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Behavioral Economic Analysis of Opioid Consumption In Heroin-Dependent Individuals: Effects of Alternative Reinforcer Magnitude and Post-Session Drug Supply

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Abstract

This study investigated the extent to which hydromorphone (HYD) choice and behavioral economic demand were influenced by HYD unit price (UP), alternative money reinforcement magnitude and post-session HYD supply. Heroin dependent research volunteers ($n=13$) stabilized on buprenorphine 8 mg/day first sampled two HYD doses (12 and 24 mg IM, 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 earn a HYD unit dose (2 mg, fixed) or money (\$2 or \$4, varied across sessions), administered immediately after the work session. Before the PR task, volunteers were told which HYD supplemental dose (none, Drug A or B) would be available 3 hr after receiving the PR-contingent dose. PR-contingent HYD choice significantly decreased when \$4 relative to \$2 was concurrently available. Information about the post-session HYD supplement moderated this effect: when subjects were told a supplemental dose was available, HYD-seeking behavior decreased when the money alternative was smaller (\$2), but this information did not further attenuate HYD choice, which was already low, when the money alternative was higher (\$4). HYD demand elasticity was only increased by the \$4 relative to \$2 alternative without the HYD supplement. In summary, opioid-seeking behavior is influenced by the availability of concurrent non-drug and drug alternatives. These findings show that drug availability and non-drug alternatives interact to modulate drug-seeking behavior.

Keywords

Behavioral economic analysis; Heroin dependence; Buprenorphine; Drug supply; Unit price; Drug seeking behavior

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1. Introduction

Behavioral economic studies of drug self-administration typically focus on drug “purchasing” behavior (i.e., the expenditure of responding or allocation of choices) and consumption (i.e., the actual use of purchased commodities) as a function of its price, relative to available resources (income). The purpose of such studies is to provide a microeconomic model of the behavioral mechanisms that contribute to naturalistic drug seeking and use for individuals and small groups (markets), and how knowledge gained might apply to treatment, macroeconomic trends and policy development (Bickel et al., 1993; Bickel and DeGrandpre, 1996; Caulkins and Reuter, 1996; Vuchinich, 1997). The simultaneous analysis of drug purchasing (a bi-tonic function of price) and consumption (a monotonically decelerating function of price) affords an innovative perspective that is not evident in simple operant or choice paradigms.

A key factor that constrains drug expenditure is its *unit price* (UP), which has often been examined in the experimental setting as a cost/benefit ratio of response requirement (fixed ratio, FR) per unit drug dose (mg). Numerous studies with laboratory animals and human subjects have clearly demonstrated that experimental increases in UP reduce drug demand (Bickel et al., 1990, 1991, 1995; DeGrandpre et al., 1993a; Greenwald, 2008; Hursh, 1993; Hursh and Silberberg, 2008). This effect is paralleled by naturalistic drug use patterns; for example, non-dealing opioid-dependent individuals report that they consume significantly less heroin per day as its UP increases, i.e. own-price elasticity (Bretteville-Jensen, 1999; Roddy and Greenwald, in press), and methadone patients who value money (e.g. travel, child care) costs at a higher rate exhibit significantly reduced attendance to consume their daily dose relative to patients who value those costs at a lower rate (Borisova and Goodman, 2004).

Two competing types of income constrain drug expenditure. The first is *drug supply*, which has been studied in the human laboratory setting by making available different doses of the response-contingent drug (e.g., Heishman et al., 2000; Sofuoglu et al., 2008), supplement drug doses (Bickel et al., 1997; Mitchell et al., 1994), or agonist medications that can substitute for the abused drug (e.g., Greenwald et al., 2002; Shahan et al., 2000). The second is *non-drug commodity supply*, which has been studied in the human laboratory setting by varying income (DeGrandpre et al., 1993b) or response-contingent availability of a money alternative in the laboratory (e.g., Comer et al., 1998; Petry and Bickel, 1999); or, in the treatment setting, by drug abstinence-contingent access to vouchers or prizes (e.g., Carroll et al., 2002; Petry et al., 2004).

Behavioral economic studies have not systematically examined interactions of drug price with the supply of drug and non-drug reinforcement. Greenwald and Hursh (2006) demonstrated in heroin-dependent research volunteers the expected decrease in opioid-seeking behavior as UP increased, but also showed that this price-elastic effect was enhanced in the presence of supplemental (extra-session) opioid doses. In different sessions of that study, a hydromorphone (HYD) supplement of 12 mg or 24 mg was offered (open economy) or the supplement was not available (closed economy) prior to work sessions in which the unit price of HYD or money alternative was increased on a choice, progressive ratio schedule of reinforcement. Choice of HYD unit doses (1 or 2 mg in different sessions, relative to a fixed money amount of \$2.00) decreased when pre-session HYD supplements were available (notably, every subject consumed all available supplements). Although *mu*-agonist effects of the supplement doses could have directly decreased HYD-seeking behavior, a 3-hr delay was interpolated to ensure that the behavioral, subjective and physiological effects of supplements had returned to baseline prior to beginning the choice session.

Greenwald and Hursh (2006) also observed that pre-experimental cocaine use (i.e., past 30 days, as measured by urinalysis and self-report methods) was associated with significantly

greater HYD choice in the laboratory, relative to the absence of this recent behavioral history. That preliminary finding was consistent with data from clinical trials (e.g., DeMaria et al., 2000; Dolan et al., 2001; Downey et al., 2000; Perez et al., 1997; Preston et al., 1998; Sofuoglu et al., 2003), suggesting that cocaine use – even at sporadic levels that do not meet criterion for abuse/dependence diagnosis – may enhance the reinforcing effects of opioids and undermine treatment outcome. However, because it was based on a relatively small sample, we wished to determine whether that finding could be replicated.

