of $30 (range, $10–$100). Ten participants reported daily tobacco use and smoked a median of 12 cigarettes/day (range, 5–35). Based on self-report and urinalysis testing, 5 of the 11 participants used cocaine sporadically during the past 30 days before screening and/or during the BUP stabilization period prior to inpatient admission.

3.2. Sampling Sessions

3.2.1. Subjective effects and vital signs—Table 1 summarizes the results from subjective and physiological measures of drug effects during the initial two HYD sampling sessions. Relative to placebo (SAL), HYD 24 mg markedly altered subjective and physiological effect measures. There were significant increases in the opioid agonist symptom total score and in VAS ratings of `any drug effect', `good drug effect', `drug liking', and feeling `high', `stimulated', and `sedated'. Opioid withdrawal scores, which remained low throughout the study, were statistically (but not clinically) significantly greater after HYD than SAL; however, this effect was due to an elevated baseline score prior to HYD injection (see Dose main effect for this measure). Relative to placebo, HYD significantly decreased oxygen saturation and diastolic BP, and produced marginally significant decreases in respiration rate and heart rate. There were no significant effects of HYD on heroin craving scores or VAS ratings of bad drug effect.

3.2.2. Drug economic value—The mean (± SD) Multiple Choice Procedure crossover point, or money value, of HYD was significantly greater following administration of 24 mg ($15.55 ± 7.99) than 0 mg ($1.98 ± 4.68), Dose $F(1,10) = 36.79$, $P < .0001$.

3.3. Choice Sessions

3.3.1. Drug choice measures—Table 2 provides descriptive statistics (means and SEs) for all measures of HYD reinforcing efficacy. Relative to the *Drug Only* condition, the *Drug Only* + Money Loss and *Drug or* Money conditions significantly decreased HYD breakpoints (Figure 1, left panel), Contingency Condition $F(2,10) = 30.71$, $P < .0001$. *Post hoc* comparisons showed that the effects of *Drug or* Money and *Drug Only* + Money Loss did not statistically differ from one another. Relative to the SAL post-session supplement, anticipation of the HYD post-session supplement significantly decreased HYD breakpoints, $F(1,10) = 5.69$, $P < .04$. There was no significant interaction.

Comparable economic contingency effects were observed for $\log_{10}$ breakpoint, $F(2,10) = 12.51$, $P < .0001$; cumulative responding: $F(2,10) = 27.43$, $P < .0001$; for $\log_{10}$ cumulative responding: $F(2,10) = 11.78$, $P < .0001$; and for drug choices, Contingency Condition $F(2,10) = 22.50$, $P < .0001$. Unlike breakpoints, none of these measures of HYD reinforcing efficacy showed any significant effect of post-session supplement availability (*P*s > .05).

Figure 1 (right panel) indicates the proportion of subjects who chose the HYD supplement in each experimental condition. Nine of the 11 participants (82%) chose the HYD post-session supplement in every contingency condition whereas only ≈20% of the participants chose the SAL supplement. Binomial tests found that the HYD supplement maintained choice that was significantly (*P*s < .05) greater than chance levels in each of the contingency conditions.

The cumulative HYD dose consumed in each experimental condition equaled the sum of response-contingent choices during the PR task and the supplement choice; because subjects frequently chose the 24-mg supplement, HYD cumulative dose was significantly influenced by HYD supplement, $F(1,10) = 9.96$, $P < .01$. As with the other measures of HYD reinforcing efficacy, there was also a significant effect of Contingency Condition $F(2,10) = 7.88$, $P < .0001$, with no significant interaction ($P = .08$).

3.3.2. Behavioral economic measures—As shown in Figure 2, group-percent HYD choice exhibited a positively decelerating relationship with unit price (UP). The left panel of Figure 2 illustrates unadjusted demand curves based on the raw values for group-percent choice. Unadjusted HYD demand for the *Drug Only* and *Drug or Money* conditions converged toward 100% at the lowest UP. In contrast, the unadjusted *Drug Only* + Money Loss demand curve failed to converge: There was a parallel downward shift in the latter condition, such that fewer participants chose HYD even at the lowest UPs. This violates an assumption for exponential curve fitting (i.e., *L* parameter should equal 100%), so it was necessary to normalize the group percent-choice values in the *Drug Only* + Money Loss condition (i.e., use a constant multiplier across all UPs) to make HYD choice converge at 100% in the lowest UP condition. Hursh and colleagues (e.g., Winger and Hursh, 1995;Hursh and Silberberg, 2008) have proposed that this standardization can be used to assess a drug's "essential value". Using these normalized demand curves (right panel of Figure 2), it becomes possible to solve selectively for the change in slope (*A* regression parameter; see section 2.8.2), or HYD "essential value", for each economic contingency condition.

