

Methadone doses of 100 mg or greater are more effective than lower doses at suppressing heroin self-administration in opioid-dependent volunteers

Eric C. Donny¹, Susan M. Brassler², George E. Bigelow¹, Maxine L. Stitzer¹ & Sharon L. Walsh¹

Behavioral Pharmacology Research Unit, Department of Psychiatry, Johns Hopkins School of Medicine, Baltimore, MD, USA¹; Currently at the Department of Anatomy and Neurobiology, University of Tennessee Health Science Center, Memphis, TN, USA²

Correspondence to:

Sharon L. Walsh

Center for Drug and Alcohol Research

University of Kentucky

43 Maxwellton Court

Lexington

KY 40506-0350

USA

Tel: 859-323-6126

Fax: 859-323-1193

E-mail: sharon.walsh@uky.edu

Submitted 5 November 2004;

initial review completed 23 February 2005;

final version accepted 30 April 2005.

ABSTRACT

Aims Methadone maintenance has been an effective pharmacotherapy for the treatment of heroin dependence for nearly four decades. Recent clinical research suggests that methadone doses larger than those used in most clinics are more effective at suppressing illicit heroin use. This greater efficacy may result from greater cross-tolerance to the reinforcing effects of heroin.

Design The purpose of this double-blind, within-subject study was to examine the relationship between methadone maintenance dose and the reinforcing effects of heroin.

Setting Participants were stabilized on 50, 100 and 150 mg methadone (ascending order) during separate outpatient periods before being admitted to an inpatient research unit for testing at each maintenance dose.

Participants Five opiate-dependent volunteers completed the study.

Measurements During each 4-week inpatient testing period, participants sampled three doses of heroin (0, 10, or 20 mg; random order; one dose per week) and were subsequently allowed seven opportunities to choose between another injection of that week's heroin dose and varying amounts of money (\$2–38).

Findings The number of heroin injections chosen decreased as methadone dose was increased. Larger alternative monetary reinforcers were required to suppress heroin self-administration during maintenance on 50 compared to 100 or 150 mg methadone. Larger methadone doses also completely blocked the subjective effects of heroin and produced greater withdrawal suppression during the outpatient periods.

Conclusions These results support other clinical and laboratory-based research indicating that persistent heroin use may be reduced by providing larger methadone maintenance doses that produce more effective cross-tolerance to heroin.

KEYWORDS Heroin, human, methadone, opioid, reinforcement, self-administration.

INTRODUCTION

Methadone, a mu-opiate receptor agonist, has been used widely as a pharmacological treatment for opioid dependence and has demonstrated efficacy in reducing heroin use (Dole & Nyswander 1965). Despite the clinical benefit of methadone in the treatment of opioid abuse and

dependence, a significant number of patients maintained on methadone continue to use heroin, as well as other drugs of abuse, regularly. Understanding why methadone-maintained individuals continue to use heroin and what factors limit the therapeutic efficacy of methadone would be an important step towards improving treatment.

Methadone exerts its therapeutic effects in the treatment of illicit opioid abuse through several mechanisms; it relieves opioid withdrawal, attenuates the subjective and reinforcing effects of continued opioid use, reduces craving for opiates, and normalizes physiological functioning. Continued heroin use in methadone-maintained patients may be indicative of a failure in one or more of these treatment functions. Clinical trials research has shown that larger methadone doses are more effective than relatively small doses at suppressing illicit heroin use (Strain *et al.* 1993; Strain *et al.* 1999). In the present study, we tested the hypothesis that substantial residual heroin use among methadone-maintained individuals may be due to the use of methadone doses that fail to produce full blockade of the reinforcing effects of heroin.