The present study had four aims. The first aim was to replicate our initial findings that drug UP produces own-elastic effects on HYD seeking. Second, we wished to determine whether the magnitude of a money alternative (i.e., supply of a non-drug commodity) would reduce opioid seeking and, if so, whether this factor would interact with UP or post-session supplement availability. The third aim was to assess whether the opportunity to take inexpensive supplemental HYD doses relative to no supplement (open vs. closed economy) *following* the choice session influenced HYD seeking. A simple instructional manipulation was used to address the alternative explanation of our earlier findings noted above, i.e., if HYD seeking decreased due to *anticipation* of post-session supplement availability, this reduction would not be a direct pharmacological effect. Finally, because Greenwald and Hursh (2006) initially observed that individual differences in HYD choice were associated with recent pre-experimental cocaine use, we sought to replicate that finding in this study.

2. Methods

2.1. Participant recruiting and selection

The Wayne State University Institutional Review Board approved all procedures. This study was carried out in accordance with the Declaration of Helsinki as adopted and promulgated by the National Institutes of Health (NIH). This study is registered as NIH clinical trial NCT00218361. Heroin-dependent males and females, ages 18 to 55 years, were recruited from the Detroit area by advertisements and word-of-mouth. Volunteers were not seeking treatment and were willing to participate in a short-term study of opioid drug choice involving buprenorphine (BUP) maintenance, followed by detoxification. Volunteers provided a medical history, blood and urine samples, and received an electrocardiogram, tuberculin screening, and a physical exam. Those selected reported no chronic health problems and were not taking prescribed medications. An experienced 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 (estimated IQ < 80) based on the Shipley Institute of Living Scale (Zachary, 1991).

During screening, volunteers were required 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 who met DSM-IV diagnostic criteria for Cocaine Abuse/Dependence or Marijuana Abuse/Dependence were excluded. Volunteers also had to provide an alcohol-free breath sample (< .002%). After the procedures were fully explained, all volunteers provided written informed consent.

Due to the need to withdraw blood during screening, and because intramuscular (IM) injections regularly occurred in this study, individuals with fear of blood withdrawal or injections were excluded. All participants completed the Injection and Blood Withdrawal Phobia subscale (10 items) of the Medical Fear Survey (Kleinknecht et al., 1999). Each item is answered on a scale ranging from 0 (“no fear or concern at all”) to 4 (“terror”). Volunteers scoring above 15 on this scale were excluded, as these scores were associated with spontaneous reports of injection concerns.

2.2. Study Design

The present study design and procedures parallel a recent companion study (Greenwald and Hursh, 2006). This experiment had two parts. In part 1 (drug sampling), each participant was exposed to two different doses of HYD (12 and 24 mg) in randomized order, counterbalanced across subjects. Individuals who responded with (1) greater reinforcing and/or subjective effects to HYD 24 than 12 mg, and (2) no adverse effects at either HYD dose were permitted to continue in the study. In part 2 (drug choice), a within-subject randomized crossover design was used to test effects of post-session supplemental HYD availability (3 levels: none, 12 or 24 mg) and magnitude of the alternative reinforcer (2 levels: \$2 or \$4 per choice trial) on HYD choice and consumption. In this study, the HYD unit dose was fixed (2 mg per choice trial). Within each of the final 6 test sessions, the sequence of 12 response requirements in the PR schedule, described below, generated a 2 log-unit range of unit prices (fixed ratio [FR] ÷ HYD unit dose; 62.5 – 6250).

2.3. Settings and Protocol Timeline

Participants were initially outpatients while being stabilized on BUP 8 mg/day for at least 10 days; variations in this flexible interval were due to participant and staff scheduling constraints. Actual duration of outpatient BUP maintenance was 18.2 ± 1.5 (mean $\pm$ standard deviation; range, 11 to 29) days. All participants were admitted on a Tuesday, and no experimental procedures were conducted during the two weekends of the inpatient stay. Residential living combined with staff observation and daily urine testing was used to ensure illicit drug abstinence during the experimental procedures. On test session days, participants were escorted from the inpatient unit to the Human Pharmacology Laboratory, and returned to the inpatient unit after completing each session. On non-session days and during non-experimental periods on session days, volunteers could engage in recreational activities available on the unit, e.g., reading books and magazines, smoking cigarettes, listening to music, riding an exercise bicycle, watching television or movies, doing arts and crafts, and making telephone calls.

2.4. Procedures

2.4.1. Sampling sessions—Hydromorphone sampling sessions were conducted on the first Wednesday and Thursday (1130–1500) of the inpatient stay. The HYD dose administered during the first session (day 1) was identified as “Drug A” and the HYD dose administered during the second session (day 2) was identified as “Drug B.” Participants were asked to attend closely to the effects produced by each drug administration because, in later sessions, they would be able to choose each of these drugs relative to money. Whether 12 mg or 24 mg 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 the first Friday and Monday through Friday of the next week. For each participant, the same testing room was used for sampling and choice sessions. Figure 1 shows the timeline for each choice session. At 8:50 am, the volunteer was told: “Today, you will (not) have *free access* to drug *following* the session, and you can *work for* Drug ____ (A or B) or money *during* the session.” The purpose of this instruction was to provide explicit information about the presence/absence of a supplement and magnitude of drug effect that could be obtained if subjects chose the supplemental drug. All subjects could work for the same unit HYD dose, 2 mg, but the label differed across subjects. (The next sentence was given only if the participant had access to supplemental drug that day.) “If you choose to take the free drug, it will be administered at 3:15 pm. From 9:00 am to 12:00 pm, you can work for all or part of Drug ____ (A or B), money or neither. There will be 12 trials. On each trial, you will see the words ‘Drug’

and 'Money' on the computer screen. Once you complete a single key press on one 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 ____ (\$2 or \$4) per trial that you complete. If you respond for drug, you will earn 1/12th of the total drug (A or B) per trial that you complete. If you choose neither, then you will not earn any money or any drug for that trial. Please be aware that even if you choose all money, you will still receive a placebo (blank) injection." This last contingency (in addition to excluding individuals with injection phobia) was designed to reduce the possibility that participants would choose money simply to avoid an injection and, when injections were administered, that participants would not report them as aversive. The screening procedures, experimental instructions and periodic assessments of subjective effects confirmed this assumption, and this issue is not discussed further.