At UPs < 1100, normalized HYD demand was uniformly inelastic across all experimental conditions. At UPs > 1100, normalized demand became elastic but this transition depended on the Contingency Condition. As Table 2 indicates, normalized P_{max} values varied 11.1-fold (from 1123 to 12516). The three conditions significantly differed overall in normalized demand elasticity (*A* parameter) with the SAL supplement, Contingency Condition $F(2,30) = 152.50$, $P < .0001$; and with the HYD supplement, $F(2,30) = 41.47$, $P < .0001$ (Table 2). *Post hoc* tests within the SAL supplement context indicated that, relative to *Drug Only*, the *Drug Only + Money Loss* condition significantly increased demand elasticity, and that *Drug or Money* produced a further significant increase in demand elasticity (Figure 2). *Post hoc* tests within the HYD supplement context indicated that, relative to *Drug Only* and *Drug Only + Money Loss* conditions (which did not differ, $P = .74$), *Drug or Money* significantly increased demand elasticity. Regression curve fits (r^2 values) for normalized demand ranged from 0.68 to 0.93 across experimental conditions and, within each contingency condition, regression curve fits were slightly better for the SAL supplement than the HYD supplement (Table 2).

These differences in the rate of change in normalized demand take on further importance when translated into changes in group-percent choice as UP increases. Using the best-fit demand curves in the SAL supplement context (right panel of Figure 2), a 15-fold increase in UP from 100 to 1500 decreased group-percent HYD choice by 9%, 25% and 75% in the *Drug Only*, *Drug Only + Money Loss* and *Drug or Money* conditions, respectively.

As shown in Table 2, normalized O_{max} values varied 9.9-fold (from 597 to 5907) across experimental conditions. Figure 3 shows that, with the SAL supplement (left panel), there was markedly greater drug-seeking behavior (higher O_{max} value) in the *Drug Only* condition than the *Drug Only + Money Loss* and *Drug or Money* conditions; furthermore, *Drug or Money* suppressed drug seeking more than *Drug Only + Money Loss* at higher UPs. A similar, albeit slightly attenuated, effect was observed with the HYD supplement (right panel). Anticipation of the post-session HYD supplement tended to decrease drug seeking (lower O_{max} values) than the SAL supplement; however, the size of these effects was smaller (9–33% reduction across contingency conditions; compare left and right panels of Figure 3) than the effects of *Drug*

Only + Money Loss and *Drug or Money* on drug seeking (59% and 89% reduction in O_{max} relative to *Drug Only*, respectively).

3.3.3. Individual differences—Relative to *Drug Only*, the ability of *Drug or Money* to increase HYD demand elasticity (i.e., reduce P_{max}) and attenuate drug seeking (i.e., reduce O_{max}), significantly more so than *Drug Only + Money Loss*, raises the question as to how robust this effect may be. Thus, individual differences in the degree of suppression of HYD responding relative to *Drug Only* were calculated for each participant, using drug-choice difference scores: Unemployment – Employment (*Drug Only minus Drug or Money*), and Unemployment – Punishment (*Drug Only minus Drug Only + Money Loss*). These scores were calculated in the SAL and HYD post-session supplement conditions. These choice values from individual subjects were correlated to determine whether some subjects were more *sensitive* (i.e., large difference scores overall) or *biased* (i.e., larger difference score to only one economic contingency), and whether the HYD relative to the SAL supplement shifted choice sensitivity or bias.