The opioid blockade effects of methadone were first described by Dole, Nyswander & Keek (1966). In this seminal work, opiate-dependent participants maintained on 80–100 mg of methadone were administered increasing doses of intravenous heroin (5–160 mg). Heroin produced little evidence of euphoria in these participants. The degree of cross-tolerance was greatest in participants who had been maintained on methadone for a long period of time (e.g. 150 days). Likewise, a study by Zaks, Fink & Freedman (1971) found that participants maintained on 100 mg of methadone were completely tolerant to up to 75 mg of intravenous heroin 6 h after dosing. Subsequent research by Volavka *et al.* (1978) first demonstrated that cross-tolerance to intravenous heroin was dependent on the dose of methadone. In this study, recently detoxified participants received 15 mg/70 kg heroin or placebo prior to methadone maintenance, between the eighth and twelfth day of induction onto methadone (at 25 or 50 mg), and at the end of the 18–22-day period when the methadone dose had been increased to either 40 or 80 mg/day. Heroin's subjective and pupillary effects were dose-dependently diminished by methadone; however, blockade of this relatively small dose of heroin was incomplete for both 40 and 80 mg methadone. Recent research from our own laboratory is consistent with these early observations (Donny *et al.* 2002). Participants maintained on 30, 60 and then 120 mg methadone for three weeks at each dose were challenged with increasing doses of heroin (0, 10 and 20 mg/70 kg; 45 min interdose interval). Heroin administered 4 h after the last methadone dose produced subjective reports of euphoria when participants were maintained on 30 or 60 mg methadone; in contrast, no subjective effects were reported during maintenance on 120 mg methadone. Modest subjective effects of heroin re-emerged when heroin was administered 28 or 52 h after the last 120 mg methadone dose. Importantly, this (Donny *et al.* 2002) and other (Volavka *et al.* 1978; McCaul *et al.* 1983) studies indicate that doses of metha-

done commonly used in clinical practice (e.g. <80 mg in the United States; D'Aunno and Pollack 2002) produce only partial blockade of the subjective effects of heroin.

Only one study to date has examined the ability of methadone to suppress opiate-reinforced behavior under controlled laboratory conditions. Jones & Prada (1975) allowed six participants to work for intravenous injections of 4 mg hydromorphone before, during and after induction onto 100 mg of methadone. As the dose of methadone was gradually increased, the number of participants working for injections of hydromorphone declined. Maintenance on 100 mg largely eliminated responding for hydromorphone in five of the six participants. Although these results indicate that the reinforcing effects of opioids may be dose-dependently attenuated by methadone, a systematic evaluation of the relationship between methadone dose, heroin dose, and heroin-reinforced behavior has not been reported.

The purpose of the present study was to examine the reinforcing properties of different doses of heroin, as assessed by the choice to take either heroin or an alternative monetary reinforcer, over a range of methadone maintenance doses representing and exceeding those typically used in clinical practice. Withdrawal signs/symptoms were assessed throughout the study to determine whether withdrawal discomfort varied significantly across the range of methadone doses tested and to determine whether withdrawal might be a driving factor in heroin self-administration during methadone maintenance. Additional assessment of the subjective and physiological effects of heroin were conducted to replicate and extend the laboratory data summarized in our earlier report (Donny *et al.* 2002).

MATERIALS AND METHODS

Participants

Thirteen volunteers were recruited from the community through local newspaper advertisements and word-of-mouth. Eight volunteers failed to complete the protocol due to the following reasons: poor clinic attendance ($n = 3$), symptoms of benzodiazepine dependence ($n = 1$), lost to contact ($n = 1$), personal reasons ($n = 1$), problems with our supply of heroin ($n = 2$; described below). Data from these eight participants were not included in any analyses.

Two African-American, two Caucasian, and one African-American/Caucasian males [average age: 37.4 ± 3.6 (SD)] completed the study. The study was stopped after these five participants completed because additional participants were cost prohibitive and because orderly results were obtained based on this relatively small sam-

ple size. All participants reported using opioids on a regular basis (e.g. 5–7 times/week) and provided two opioid-positive urine samples prior to admission. Any volunteer seeking treatment for opioid dependence was excluded from participation and referred to a treatment provider. No participants were maintained on methadone at the time of admission. Other drug and alcohol use was determined by self-report, urinalysis, and/or breathalyzer tests. Individuals physically dependent on benzodiazepines or alcohol were excluded from participation. All participants completed a standard physical examination, including EKG, blood chemistry, hematology, and routine medical urinalysis and were determined to be in good health. Individuals with chronic health problems or significant psychiatric conditions other than drug abuse were excluded. Participants provided written informed consent prior to research participation. They were paid for their time and inconvenience.