Participants began the choice PR task at 9:00 am. A sign was posted on the wall above the computer to remind the participant which drug (A or B) and how much money (\$2 or \$4 per trial) they could work for during each session, as well as the post-session supplemental drug (A or B). Across the top of the computer screen two colored rectangular boxes arranged side-by-side were labeled Money (green) and Drug (red); across the middle of the computer screen, rectangular boxes arranged side-by-side (in corresponding colors) indicated the number of units (range, 1 to 12) earned for money and drug; and at the bottom of the computer screen, another box counted down the time (sec) remaining in the 3-hr total work session. Immediately after the participant completed each choice, a tone sounded to indicate that the unit of money or drug had been earned. Next, a different screen appeared for 10 sec (inter-trial interval), during which responding had no consequences and a timer counted down. After this time-out period, the original display re-appeared to begin the next choice opportunity.

During the 3-hr choice PR task, there were few alternative activities available: Participants were prohibited from reading, smoking cigarettes, eating, watching television, and remained seated (except for bathroom breaks) until the time expired. Participants could drink water but not other beverages. Three hours after the task began (12 noon), the computer program quit unless the participant had already completed all 12 choices (at which time the program quit), and the amount of HYD earned was delivered. The participant was told the number of drug and money choices earned in each session, and had to sign his/her subject identification code to provide a written record of their drug and money earnings.

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

2.5. Drug Administration

All drugs were administered under double-blind conditions. Drug administration differed based on the phase of participation: (1) outpatient BUP maintenance, (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, SubutexTM; Reckitt-Benckiser, Hull, UK; supplied by Research Triangle Institute, Research Triangle Park, NC, USA). BUP tablets were held under the tongue until dissolved, as supervised by a research assistant.

During phase 1 (Monday–Friday), participants attended the outpatient laboratory in the morning to receive their daily dose of 8 mg; on Saturday, they received a double dose (16 mg)

so they did not have to attend the laboratory on Sunday. There were no contingencies associated with opioid use during the outpatient lead-in period. During phase 2 (inpatient, 7 days/week), participants received their daily BUP dose of 8 mg at 8:00 pm. During phase 3, participants attended the outpatient 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. Volunteers were told they would be fully free of BUP at the end of the study, and were reminded they could receive a treatment referral if they wished. Volunteers could also participate in a secondary study of contingency management for relapse prevention during the BUP dose tapering period (Greenwald, 2008).

An intermediate BUP maintenance dose (8 mg/day) was chosen for two reasons. First, a sufficient dose was desired to suppress opioid withdrawal symptoms, so that participants would be comfortable while living on the inpatient unit without access to heroin. Second, the BUP dose could not be too high, because it was desired to observe agonist – including reinforcing – effects of HYD. The time of daily BUP dosing was shifted from the morning (outpatient) to the evening (inpatient) to minimize agonist effects of BUP during the laboratory test sessions, which were conducted in the morning and afternoon hours. For scientific reasons, it is important to recognize that BUP dosing itself provides an open (albeit constant) economy for the entire class of opioids beyond HYD availability in this laboratory model. However, the operational definition of a closed vs. open economy in this experimental context refers only to the availability and response-contingent delivery of HYD.

Doses of HYD (Dilaudid-HP™ in 10 mg/ml ampoules; Knoll Pharmaceuticals, Whippany, NJ, USA) were administered as IM injections (constant volume = 2.4 ml). Doses administered were 12 mg (filled with 1.2 ml physiological saline to 2.4 ml) or 24 mg or, after choice PR performance, the response-contingent dose.

2.6. Income

Participants were compensated \$40 per night for living on the inpatient unit in this study; this money was paid in three weekly installments starting the day of discharge and extending into the detoxification period. This fixed-rate income variable is important, because the amount of money that could be earned in the present study (\$2 or \$4 per choice opportunity, for a maximum of \$24 or \$48 per session) by responding on the choice PR task is a behavioral-economic factor relative to this income level, and enables comparison with a similar previous study (Greenwald and Hursh, 2006). Participants were paid \$30 flat rate for each of the two drug sampling sessions, but they did not earn any flat rate payment for choice sessions, i.e., all money earned in those six sessions derived from their responding on the choice task. All money earnings from the choice sessions were combined (along with one-half of the inpatient night money) into a single paycheck given on the day of discharge from the inpatient unit. Total compensation for participants who completed the study averaged $\$957 \pm \70 (range, \$812 to \$1,054).

2.7. Measures

2.7.1. Urinalysis—Urine samples for toxicology testing were obtained once during screening and, for enrolled volunteers, thrice weekly (Mon-Wed-Fri) during outpatient BUP stabilization (phase 1) and detoxification (phase 3), and on the morning of each inpatient day (phase 2). Urine collection cups containing a temperature-sensitive strip combined with a multi-drug dipstick immunoassay card (Clia Waived, San Diego, CA, USA; www.drugtesting-kits.com [accessed on 3/18/09]) were used for qualitative urine toxicology. The research assistant first verified that urine temperature was in the valid range (92-96° F). The test-strip portion of the dipstick card was placed in the sample for at least 10 sec and results were read 5 min later (per manufacturer instructions) 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 (see Schuster et al., 1995). Seven visual analog scale (VAS, 0-100 line) 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 (MCP; Griffiths et al., 1993) was used. Three hours after each HYD dose, the participant was given a questionnaire to make 44 independent choices between the drug dose just received and various money amounts, with values ranging from \$0.25 to \$25.00. Values increased by \$0.25 steps from the lowest amount until \$2.00, by \$0.50 steps until \$15.00, and by \$1.00 steps until the highest amount. The money amount at which the participant switched from choosing drug to money, i.e., the crossover point, was a proxy measure of the reinforcing value of each drug dose. The purpose of this hypothetical reinforcement measure was to ensure that 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 (identical to Greenwald and Hursh, 2006). On each trial, volunteers could earn a unit dose of HYD (2 mg, constant across sessions) or money (\$2 or \$4 per trial, varied between sessions). Across trials within each session, the FR requirement on each option increased independently in an exponential function (Figure 1). Participants were instructed that they would not be forced to respond for drug or money, i.e., they did not have to respond at all, and could rest. Therefore, choosing one alternative would not necessarily be due to avoidance of the other option.