Figure 4 depicts the correlation of these individual-subject choice values ($r = 0.50$, $P < .05$). Two subjects showed no bias in response to the Employment *vs.* Punishment manipulations (i.e., data points on/near the dashed diagonal), but one showed high sensitivity (upper right points). In the SAL supplement conditions, 6 individuals showed a stronger effect of Employment (i.e., open diamonds below the diagonal), whereas 3 individuals showed a stronger effect of Punishment (i.e., open diamonds above the diagonal), but the mean Punishment change score for these individuals is greater than the mean Employment change score. Thus, the stronger effect of the Employment analog in decreasing drug choice was due to more participants in this group showing the effect (i.e., prevalence), rather than the magnitude of the effect *per se*. In the HYD supplement conditions, 4 subjects shifted towards greater suppression of opioid seeking in the Punishment condition (i.e., longer solid lines where black circles are shifted up or left relative to open diamonds). Six subjects were consistent across the post-session supplement conditions (i.e., short solid lines, or circled identical values), whereas only one subject shifted towards less suppression with Punishment.

4. Discussion

This study determined whether, relative to simulated Unemployment, analogs of Employment and Punishment differentially reduce opioid seeking and consumption. The effects of these economic contingencies were evaluated in two drug supply scenarios, which were defined by pre-session instructions about the availability of two drug supplements (HYD vs. SAL) following the choice progressive ratio task.

The first major finding is that Unemployment (*Drug Only*, no money alternative) produced the highest levels of drug seeking that we have observed in this paradigm (Greenwald and Hursh 2006; Greenwald and Steinmiller 2009). The mean number of HYD unit choices (≈10 of 12 possible) and breakpoint (≈7000) were markedly higher in the present *Drug Only* condition compared to those prior studies, which scheduled a concurrent money alternative that resembled the *Drug or Money* (Employment) condition in the present study. The purpose of the Unemployment condition was to establish an unconstrained baseline, from which reductions in drug seeking could be observed.

The second major finding is that analog Employment (*Drug or Money*) significantly reduced opioid seeking and consumption relative to Unemployment; however, different measures of drug reinforcement suggest different conclusions about the efficacy of Employment and Punishment. Based on conventional ANOVAs, Employment ($4 gain for each money choice) and Punishment ($4 loss for each HYD choice) yielded significant and similar-size decreases

in HYD choices, breakpoints, and cumulative responding. However, a limitation of analyzing the number of unit choices with this PR schedule is that each response requirement increases exponentially across trials; this maximizes response output differences between earlier and later choices within the session. Thus, analyses of breakpoints (Figure 1, left panel) and behavioral economic demand elasticity or P_{max} (Figure 2, right panel) are more meaningful. Breakpoint and P_{max} are theoretically related and often empirically associated (Bickel et al., 2000); indeed, there was a strong positive correlation between these measures across experimental conditions in this study ($r = 0.85$; see Table 2).

Behavioral economic studies explicitly challenge subjects to defend their drug consumption against unit price escalations. Initial analysis showed that Punishment (*Drug Only + Money Loss*), relative to Unemployment (*Drug Only*), produced a parallel downward shift in the demand curve, such that fewer participants chose HYD overall even at low UPs. However, one assumption for curve fitting is that consumption level at low UPs (*L* parameter) converges to 100%, because low drug prices do not generally deter use. Group percent-choice values in the Punishment condition were therefore adjusted to make HYD choice at low UPs converge to 100%. Hursh and colleagues suggest that this normalization method is useful for ascertaining a drug's “essential value” (Winger and Hursh, 1995; Christensen et al., 2008a, 2008b; Hursh and Silberberg, 2008). By controlling for the *L* parameter, it becomes possible to solve the regression function for the remaining parameter *A*, rate of change (acceleration) in slope. In this study, this approach was used to measure HYD's “essential value” in each economic contingency and post-session supplement condition.

The SAL post-session supplement condition, where the total HYD dose that subjects could consume was solely based on the choice PR task, offers a relatively pure measure of HYD's essential value. In this constrained environment, Employment dramatically decreased HYD seeking (9-fold lower O_{max}) and increased demand elasticity (10.5-fold higher *A* parameter and lower P_{max}) relative to Unemployment. Furthermore, Employment yielded 3.7- to 5-fold greater changes in these parameters compared to Punishment. These findings support two conclusions: first, HYD essential value was significantly devalued by the opportunity to earn money, relative to both Punishment and Unemployment; and second, Punishment less robustly decreased HYD essential value than did Employment.