All participants met DSM-IV criteria for current opioid dependence (APA 1994 as assessed by the Structured Clinical Interview for DSM IV; First *et al.* 1995). Participants reported using opiates for a mean of 10.8 years (± 6.2) and spending an average of \$14.00 (± 4.18) on heroin on 29.6 (± 0.9) of the last 30 days. Participants reported an average of 2.4 days (± 4.3) of cocaine use and 3.2 days (± 6.6) of alcohol use in the last 30 days.

Overview of the study design

This study used a multi-dose, within-subject design with three alternating outpatient and inpatient phases (i.e. outpatient, inpatient, outpatient, inpatient, outpatient, inpatient) corresponding to three methadone maintenance doses. Research personnel involved in data collection and study participants were blind to methadone and heroin dose except during the heroin detection test when research personnel were aware of the heroin doses. Participants were informed that methadone dose would 'be similar to or higher than those usually offered in treatment.' The study design and experimental procedures were approved by the Johns Hopkins Institutional Review Board.

Outpatient phase

Induction and stabilization on each methadone dose occurred on an outpatient basis over approximately 3–4 weeks. Participants were required to visit our research clinic daily (except for scheduled take-homes given on major holidays or due to inclement weather). Methadone dose was increased by increments of 10 mg/day to reach the assigned maintenance dose; participants received that dose for at least two weeks prior to each inpatient admission. Longer outpatient dosing was

required if participants missed a dose. On average, participants were maintained on the target methadone dose for 23 days prior to admission (range: 14–36 days). Only 14 (4%) of the 341 scheduled doses were missed. Missed doses were not related to methadone dose (5, 2, and 7 in 50, 100 and 150 mg methadone conditions, respectively). Participants missing more than two days in a row were discharged and are not reported here.

Inpatient phase

Following each outpatient phase, participants were admitted to a residential research unit for approximately four weeks. Participants received their current methadone dose at 7:00 p.m. daily throughout their stay. The first week served as an inpatient stabilization period. During this time, participants completed a battery of cognitive measures to assess the effects of the current methadone dose (data not reported here). The effects of heroin were subsequently assessed during three types of sessions: (1) a heroin detection threshold session (2) sample sessions and (3) choice sessions.

All heroin sessions were conducted in a testing room designed to provide a constant environment. The participant was seated throughout the session in front of a personal computer (Apple IIGS, Apple Computer, Cupertino, CA) that recorded subjective and physiological responses. A slow drip i.v. line remained in place throughout each session. Heroin was administered via an indwelling catheter at 9:00 AM and/or 2:00 p.m., 14 h and 19 h after methadone dosing, respectively. Naloxone and supplemental O₂ were available at all times, although they were not needed. During each session, the research assistant remained seated behind the computer, initiated the data collection, monitored the participant and provided observer ratings. The assessment battery included physiological measures, subjective reports and observer ratings (described in detail below).

Heroin detection test

This session was designed to quantify the dose of heroin at which subjective effects could be detected. The session involved a titration procedure in which up to 10 3 mg/70 kg i.v. heroin injections were administered at 10 min intervals (a total possible dose of 30 mg/70 kg). Participants were instructed that they could receive up to 10 injections that could contain either placebo or active heroin. They were also told that a \$25 session bonus would be given if they correctly identified if and when they received an active dose. Dosing was terminated when either a drug effect was reported or all 10 doses were given with no drug effect reported. Subjects were always

told that their responses were correct and were paid the bonus. Physiological variables (e.g. respiratory rate, O₂ saturation, temperature, heart rate, and blood pressure) were also monitored throughout the session. There was a minimum 72 h interval after the heroin detection test before sample/choice sessions began.