Several measures of HYD relative reinforcing efficacy were analyzed to provide a comprehensive behavioral assessment in this laboratory model, and to compare with our recent study. One primary outcome in each experimental condition was the total number of drug choices. A related outcome was the number of drug choices completed first, prior to any money choice, in each condition – an index of “drug priority”. This measure could provide a different pattern of results from total drug choices if participants switched between drug and money throughout the session; this is a shorthand index of the within-session pattern of responding. Another primary outcome measure was the total HYD dose (mg) consumed per condition, which included both the HYD supplement dose (if available) and the response-contingent HYD dose. This was used to evaluate whether consumption of the supplements led participants to regulate their drug intake (see Lynch and Carroll, 2001). Several secondary measures were also analyzed. One was $\log_{10}$ -transformed breakpoint. Another measure was $\log_{10}$ -transformed cumulative drug responding, which included non-completed responding for HYD when the 3-hr session terminated. A final set of measures involved time (min) allocated to drug, money and rest during the 3-hr choice task. This was based on the idea that each option is a commodity, with drug and money being positively defined and rest being negatively defined, and that the extent of time allocation to drug may depend on the substitutability of these alternative options (Rachlin, 2003).

2.8. Data Analyses

2.8.1. Sampling—Subjective effects and vital signs measures from sampling sessions were analyzed using two-way HYD Dose (12 and 24 mg) $\times$ 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 post-session drug supply (none, 12 and 24 mg) and magnitude of the alternative reinforcer (\$2 and \$4 per trial) on the number of HYD choices. Parallel ANOVAs were conducted for other measures of HYD reinforcement. Whether or not the post-session supplemental drug was consumed was an additional dependent measure (proportion of the sample taking the available dose in each condition), and was analyzed with a binomial test.

Group-Percent Choice: Unit prices (UPs) were defined as the FR requirements (12 values) of the PR schedule divided by the unit dose (2 mg). Demand curve analyses were only conducted on the group-average data. When these binary choice data are summed across volunteers within each experimental condition, the percentage of the group (market) that chooses drug at each UP can be analyzed under the assumptions of behavioral economics. This measure is referred to as “group-percent choice”, which is similar to normalized consumption (Hursh and Winger, 1995). Using the software GraphPad Prism[®] 4.0 (www.graphpad.com [accessed on 3/18/09] San Diego, CA, USA), a demand curve on UP was fit to log₁₀–transformed group-percent choice, using the exponential regression equation: $Y = \log(L) * \exp(-A * X)$

In this equation, parameter L (initial level of drug choice) was set to 100% for all experimental conditions (i.e., normalized); 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 the alternative reinforcer and post-session drug supply, ANOVA (within 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 total number of responses summed across the group ($n = 13$) was calculated. This corresponds to the total number of responses (analogous to money) “spent” on drug at a given price by this market. The 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 fit to the consumption data using the exponential demand equation, above. Maximal responding coincides with the location on a demand curve where slope in log-log space equals -1, unit elasticity. When parameter $L = 100$, the price at unit elasticity ($P_{\max}$) is closely approximated by the simple expression: $P_{\max} = 0.29 \div A$, where A is the slope parameter from the exponential equation. Each non-linear regression in GraphPad Prism (which generates the actual array of numbers that correspond to the curve) was used to interpolate $O_{\max}$ on the fitted curve at $P_{\max}$.

3. Results

3.1. Participant Characteristics

A total of 111 individuals, reflecting the local demographics for such studies (48 male and 23 female African Americans, 25 male and 8 female whites, 2 male and 1 female Hispanic, 2 Asian males, 1 Native American male, and 1 mixed-race female), attended the first screening visit. Of these individuals, 91 were excluded for the following reasons: did not complete screening ($n = 15$), medical problem ($n = 32$), psychiatric or substance use disorders other than opioid and nicotine dependence ($n = 30$), inadequate venous access ($n = 3$), and poor reading ability or unreliable self-report ($n = 11$). Twenty volunteers enrolled; of these, 4 discontinued before inpatient admission. Sixteen participants began the first sampling session; of these, 3 were excluded (two for medical reasons [bradycardia and allergic rash], and one who did not discriminate the two HYD doses).

The 13 participants who completed the study were 5 African American and 5 white males, and 1 African American and 2 white females. These individuals were (mean $\pm$ SD) 42.8 ± 6.5 years old, had 12.0 ± 2.0 years of education, and used heroin regularly for 20.6 ± 11.7 years. The primary route of heroin use was intravenous for 8 volunteers and intranasal for 5 volunteers. Based on a semi-structured interview during screening, these participants reported median total past 30-day income of \$1350 (range, \$165 – \$3,240). During the same period, they spent 72% of this income on heroin as opposed to only 9% on shelter/utilities and 8% on food (which were often subsidized by family and friends). They used a median of 4 bags of heroin/day (range, 1 – 6) at a cost of \$10/bag (range, \$5 – \$30), and their estimated purity of the heroin they bought was 60% (range, 20% – 85%). These individuals reported a median round trip time of 60 min (range, 5 – 120 min) to complete each heroin purchase, with 14 heroin purchases per week (range, 5 – 28). All participants reported daily tobacco use (spending 3% of their past 30-day income on cigarettes), and smoked a median of 15 cigarettes/day (range, 5 – 20).

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. Relative to session baseline, both HYD doses altered opioid subjective and physiological effects. Following administration of the 24 mg HYD dose, the Opioid Agonist symptom score and VAS ratings of Drug Liking and Stimulated were significantly greater than for 12 mg HYD; similar, but statistically marginal dose-related increases were also observed for VAS ratings of Any Drug Effect and High. Hydromorphone also produced significant dose-related decreases in respiration rate, oxygen saturation, and heart rate. The HYD-induced increases peaked at 1 hr after drug, and persisted for 2.5 to 3 hr post-drug. Opioid withdrawal scores were consistently low (within and between individuals) and unaffected by HYD dose. There were no significant dose-effects of HYD on heroin craving; VAS ratings of Good Drug Effect, Bad Drug Effect or Sedated; or blood pressure.