The observation that Employment increased opioid demand elasticity without altering demand intensity contrasts with observations by Bickel et al. (1995) that cigarette demand intensity decreased without changes in elasticity using a money or recreational alternative. Reasons for this discrepancy could involve methodological factors such as subject population (heroin- vs. nicotine-dependent), route and doses of the drug reinforcer (intramuscular HYD vs. smoked nicotine), and magnitude of the economic alternative option ($4 in this study vs. range of $0.15–$0.50 for each FR 400 completed) in the two studies. The finding that Employment was more effective than Punishment at reducing opioid seeking/consumption is consistent with data from Roll and Howard (2008). Those investigators demonstrated in cigarette smokers that a positive reinforcement contingency (zero base earnings, with escalating amounts earned for providing negative carbon monoxide [CO] readings) was superior to a punishment contingency (begin with maximum amount, and subtract earnings for positive CO readings) for improving smoking abstinence. Thus, in two direct experimental comparisons to date (the present study and Roll and Howard, 2008), positive reinforcement has been more effective than punishment in reducing drug use. Further examination of this apparent difference in efficacy between “carrots” (positive reinforcement) and “sticks” (punishment) seems worthwhile, given that these experimental analogs do not fully capture complexities in the natural setting.

The third major finding is that the HYD post-session supplement modestly reduced HYD breakpoint and demand during the PR task. The ability of the HYD (but not SAL) supplement

to function as a reinforcer is consistent with its psychopharmacological effects during sampling sessions: HYD significantly increased subjective drug effects (e.g., opioid agonist symptoms, drug liking), and significantly altered physiological measures (e.g., respiration depression, bradycardia) relative to SAL. Thus, the minimal impact of the HYD supplement on choice PR responding was not due to its lack of psychoactive effect. Most participants took the HYD supplement when available, which increased the total session HYD dose consumed. In theory, participants could use the additional drug to compensate for reduced levels of HYD consumption earned during the PR task, as seen in the Employment and Punishment conditions. In fact, participant's choice of the HYD post-session supplement in the Employment and Punishment conditions restored total-session HYD consumption to the level observed in the Unemployment condition with the SAL supplement (Table 2). In short, these heroin-dependent individuals partially self-regulated overall opioid intake through access to the HYD supplement (which acted as an economic substitute), whereas overall intake was much lower when participants could not compensate during SAL availability. In general, however, the effect of the HYD supplement was not robust, relatively to the contingencies. One explanation could be that BUP maintenance, which acts as a substitute, may have overshadowed and weakened the effect of the HYD supplement on opioid seeking behavior.

This study included a *placebo* supplement (SAL injection) rather than the *absence* of a supplement (no drug injection at all), which had been used in our previous studies. This design feature was intended to address an alternative explanation of our earlier findings that both pre-session (Greenwald and Hursh, 2006) and post-session (Greenwald and Steinmiller, 2009) supplement availability reduced HYD seeking on the PR task to a similar extent. The findings from those studies suggested that participant's *expectancy* of consumable drug outside the work session, rather than *satiation*, contributed to reduced HYD seeking. Thus, the SAL injection control in the current study offers a stronger test of this hypothesis. The results indicate that anticipation of the HYD vs. SAL supplement significantly increased normalized HYD elasticity only in the *Drug Only* condition (Table 2). Thus, it seems that the effect of expectancy of drug income on drug demand is context-dependent, perhaps depending more on high baseline rates of drug responding (Unemployment) rather than on environments where positive reinforcement density is low (Unemployment and Punishment).

The present findings have at least two theoretical and practical implications worth emphasis. First, Employment clearly reduced opioid seeking and consumption, consistent with our recent data (Greenwald and Steinmiller, 2009) and meta-analysis of clinical trials that demonstrated the magnitude-dependent efficacy of abstinent-contingent reinforcement (Lussier et al., 2006). Offering a more highly valued economic alternative than drug choice increases opportunity cost (i.e., numerator of the UP cost/benefit ratio). Thus, non-pharmacological approaches that enrich the addicted person's environment will indirectly increase drug UP and push drug demand from an inelastic toward an elastic state (Bickel et al., 1993). For drug-dependent individuals, providing a low-cost occasion to earn non-drug reinforcement (Employment) may dampen the `behavioral momentum' (Nevin, 1995; Nevin and Grace, 2000) of habitual drug seeking, perhaps more so under impoverished conditions (Unemployment). Such an opportunity enables the individual to sample a novel behavioral option (i.e., drug abstinence) outside the engrained repertoire but without a firm commitment. Recognizing that drug abstinence has its own costs (e.g., physiological withdrawal symptoms, or foregoing social interaction with drug-using associates), a key challenge in the treatment setting is to engineer environments that can animate and maintain non-drug choice as the price of abstinence mounts.