Heroin sample and choice sessions

At the beginning of each test week, participants received a different 'sample' dose of i.v. heroin (0, 10, or 20 mg/70 kg, randomized across weeks) and subsequently participated in seven choice sessions in which they were given the opportunity to choose between the sample dose and money. The money choices were \$2, \$8, \$14, \$20, \$26, \$32 and \$38 and were randomized across the choice sessions within each week. The sample and choice sessions were completed over four consecutive days, with subjects completing two sessions per day, approximately 5 h apart [i.e. Day 1: Sample (9 AM)/Choice (2 p.m.), Days 2–4: Choice (9 AM)/Choice (2 p.m.)].

Heroin (or placebo) was administered under double-blind conditions during the sample sessions. Subjective and physiological measures were assessed at baseline and at regular intervals throughout the session. Participants were instructed that this dose would be available for them to choose during the remainder of that week. During choice sessions, participants were allowed to choose between the available dose and the specified amount of money. If the participant chose the drug, an injection was administered immediately. If the participant chose the money, cash was handed to the participant immediately. The cash was collected at the end of the session and the participant was given a receipt indicating this amount had been added to his account. For security reasons, participants were not allowed to keep cash on the residential unit.

Aftercare

Participants were enrolled in a 90-day detoxification program through the outpatient methadone clinic following completion of the final residential phase of the study. They were encouraged to seek continuing treatment during this time.

Measures

Urinalysis. Urine samples were collected every Monday, Wednesday and Friday during each outpatient phase for monitoring opioid, cocaine and benzodiazepine use. Percent positive urines were calculated for each drug class for each participant at each target dose of methadone. Only two scheduled urine samples were not collected

because the participant failed to attend the clinic; these missing values were excluded when calculating the percent positive calculations.

Choice. Discrete choices for an injection or money during the inpatient choice sessions were first examined as raw data and then summarized as four related measures: the total number of injections chosen, the total amount of money earned, the maximum dollar value at which the participant chose to take an injection (i.e. maximum amount paid), and the minimum amount of money that was chosen over an injection (i.e. smallest effective alternative reinforcer).

Participant-rated measures. Outpatient participant-rated measurements included a visual analog scale, an adjective rating scale (Opioid Agonist Scale, Withdrawal Scale) and a symptom checklist. The visual analog scale was completed once each week and consisted of the following questions rated on a 0–100 scale: 'How well has this dose of medicine been holding you for the past week (last 7 days)?' (anchored by 'Too low' and 'Too high'), 'For the past week (last 7 days), how much have you felt hooked by the medicine?', 'For the past week (last 7 days), how much have you liked the medicine?', 'How much have you craved cocaine for the past week (last 7 days)?' and 'How much have you craved heroin for the past week (last 7 days)?' (anchored by 'Not at all' and 'A lot'). The participant-rated adjective checklist was completed three times each week and consisted of the following 37 items that the participants rated from 0 (indicating 'not at all') to 4 (indicating 'extremely'): muscle cramps, flushing, painful joints, turning of stomach, yawning, nodding, restless, skin itchy, watery eyes, heavy/sluggish feeling, runny nose, relaxed, chills/goose flesh, dry mouth, sick to stomach, coasting, sneezing, carefree, talkative/soap boxing, friendly, good mood, abdominal cramps, pleasant sick, irritable, energetic, backache, drive, tense and jittery, sweating, depressed/sad, sleepy, shaky hands, hot or cold flashes, drunken, bothered by noise, nervous, skin clammy/damp. Subsets of these items were summed to derive the Opiate Agonist Scale and the Withdrawal Scale as described previously (Preston, Bigelow & Liebson 1988). A symptom checklist was completed once each week and consisted of the following 22 items rated on a scale of 0 (indicating 'not at all') to 4 (indicating 'very severe'): blurred vision, constipation, diarrhea, dizziness/faintness, dreaming more, dry mouth, headache, heart racing, loss of interest in sex, nausea, thirsty, ringing in ears, skin rash, sleepy after meds, tremors, trouble with sex, trouble swallowing, trouble urinating, upset stomach, vomiting, nervousness and sweating.