3.2.2. Drug reinforcement—The mean ($\pm$ SD) Multiple Choice Procedure crossover point, or money value, of HYD was significantly greater following administration of 24 mg ($\$13.46 \pm 1.77$) than 12 mg ($\6.88 ± 1.64), Dose $F(1,12) = 24.62$, $P < .005$.

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. Figure 2 illustrates HYD choice behavior, including the total number of response-contingent drug choices and breakpoints (left and right ordinates of the upper panel) and drug-first choices (lower panel). The higher, relative to the lower, money alternative (\$4 vs. \$2) significantly decreased HYD choice, $F(1,12) = 6.03$, P

< .03. Post-session drug supplements significantly decreased HYD choice only in the presence of the \$2 alternative but not the \$4 alternative, Money $\times$ Supplement $F(2,24) = 5.60$, $P < .02$. A similar pattern was observed for drug-first choices, although only the interaction was significant, Money $\times$ Supplement $F(2,24) = 4.06$, $P < .04$.

Figure 3 indicates the proportion of subjects who chose the HYD supplement in each experimental condition (upper panel) and the cumulative HYD dose consumed during each condition as the result of response-contingent choices based on PR task and supplement choices (lower panel). Binomial tests found that the higher supplement dose of HYD maintained choice that was significantly ($P_s < .05$) greater than chance levels following both the \$2 and \$4 alternative sessions (proportions of subjects = 0.92 and 0.85), whereas the lower supplement dose did not maintain choice that was greater than chance levels with either the \$2 or \$4 alternatives (proportions of subjects = 0.69 and 0.54). Because subjects chose the higher-dose supplement at significantly higher rates, this contributed to significantly greater cumulative HYD consumed in these conditions, Supplement $F(2,24) = 33.64$, $P < .0001$. As with drug choices, the total dose consumed was also significantly decreased by the \$4 relative to \$2 alternative, Money $F(1,12) = 9.79$, $P < .01$. There was no significant interaction between these factors.

Log₁₀-transformed breakpoints and log₁₀-transformed cumulative responding were not significantly altered by Supplement or Money conditions (although the Money factor demonstrated trends for both measures, $P_s < .06$), but these variables showed the same general patterns as the other measures of HYD reinforcing efficacy (see Table 2). Across the six experimental conditions, participants allocated 12-38% of the 3-hr session to drug responding, 8-34% to money responding, and 44-63% to rest. For time spent on drug responding (see Table 2), there was a significant Money $\times$ Supplement interaction, $F(2,24) = 3.63$, $P < .05$, such that substantially more time was allocated to drug in the low money alternative/no-supplement condition relative to the other conditions.

3.3.2. Behavioral economic measures—As shown in Figure 4 (upper panels), group-percent choice showed a positively decelerating relationship with UP. At prices greater than 1000, HYD demand became elastic; as Table 2 indicates, $P_{\max}$ varied from 1063 to 2886 across experimental conditions. Regression curve fits (r^2 values) ranged from 0.77 to 0.96 across conditions.

There was a significant difference in the elasticity parameter A across the HYD supplement conditions (Table 2), $F(5,60) = 9.87$, $P < .0001$. *Post hoc* comparisons indicated that HYD elasticity significantly differed between supplement levels in the lower, but not the higher, money alternative conditions. Also, the higher relative to lower money alternative significantly increased HYD elasticity in the no-supplement condition. These differences in the rate of change in elasticity translate into changes in group-percent choice as UP increases. Using the best-fit demand curves, a 50-fold increase in UP from 77 to 3850 decreased HYD choice by 32%, 50% and 65% in the no-supplement, 12-mg and 24-mg supplement conditions with the \$2 money alternative, and 49%, 53% and 51% in the no-supplement, 12-mg and 24-mg supplement conditions with the \$4 money alternative. Thus, availability of post-session supplements dose-dependently increased HYD elasticity in the presence of a lesser-magnitude non-drug alternative but there was no supplement effect with the higher-magnitude alternative, possibly because demand was already moderately elastic. These effects were also reflected in the price at unit elasticity or computed $P_{\max}$, which is derived from the A parameter.

As shown in Figure 4 (lower panels), the higher money alternative was associated with reduced $O_{\max}$ values compared to the lower money alternative, especially in the absence of a

supplement. Post-session drug supply also monotonically reduced $O_{\max}$ values, independent of the money alternative (see Table 2).

3.3.3. Individual differences—During choice sessions, subjects who had not used cocaine ($n = 3$), relative to those who had used cocaine ($n = 10$), as outpatients prior to the experiment responded significantly less for HYD in the presence of the \$4 money alternative. This pattern was observed for three measures of HYD reinforcing efficacy: total drug choices, $\log_{10}$ breakpoint and $\log_{10}$ cumulative responding (Table 3).

During sampling sessions, subjects who had not used cocaine, relative to recent cocaine users, reported significantly higher overall levels of opioid withdrawal symptoms including pre-HYD baseline ($M_s = 12.4$ vs. 2.8), Group $F(1,11) = 4.50$, $P < .06$, but more so at the higher HYD dose, Group $\times$ Dose $F(1,11) = 6.06$, $P < .04$; significantly higher overall levels of opioid agonist symptoms ($M_s = 21.5$ vs. 9.6), Group $F(1,11) = 25.14$, $P < .0001$; and significantly lower VAS ratings of feeling “Stimulated” in response to low-dose HYD, Group $\times$ Dose $\times$ Time $F(6,66) = 2.90$, $P < .05$.

Subjects who had not used cocaine purchased more \$10 bags of heroin daily during the 30 days prior to screening ($M_s = 4.5$ vs. 2.0), $F(1,11) = 8.60$, $P < .02$; and smoked fewer cigarettes daily prior to screening ($M_s = 15.9$ vs. 6.7), $F(1,11) = 10.43$, $P < .01$, relative to recent cocaine users. These two subgroups did not significantly differ on demographic, other substance use, or HYD sampling response measures.

4. Discussion

The present study had four aims: (1) replicate our findings that drug unit price (UP) produces elastic effects on HYD seeking; (2) determine whether magnitude of a money alternative would reduce HYD seeking; (3) determine whether post-session supplemental HYD doses affects HYD seeking and, if so, whether this factor would interact with drug UP or money alternative amount; and (4) replicate our finding that individual differences in pre-experimental cocaine use influence HYD seeking.