Second, Punishment reduced opioid demand initially at low UPs without much additional effect at higher UPs; this was due to fewer participants choosing any HYD in this condition (Figures 2 and 4). Thus, individual differences in sensitivity to punishment, independent of UP, must

be accounted for when assessing drug demand. When this reduction in demand intensity was statistically controlled (normalized), Punishment was less effective than Employment for attenuating HYD essential value. As noted, the finding that positive reinforcement is more effective than negative punishment for attenuating drug demand in chronic heroin abusers is consistent with recent data in cigarette smokers (Roll and Howard, 2008). Yet, if one refers to behavior-analytic studies showing that punishment procedures produce an asymmetrically larger effect than positive reinforcement procedures (e.g., Critchfield et al., 2003; Rasmussen and Newland, 2008), then these findings seem counterintuitive. Specifically, in the present study and Roll and Howard (2008) where the magnitude of money gain and loss was equated, one might have expected that punishment would reduce drug seeking more due to risk aversion. Several factors that could account for this discrepant result (e.g., schedules of reinforcement, type and magnitude of punisher, subject population) are worth future study.

If this economic contingency difference were replicated and extended in multiple contexts, such empirical support could impact treatment and policy. Although these contrasting contingency management approaches have been philosophically debated, combinations of positive reinforcement and negative punishment have been used effectively during opioid maintenance treatment (e.g., Iguchi et al., 1988; Chopra et al., 2009), cocaine treatment (e.g., Schumacher et al., 2007), and smoking cessation (e.g., Roll and Higgins, 2000). A multi-stage hypothesis of treatment efficacy worth examination in future studies is that (1) providing early opportunities for non-drug positive reinforcement may help initiate drug abstinence by offering an incentive to switch choice, (2) escalation of positive reinforcement may be necessary, but not sufficient, to offset costs of abstinence, and (3) subsequent punishment may deter preference reversal (i.e., relapse) by increasing response cost once gains from abstinence have accumulated. There is no question that contingency-based procedures for reducing substance abuse are generally effective; nonetheless, gaps remain in our understanding of the optimal combination of parameters and procedures that are needed to produce these desired behavioral outcomes and how these can be tailored to individual patients.

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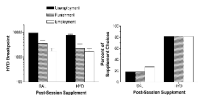

Figure 1.
Left panel: Mean (+ 1 SEM) breakpoints for hydromorphone (HYD) on the choice progressive ratio task; note the logarithmic ordinate. Breakpoints in the analog Employment (*Drug or Money*) and Punishment (*Drug Only + Money Loss*) conditions – which did not significantly differ from one another – were both significantly lower than the Unemployment (*Drug Only*) condition, regardless of post-session HYD (24 mg) vs. SAL (0 mg) supplement availability. *Right panel*: Percent of subjects (n = 11) choosing to take the post-session drug supplement. The HYD supplement dose functioned as a reinforcer equally in all contingency conditions (82% of subjects chose it), compared to the SAL supplement (18–27% of subjects chose it across contingency conditions).

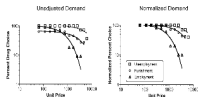

Figure 2.

Hydromorphone (HYD) demand curves under the three contingency conditions with the saline post-session supplement for non-normalized percent choice (*left panel*) and normalized percent choice (*right panel*). Punishment decreased HYD demand intensity (downward shift in curve, parallel to Unemployment, in the left panel), an effect that was controlled when the curves were normalized (right panel). In contrast, Employment increased HYD demand intensity (increased curvature with increasing unit price; left panel), and this effect was preserved after normalization (right panel). For normalized demand curves (right panel), P_{max} values were 12516, 5970 and 1197 for the Unemployment (*Drug Only*), Punishment (*Drug Only + Money Loss*) and Employment (*Drug or Money*) conditions, respectively (see Table 2, which also includes the precision of exponential regression curve fit for each condition).