Inpatient participant-rated measurements included visual analog scales, the Addiction Research Center Inventory (ARCI) short form (Martin *et al.* 1971), a street

value question and the adjective rating scale described above. The visual analog questions included 'How high are you?', 'Do you feel any drug effect?', 'Does the drug have good effects?', 'Does the drug have bad effects?', 'Do you like the drug?', 'Does this drug make you feel sick?', 'How much do you desire opiates right now?' and 'Do you feel sick from withdrawal?' These items were presented at baseline, once each minute for 8 min after the start of the sample injection, and at 15, 30, 45, 60, 90 and 120 min after the injection. The ARCI short form consisted of 49 true/false questions presented at baseline (20 min before the sample injection) and 30, 60 and 120 min after the sample injection. The ARCI questions are subdivided in scales that are sensitive to euphoria [Morphine-Benzedrine Group (MBG)], sedation [Phenobarbital-Chlorpromazine-Alcohol Group: (PCAG)], dysphoria [Lysergic Acid Diethylamide (LSD)] and amphetamine-like effects [Benzedrine Group (BG) and Amphetamine (A)]. Street value was estimated by asking 'How much would you pay for this drug?' at 60 min after the injection. Participant-rated adjectives were presented 20 min prior to the sample injection and at 15, 30, 45, 60, 90 and 120 min after the injection.

Observer-rated measures

The observer-rated opioid adjective scale included nodding, scratching, magnitude of drug effect, restlessness, talkative, sleepy/sedated, energetic, irritable, friendly, vomiting, drunken and nervous. Adjectives were rated on a 0–4 scale. Observer-rated measurements were taken 20 min before the sample injection, and at 6, 15, 30, 45, 60, 90 and 120 min after the injection.

Physiological measures

Physiological measures, including skin temperature, systolic and diastolic blood pressure, heart rate, pupil diameter, respiration rate, and O₂ saturation, were monitored throughout each session. Respiratory rate was recorded by the research assistant who counted the number of breaths taken by the participant for a 30-s period at 20 min prior to the sample injection and at 5, 15, 30, 45, 60, 90 and 120 min following each sample injection. Skin temperature, systolic and diastolic blood pressure and heart rate were collected every minute via an automatic physiologic monitoring device (Non-invasive Patient Monitor model 506, Criticare Systems, Waukesha, WI, USA) that was interfaced with a Macintosh computer. Photographs of the eye for assessment of pupil diameter were taken using a camera (Polaroid, Cambridge, MA) modified with close-up lenses and a mounted bracket to ensure a standard distance from the eye. The

photographs were taken 20 min prior to the sample injection and at 5, 15, 30, 45, 60, 90 and 120 min after the injection.

Drugs

All doses of methadone HCl USP (Mallinckrodt Inc., St. Louis, Missouri, USA) were measured by the weight of the salt. Heroin HCl (Macfarlan Smith Limited, Edinburgh, UK) was dissolved in 0.9% sterile saline using aseptic techniques in a certified laminar flow hood and filtered through a 0.22 µm filter (Millipore Products Division, Bedford, Mass., USA) into a sterile pyrogen-free vial. Heroin (10 and 20 mg/70 kg) and placebo were administered intravenously in a volume of 1 mL over 10 s. Heroin was administered under an Investigator-initiated Investigational New Drug exemption from the US Food and Drug Administration.

The final two study enrollees both developed itching, redness and swelling after an injection of heroin. Both volunteers were discontinued for safety reasons. Subsequent tests determined that the heroin had prematurely degraded. No additional volunteers were recruited after this period. There was no indication that the data from previous volunteers was affected; the last participant included in this report completed the study approximately four months prior to this incident.