First, this study replicated our earlier demonstration of the effect of UP on HYD demand with a \$2.00 unit money alternative choice (Greenwald and Hursh, 2006). The present data demonstrate mixed elasticity, such that UPs less than 1000 (i.e. fixed ratios < 2000 in conjunction with the fixed HYD unit dose of 2 mg) were associated with inelastic demand, and that higher UPs led to elastic demand (Figure 4). Demand curve fits were generally high ($r^2 \geq 0.88$), with one exception ($r^2 = 0.77$ in the condition with the \$4 money alternative and no HYD supplement). Values for $P_{\max}$ and $O_{\max}$ were highest in the \$2 alternative/no-supplement condition, intermediate in the \$2 alternative/12 mg-supplement condition, and uniformly lower for the other experimental conditions (Table 2). Other measures of HYD reinforcing efficacy (e.g. drug choices, breakpoint, cumulative responding) were consistent with this pattern (Table 2). In contrast, total consumed dose exhibited a different pattern: there were linear increases as a function of post-session supplement, and consumption levels were systematically lower in the \$4 relative to \$2 alternative condition (Figure 3).

Second, studies with human subjects that have varied the amount of money in a controlled laboratory setting (e.g. Comer et al. 1997, 1998; Petry and Bickel, 1999; Heishman et al., 2000; Stitzer et al., 1983) or vouchers in a treatment setting (e.g. Dallery et al., 2001; Kosten et al., 2003) have demonstrated that a larger-magnitude non-drug reinforcer can reduce choice of opioids and thereby shift choice toward the alternative option. The present experiment replicated and extended these findings by showing that the two-fold greater money alternative (\$4 vs. \$2 per choice) – which simulates a more robust employment wage rate (Bickel and

DeGrandpre, 1996) – significantly increased HYD elasticity, while decreasing $P_{\max}$ and $O_{\max}$, selectively in the absence of a post-session supplemental dose (closed economy). The present findings illustrate that the ability of non-drug reinforcement to modulate drug seeking is malleable, depending upon the prevailing drug supply. Interestingly, in rats whose heroin intake had escalated, non-drug (food) reinforcement retained its ability to increase heroin demand elasticity (Lenoir and Ahmed, 2008), although the magnitude of non-drug reinforcement was not manipulated in that study. This factor is important to model because individual differences in non-drug reinforcement magnitude-sensitivity may be mechanistically related to the reduction of drug demand. To the extent that non-drug alternatives can function as substitutes for drug use, then treatment efficacy should be predicted by the individual's willingness to consume these alternatives at lower drug prices despite a plentiful drug supply. Experiments with nicotine-dependent smokers have examined the effect of concurrent supplies of pharmacological and non-pharmacological sources of reinforcement on cigarette demand (e.g. Bickel and Madden, 1999; Johnson and Bickel, 2003, 2006). For instance, Johnson and Bickel (2003) found that cigarette consumption decreased somewhat when nicotine gum was available, but to a larger extent when money or both alternatives were available; however, the magnitudes of these sources of reinforcement (i.e. money amount, dose of gum) were not manipulated, so it is presently unknown whether these commodities statistically interact (as found in the present experiment).

Third, the present study showed that providing information about the availability of a post-session HYD supplemental dose – a *signaled* open economy (i.e. because the supplement could not be consumed until later) – significantly reduced HYD seeking on the PR task. That is, knowledge of near-future drug income decreased immediate drug-acquisitive behavior. On the other hand, availability of the supplement was only effective in reducing HYD seeking in the context of the smaller-magnitude money alternative. Thus, when money income was more lean (\$2 per choice), the prospect of additional drug income (post-session supplement) assumed greater control over current drug responding; whereas, more abundant monetary income (\$4 per choice), which itself attenuated HYD seeking, buffered the ability of drug income (supplement) to further decrease HYD seeking (Figure 2).

When supplements were made available, participants chose to take the 24 mg supplement significantly more often (about 90% of subjects) than the 12 mg supplement (about 60% of subjects). Thus, experimental instructions about post-session drug availability were reflected by greater consumption. This provides internal validity that the higher dose functioned as a more effective reinforcer. The observed dose-dependent pattern of supplement choices afforded a significant increase in the total HYD dose consumed during the entire-day session, which offset the lower HYD seeking behavior (PR task) produced by the signaled open economy (Figure 3).

Our findings that HYD seeking is decreased by pre-session supplements, the pharmacological effects of which had subsided before the PR task (Greenwald and Hursh, 2006) as well as post-session supplements (the present study) are consistent with the hypothesis that it is *not* the direct pharmacological effects of HYD supplements that produce opioid demand reduction. As we noted (Greenwald and Hursh, 2006), the daily BUP maintenance dose functions as a long-acting supplement (open economy) that, by suppressing opioid withdrawal symptoms (as observed here), could alter the degree to which shorter-acting supplements can suppress drug seeking. Instead, a more plausible and parsimonious explanation is that the context of the open economy – i.e. knowledge that drug supplements are accessible and inexpensive (anticipated satiation) – is responsible for reducing HYD-seeking behavior. Taken together, the results from these companion studies suggest that participants ration their PR-reinforced and supplement choice responding to maximize total income, including both drug and non-drug sources of reinforcement. This conclusion is further supported by observations that HYD dose units were

inversely correlated with money choices during the PR task, and with post-session HYD supplement choices.

The behavioral economic phenomenon known as the “minimum needs hypothesis” (Kagel et al., 1985; Shurtleff et al., 1987) may partly impact on the results of the present study. According to this hypothesis, different reinforcers are rank-ordered in terms of their biological necessity (usually interpreted as a state of deprivation), which manifests in the observed sequence of choices between the different reinforcers within a session. The drug-first choice analysis (lower panel of Figure 2) suggests that participants may have chosen drug based on such considerations. Prior to each session in the present study, information was provided as to the response-contingent unit HYD dose (1/12th of Drug A or Drug B), the unit money alternative (\$2 or \$4), and the later availability of a HYD supplement (none, Drug A or Drug B). It is striking that subjects allocated significantly more of their initial choices to HYD when the unit dose and money alternative were lower and no post-session drug supplement was available, relative to the other experimental conditions. Subjects may have decided that –with both reduced drug and money income– accumulating drug reinforcement early during the session may have been advantageous. On the other hand, opioid withdrawal symptoms were relatively low in the present study; thus, a purely “biological need” explanation of prioritizing drug responding does not seem entirely satisfactory. The present study was not specifically designed to test the minimum needs hypothesis, but this is worthy of explanation in future work.