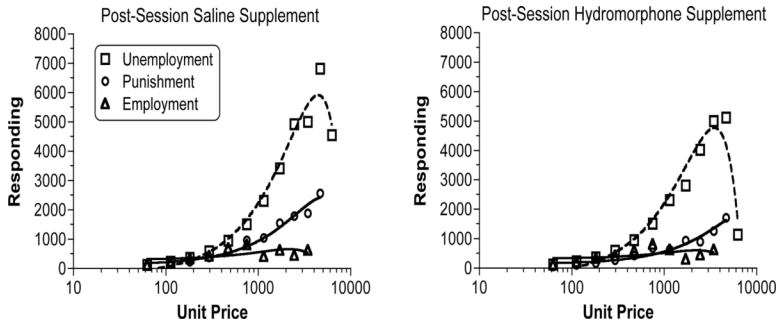

Figure 3.

Response output function produced by plotting group mean breakpoints for each economic contingency condition with the SAL supplement (*left panel*) and HYD supplement (*right panel*). Each panel shows polynomial regressions that were fitted to these data (for illustration only). The peaks of these bitonic functions estimate the O_{max} value, but the highest observed values were used as the calculated O_{max} points; these values are listed in Table 2. Each panel demonstrates that simulated Punishment (*Drug Only + Money Loss*) and Employment (*Drug or Money*) yielded progressively greater decreases in drug-seeking behavior, relative to Unemployment (*Drug Only*), with greater differences manifesting at higher UPs. Comparison across the two panels suggests that the HYD relative to the SAL supplement suppressed opioid seeking (i.e., decreased O_{max}) during the choice task for the Unemployment and Punishment analog conditions.

Figure 4.

Individual differences (n = 11, with identical data points offset for clarity) in suppression of HYD choices in the Employment analog (*Drug or Money*, abscissa) and the Punishment analog (*Drug Only + Money Loss*, ordinate), each subtracted from the number of HYD choices in the Unemployment (*Drug Only*) condition, for the post-session HYD supplement (black circles) and SAL supplement (open diamonds). Solid lines connect each subject's two data points, representing whether suppression of opioid seeking was the same or different in the presence vs. absence of the post-session supplement. The dashed line represents the absence of *bias*, i.e., equal suppression of HYD choice, whereas data below the diagonal reflect greater suppression by Employment (vs. Punishment) and data above the diagonal reflect greater suppression by Punishment (vs. Employment). The magnitude of each difference score (relative to zero on each axis) indicates subjects' *sensitivity* to the Employment and Punishment analog conditions. Some subjects were consistent across supplement conditions (i.e., short connecting lines or circled values that were identical) whereas others demonstrated a shift toward greater Punishment-induced suppression of opioid seeking in the presence of the HYD supplement.

Table 1

Statistical Summary of Hydromorphone (HYD) Sampling Responses[1]

Peak Measure (Max+, Min−)	Dose *F*[1,10] (*P*)	Dose × Time *F*[1,10] (*P*)	Post-Drug Peak *t*[10] (*P*)	Mean Peak Score (± 1 SD)	
				HYD 0mg	HYD 24mg
(−) Heroin craving (range: 10–70)	ns	ns	ns	21.8 (17.9)	16.8 (9.0)
(−) Opioid withdrawal (range: 0–64)	12.00 (.01)	ns	2.37 (.04)	2.6 (6.2)	4.1 (6.3)
(+) Opioid agonist (range: 0–64)	21.07 (.001)	8.78 (.0001)	5.48 (.0001)	11.0 (8.7)	24.6 (8.3)
(+) Any drug effect (range: 0–100)	37.10 (.0001)	12.19 (.0001)	6.43 (.0001)	16.3 (22.1)	66.5 (30.9)
(+) Good drug effect (range: 0–100)	32.25 (.0001)	12.07 (.0001)	6.69 (.0001)	14.7 (21.6)	66.2 (30.9)
(−) Bad drug effect (range: 0–100)	ns	ns	ns	0.1 (0.3)	0.1 (0.3)
(+) Drug High (range: 0–100)	31.93 (.0001)	14.67 (.0001)	6.39 (.0001)	11.5 (21.8)	66.6 (31.8)
(+) Drug liking (range: 0–100)	36.24 (.0001)	9.55 (.0001)	6.58 (.0001)	19.5 (26.0)	78.4 (31.6)
(+) Stimulated (range: 0–100)	20.99 (001)	8.42 (.0001)	6.89 (.0001)	11.2 (19.1)	58.9 (28.0)
(+) Sedated (range: 0–100)	10.03 (.01)	3.79 (.03)	3.34 (.01)	14.4 (21.3)	57.8 (33.2)
(−) Respiration rate (breaths/min)	ns	ns	2.19 (.054)	12.9 (3.1)	11.5 (1.7)
(−) Oxygen saturation (%)	50.44 (.0001)	ns	5.57 (.0001)	97.2 (1.8)	95.3 (1.9)
(−) Heart rate (beats/min)	ns	3.55 (.03)	2.21 (.052)	63.0 (5.4)	58.1 (7.2)
(−) Systolic BP (mmHg)	7.94 (.02)	ns	ns	117.8 (13.7)	101.4 (35.4)
(−) Diastolic BP (mmHg)	ns	ns	2.28 (.05)	69.5 (9.4)	66.8 (8.2)