Data Analysis

Outpatient drug use was assessed by the percent of opioid-, cocaine- and benzodiazepine-positive urine samples during maintenance on each target methadone dose. Additional analyses of the outpatient urinalysis data were conducted using raw data and the Generalized Estimating Equation (GEE) with a single factor, methadone dose. GEE has the advantage of utilizing all available data points. However, one disadvantage is that estimates of the variance can be biased with small sample sizes (Prentice 1988); therefore, the results presented should be viewed with caution. The direct agonist and withdrawal-suppressing effects of methadone were evaluated by analyzing observer-rated and subjective data collected during the outpatient phase and at baseline immediately prior to heroin sample injections. The subjective and physiological effects of the sample injection of heroin were evaluated using two different data analytic strategies: difference score (as compared to baseline) analyses to determine the time course of the effects of heroin, and maximal peak change from baseline. The strategy of basing all analyses on the change from baseline was employed to address possible baseline shifts due to the direct effects of the different methadone doses.

All data were analyzed using ANOVA with one or more of the following factors: methadone dose, heroin dose and

time. All repeated measures data were adjusted for sphericity using Huynh-Feldt corrections. Post hoc comparisons were made using Tukey's Honestly Significant Difference (HSD) test. Differences with a probability of $P < 0.05$ were considered statistically significant.

RESULTS

Outpatient evaluation

Subjective effects of methadone

Outpatient assessments revealed little direct effect of methadone dose on opioid agonist measures, but produced some evidence of mild withdrawal after 50 compared to 100 or 150 mg methadone. No significant effect of methadone dose was found on the composite adjective ratings of opioid agonist effects. Analysis of individual items revealed that only friendly and good mood were significantly related to methadone dose; post hoc comparisons revealed higher ratings while participants were maintained on 100 (friendly) or 150 (friendly, good mood) compared to 50 mg methadone ($P < 0.05$). The relationship between methadone dose and the composite withdrawal scores failed to reach significance, although there was a trend for greater withdrawal during maintenance on the 50 compared to 100 and 150 mg doses. However, analysis of individual adjective items revealed a reliable pattern of greater withdrawal symptoms during maintenance on 50 compared to 100 (chills/gooseflesh, sick to stomach, hot and cold flashes, skin clammy/damp) and 150 mg methadone (chills/gooseflesh, sick to stomach, hot and cold flashes). It is important to note, however, that throughout most of the study mean ratings for withdrawal items were low (i.e. 0–1 on a 5-point scale). Although three participants had moderate ratings of withdrawal effects during the first few days of the study, these tended to decline over time at the 50 mg dose. These initial ratings, however, did not appear to account fully for the methadone dose effect; the same pattern of results was observed even when only the last three ratings at each methadone dose (1 week prior to inpatient admission) were examined.

Analysis of the symptom checklist data was concordant with the adjective rating scale

There was a main effect of methadone on thirsty and upset stomach ($P < 0.05$), and trends for an effect of methadone dose on nausea ($P = 0.08$) and sweating ($P = 0.07$). Symptoms of withdrawal tended to decline with increasing methadone dose, although only the differences between 50 and 100, and 50 and 150 mg methadone reached statistical significance (upset stomach; $P <$

0.01). The visual analog scales failed to reveal any statistically significant effects of methadone dose during the outpatient phases. However, ratings of how well the medicine was holding, how much participants felt hooked by medicine and how much they liked the medicine tended to increase by approximately 30–95% as the dose of methadone was increased from 50 to 150 mg. Conversely, ratings of craving heroin tended to decrease approximately 44%.

Urinalysis

The probability of an opiate-positive urine sample tended to decrease with larger methadone doses during outpatient maintenance. The average percent of urine samples positive for opioids was 93, 56 and 58% for the 50, 100 and 150 mg methadone dose conditions, respectively. Analysis of the percent opiate-positive data revealed a trend for a main effect of methadone dose ($F_{2,8} = 3.5$, $p = 0.08$); pairwise contrasts failed to reach significance. These data remained largely unchanged even after accounting for recently missed methadone doses and/or only analyzing data from the last 10 days of dosing. Further analysis using GEE also failed to find a main effect of methadone dose for the likelihood of an opioid positive urine; however, pairwise comparisons revealed that the likelihood of opioid use was greater when participants were maintained on 50 mg methadone compared to either 100 (OR = 8.1; $P < 0.005$) or 150 mg methadone (OR = 7.0; $P < 0.05$). The percentage of urine samples positive for cocaine was not significantly related to methadone dose (41, 36 and 33% for the 50, 100 and 150 mg methadone dose conditions, respectively). The percentage of urine samples positive for benzodiazepines was low and was likewise not affected by methadone dose (0, 0 and 4% for the 50, 100 and 150 mg methadone dose conditions, respectively).