Fourth, participants in our previous study who sporadically used cocaine (based on self-report, interview, and repeated urinalyses) as outpatients prior to the experiment but were acutely abstinent while living on the inpatient unit chose HYD significantly more than individuals who did not use cocaine. This effect was replicated in the present study, despite (once again) small sample sizes. The pattern of results in both studies is consistent with several opioid maintenance clinical trials, in which cocaine use has been predictive of continued use of heroin and greater treatment attrition (DeMaria et al., 2000; Dolan et al., 2001; Downey et al., 2000; Perez et al., 1997; Preston et al., 1998; Sofuoglu et al., 2003). In contrast, level of pre-experimental opioid use, which was explored in the analyses, was not significantly associated with HYD choice in the laboratory setting. Although it is well established that polydrug use is associated with greater substance abuse problem severity (Dolan et al., 2001; Leri et al., 2005; Malow et al., 1992; Torrens et al., 1991; Rowlett et al., 1997), the mechanisms that underlie the specific interaction between the reinforcing of cocaine (and acute abstinence from cocaine, which occurred during the inpatient portion of this study) and opioids are complex and still not well understood (Leri et al., 2003). In the present study, subjects who had not recently used cocaine, relative to those who had used cocaine, reported at session baseline (about 13 hr after the daily BUP dose, in the absence of HYD) significantly higher levels of opioid withdrawal symptoms, but also significantly higher levels of opioid agonist symptoms. This pattern suggests that abstinence following recent cocaine use may alter endogenous opioid function (Gorelick et al., 2005; Zubieta et al., 1996).

As has been observed at a macroeconomic scale, naturalistic decreases in illegal heroin supply can stimulate treatment demand (Degenhardt et al., 2005). Of course, a longstanding and shared goal among treatment providers and policymakers has been to proactively increase the supply of treatment, even without a heroin (or other drug) drought. The findings from this controlled laboratory experiment suggest some treatment and policy implications. First, making supplemental agonist doses readily available to physically dependent patients – creating an open economy by increasing pharmacological (medication) income – can reduce drug seeking. This principle mimics standard opioid substitution therapy, including provision of take-home doses, which function as reinforcers (Amass et al., 1996; Chutuape et al., 1998; Stitzer et al., 1985) and can increase patient retention and reduce drug use (Chutuape et al., 1999; Kidorf et al., 1994; Rhoades et al., 1998), but also medically supervised heroin assisted treatment

(Fischer et al., 2002; Gschwend et al., 2004; Rehm et al., 2001). A related issue is that informing patients they can access medication dose increases (e.g. if they are experiencing withdrawal or tempted to use heroin; cf. Preston et al., 2000) might produce an anticipatory, or placebo, effect that temporarily reduces drug seeking. Second, increasing the supply of non-pharmacological alternatives – creating an open economy by enhancing non-medication sources of reinforcement – also effectively reduces drug seeking. Of course, this principle is central to contingency management treatment procedures (Bickel et al., 2008). By introducing attractive alternatives to drug choice, opportunity cost increases; this is tantamount to increasing the price of drug use. Third, when manipulating both drug and non-drug sources of reinforcement, it remains possible that the combination of these factors may not be additive. As observed here, the higher-magnitude money alternative reduced HYD seeking relative to the lower-magnitude alternative, and drug supplements did not further reduce HYD seeking at the higher-magnitude money alternative. It remains to be determined whether a further increase in economic income, BUP dose, HYD supplements or combination of these factors might completely suppress drug-seeking behavior.

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Figure 1.

Lower panel: Timeline (24-hr clock time) for each choice session. From 0830–0900, baseline subjective effects (SE) and vital signs (VS) were recorded. At 0855, the participant was instructed whether supplemental hydromorphone (HYD) would be available or not later in the session (at 1500). The 3-hr choice progressive ratio (PR) task occurred from 0900 to 1200, after which response-contingent (earned) HYD was administered as a bolus IM injection. SE and VS were measured at 1230, 1300, 1330, 1400, 1430 and 1500. If the supplement was available and the subject chose to receive it, the injection was administered at 1515. SE and VS were measured at 1545, 1615, 1645, and 1715, then the subject was returned to the inpatient unit. The daily buprenorphine (BUP) dose was administered at 2000. *Upper panel:* Sequence of 12 choice opportunities and corresponding fixed ratio (left ordinate) and cumulative responding (right ordinate) values for completing choices.

Figure 2.

Responding on the choice PR task. *Upper panel:* Mean (+ 1 SEM) number of drug choices (left ordinate) and corresponding breakpoint (right ordinate). There was a significant main effect of money alternative and a significant interaction between money alternative and post-session supplement dose. *Lower panel:* Mean (+ 1 SEM) number of drug-first choices (left ordinate) and corresponding breakpoint (right ordinate). There was a significant interaction between money alternative and post-session supplement dose. See Table 2 and text for details.

Figure 3.

Upper panel: The proportion of subjects choosing the post-session HYD supplement was significantly greater for the higher relative to lower dose, regardless of the money alternative. *Lower panel:* The cumulative dose of HYD consumed, which includes response-contingent choices on the PR task (shaded segments of bars; maximum = 24 mg, reflected by the horizontal dashed line) and the supplement, increased significantly as a function of supplement dose and decreased as a function of money alternative. Average money earnings (range, \$0 to \$24 per condition) are represented on the right ordinate.

Figure 4.

Demand functions (upper panels) and response output functions (lower panels) produced by plotting market consumption (percent of the 13 participants choosing HYD) at each unit price (UP) for each of the three HYD supplement levels for the \$2 money alternative (left panels) and \$4 money alternative (right panels). See Table 2 and text for details on elasticity (A parameter), demand curve fits (r^2), $P_{\max}$ and $O_{\max}$ values.