[1] All *P* values are Huynh-Feldt corrected. “ns” indicates $P > .05$.

Table 2

Measures of Hydromorphone (HYD) Reinforcing Efficacy[1]

	Drug Only **(Unemployment)**		***Drug Only*** **+** ***Money Loss*** **(Punishment)**		***Drug or Money*** **(Employment)**	
Measure	**SAL supplement**	**HYD supplement**	**SAL supplement**	**HYD supplement**	**SAL supplement**	**HYD supplement**
Number of HYD choices	10.82 (0.38)[a]	10.00 (0.51)[a]	5.64 (1.45)[b]	3.82 (1.41)[b]	5.27 (0.80)[b]	5.18 (0.80)[b]
HYD breakpoint	9295 (947)[a]	7513 (973)[a]	3587 (1215)[b]	2288 (1105)[b]	1720 (584)[b]	1659 (571)[b]
Cumulative HYD responding	31410 (3588)[a]	24990 (3681)[a]	11270 (4030)[b]	7612 (3958)[b]	4699 (1825)[b]	4511 (1788)[b]
Total HYD dose consumed (mg)	26.00 (3.07)[b]	39.64 (2.80)[a]	15.64 (5.13)[c]	27.27 (3.68)[b]	17.09 (4.60)[c]	30.00 (2.97)[b]
Normalized demand slope (*A* parameter)	0.00002317[a]	0.00005562[b]	0.00004858[b]	0.00006064[b]	0.0002422[c]	0.0002583[c]
Normalized demand curve fit (r^2)	0.744	0.679	0.931	0.861	0.929	0.912
Calculated P_{max}	12516	5214	5970	4782	1197	1123
Calculated O_{max}	6818	5114	2557	1705	818	818

[1] Sample means (± 1 SEM), $n = 11$.

[a] Results of *post hoc* comparisons (see text for overall statistical differences between experimental conditions). Means with shared letters do not significantly differ from one another. For behavioral economic measures, analyses were conducted only for the *A* slope parameter. Calculated P_{max} is a group-level index that is computed from the *A* slope parameter, or demand elasticity ($P_{max} = 0.29 \div A$). Calculated O_{max} is computed from the group-average responding at each unit price.

[b] Results of *post hoc* comparisons (see text for overall statistical differences between experimental conditions). Means with shared letters do not significantly differ from one another. For behavioral economic measures, analyses were conducted only for the *A* slope parameter. Calculated P_{max} is a group-level index that is computed from the *A* slope parameter, or demand elasticity ($P_{max} = 0.29 \div A$). Calculated O_{max} is computed from the group-average responding at each unit price.

[c] Results of *post hoc* comparisons (see text for overall statistical differences between experimental conditions). Means with shared letters do not significantly differ from one another. For behavioral economic measures, analyses were conducted only for the *A* slope parameter. Calculated P_{max} is a group-level index that is computed from the *A* slope parameter, or demand elasticity ($P_{max} = 0.29 \div A$). Calculated O_{max} is computed from the group-average responding at each unit price.