Table 1
Statistical Summary of Hydromorphone (HYD) Sampling Responses

Peak Measure (Max+, Min-)	Dose $F[1,12] (P)^I$	Dose $\times$ Time $F[6,72] (P)$	Absolute Peak $t[12] (P)^I$	Mean Peak Score (± 1 SD)	HYD 12 mg	HYD 24 mg
(-) Heroin Craving	ns	ns	ns	34.7 (19.7)	34.9 (20.8)	
(+) Opioid Agonist	6.44 (.03)	4.83 (.005)	2.46 (.03)	13.7 (7.4)	18.1 (8.0)	
(-) Opioid Antagonist	ns	ns	ns	3.2 (6.6)	3.5 (7.2)	
(+) Any Drug Effect	3.91 (.07)	ns	2.14 (.053)	31.5 (29.5)	49.5 (24.1)	
(+) Good Drug Effect	ns	ns	ns	38.3 (33.9)	50.2 (24.7)	
(-) Bad Drug Effect	ns	ns	ns	11.6 (25.6)	3.5 (5.7)	
(+) Drug High	3.81 (.08)	ns	2.15 (.052)	29.2 (29.9)	46.3 (29.5)	
(+) Drug Liking	ns	ns	2.20 (.05)	34.5 (29.6)	54.3 (26.3)	
(+) Stimulated	7.07 (.02)	ns	2.47 (.03)	21.3 (20.1)	37.1 (21.6)	
(+) Sedated	ns	ns	ns	33.4 (29.9)	46.8 (32.7)	
(-) Respiration Rate	5.15 (.04)	ns	2.48 (.03)	12.3 (1.3)	11.2 (1.5)	
(-) Oxygen Saturation	12.59 (.005)	ns	3.59 (.004)	95.9 (1.7)	94.6 (1.4)	
(-) Heart Rate	4.50 (.06)	ns	2.30 (.04)	63.6 (8.5)	60.3 (5.4)	
(-) Systolic BP	ns	ns	ns	107.3 (6.3)	105.9 (5.6)	
(-) Diastolic BP	ns	ns	ns	64.3 (8.2)	64.5 (8.1)	

^I All *P* values are Huynh-Feldt corrected. "ns" indicates $P \geq .10$.

Table 2

Measures of Hydromorphone (HYD) Reinforcing Efficacy¹

<i>Money Alternative Amount</i> <i>HYD Supplement Condition</i>	\$2.00 per trial			\$4.00 per trial		
	None	12 mg	24 mg	None	12 mg	24 mg
Number of drug choices ² (M, S×M)	8.08 (0.76)	6.62 (0.68)	5.00 (0.78)	4.46 (1.17)	5.31 (0.99)	5.00 (1.00)
Drug-first choices ³ (S, S×M)	4.23 (1.34)	0.39 (0.24)	0.54 (0.46)	1.23 (0.95)	1.23 (0.95)	1.92 (1.15)
Breakpoint (S×M)	4678 (961)	2583 (507)	1566 (421)	2388 (1010)	2375 (913)	2173 (800)
Log ₁₀ breakpoint	3.504 (0.139)	3.118 (0.268)	2.656 (0.339)	2.360 (0.412)	2.838 (0.291)	2.632 (0.356)
Cumulative drug responding ⁴ (S×M)	14311 (3357)	7188 (1583)	4181 (1229)	7306 (3412)	7028 (3162)	6843 (2995)
Log ₁₀ cumulative drug responding	3.928 (0.175)	3.510 (0.302)	2.989 (0.381)	2.614 (0.466)	3.145 (0.339)	2.941 (0.407)
Total drug time (min) (S×M)	69.1 (13.5)	40.9 (10.7)	22.1 (5.9)	39.8 (14.5)	34.9 (12.1)	33.1 (14.5)
Total dose consumed ⁵ (M, S)	16.15 (1.53)	21.54 (2.33)	32.15 (2.98)	8.92 (2.34)	17.08 (2.24)	30.31 (3.10)
A parameter (S×M)	0.0001005	0.0001835	0.0002727	0.0001758	0.0001972	0.0001885
Demand curve fit (<i>r</i> ²)	0.93	0.91	0.96	0.77	0.88	0.94
Computed Pmax (0.29 ÷ A)	2886	1580	1063	1650	1471	1538
Computed Omax	30025	16905	10052	10414	7951	10660

¹ Sample means ($\pm$ 1 SEM), n = 13.

² 'S', 'M', and 'S×M' refer to significant ($P < .05$) Supplement, Money and Supplement $\times$ Money effects from ANOVAs.

³ Number of completed drug choices prior to the first money choice within-session.

⁴ Includes drug option responding that was not completed before the 3-hr session expired.

⁵ Equal to the HYD supplement dose (if available) plus all unit doses earned (number of drug choices $\times$ unit dose), mg.

Table 3

Effects of Recent Cocaine Use History¹

<i>Cocaine Use Group</i> <i>Money Alternative Amount</i>	No Recent Cocaine Use (<i>n</i> =3)	Recent Cocaine Use (<i>n</i> =10)	Group × Money <i>F</i> [1,11] (<i>P</i>)
	\$2 per trial	\$4 per trial	\$4 per trial
Number of drug choices	6.78 (1.18)	2.67 (1.73)*	5.60 (0.95)
Drug-first choices	1.44 (1.09)	0.00 (1.38)	1.90 (0.76)
Log ₁₀ breakpoint	3.31 (0.42)	1.83 (0.57)*	2.84 (0.31)
Log ₁₀ cumul. drug responding	3.72 (0.47)	2.00 (0.66)*	3.17 (0.36)
Total drug time (min)	27.9 (17.7)	11.1 (19.5)	43.4 (10.7)
Total dose consumed	25.6 (3.8)	16.0 (4.5)	19.6 (2.5)

¹ Values are subgroup means ($\pm$ 1 SEM), with same measurement units as Table 2.

² Asterisks indicates that the No Recent Cocaine Use/\$4 per trial condition significantly differs ($P < .05$) from the other conditions in *post hoc* tests.