Inpatient evaluations

Opioid agonist and withdrawal-suppressing effects of methadone

Analysis of the direct subjective effects of methadone taken immediately prior to heroin sample injections failed to reveal any main effects of methadone dose on composite or single item participant-rated measures of opioid agonist effects (e.g. visual analog scales, the MBG scale of the ARCI, the Opiate Agonist Scale) or observer-rated adjectives. Similarly, there were no main effects of methadone on any physiological measures indicative of agonist effects. Pairwise comparisons revealed that larger doses of methadone produced a slight decrease in O₂ saturation; relative to 50 mg methadone, 100 ($P < 0.01$)

and 150 ($P < 0.05$) mg methadone decreased O2 saturation by 1.1–1.4%. Respiratory rate was not significantly related to methadone dose (12.8, 13.2 and 13.5 breaths/min for the 50, 100 and 150 mg methadone conditions, respectively). Pupil diameters tended to be small throughout the study and were not significantly related to methadone dose (3.9, 3.6, and 4.0 mm for 50, 100 and 150 mg methadone, respectively). The mean heart rate and skin temperature were 80 bpm and 88.8°F and were not significantly related to methadone dose. Systolic blood pressure increased from approximately 5 mmHg from 50 to 100/150 mg methadone; however, this difference failed to reach statistical significance ($P > 0.05$).

Opioid withdrawal symptoms were suppressed similarly by all three doses of methadone

There were no significant main effects of methadone dose on either the composite adjective withdrawal scale or individual items. The largest methadone dose (150 mg) produced slightly lower scores on the adjective withdrawal scale compared to 100 mg methadone ($P < 0.05$); however, the magnitude of the difference was exceedingly small (i.e. 1.3 points on a 84 point scale). Although they failed to reach statistical significance, larger doses of methadone tended to decrease visual analog ratings of desire for opiates (means: 28, 23 and 16 for 50, 100 and 150 mg methadone, respectively).

Heroin detection test

Heroin was detected in only 5 of the 15 sessions; in the remaining 10 sessions, all 10 3 mg injections were administered without the participant reporting that he received heroin. One volunteer reported detecting heroin

after the first injection at all three methadone doses. The other two detected injections were made during maintenance on 50 mg methadone; one participant detected heroin after the first injection and the second participant detected heroin after the sixth injection. The relationship between methadone dose and the ability to detect heroin was not statistically significant.

Subjective and physiological effects of heroin

Heroin produced prototypic mu-like subjective effects that were significantly related to both heroin dose and methadone dose. The time course of the effects of heroin on the visual analog question 'How high are you?' is shown in Fig. 1 as an illustrative example. Analysis of this item revealed a significant main effect of methadone dose ($F_{2,8} = 7.1, P < 0.05$), as well as a methadone dose by time ($F_{26,104} = 4.8, P < 0.05$) and methadone dose by heroin dose by time interaction ($F_{52,208} = 3.4, P < 0.05$). Subjective ratings of 'High' after 10 and 20 mg of heroin were inversely related to the methadone maintenance dose; that is, the lower the methadone dose, the greater the rating of 'High' for a given dose of heroin. These differences reached statistical significance when 100 or 150 mg methadone were compared to 50 mg methadone, but not when the two larger doses were compared to each other. Time course analysis of VAS ratings of Liking, Good Effects, and Drug Effect revealed a similar pattern. VAS ratings of Sick, Withdrawal, Desire, and Bad Effects were unrelated to the dose of either heroin or methadone.

Analyses of the change from baseline scores were generally concordant with the time course analyses described above. Visual analog ratings of 'High', 'Drug Effect' (Fig. 2), 'Good Effect' and 'Liking' were significantly affected by both methadone dose ($F_{2,8} > 8.5$,

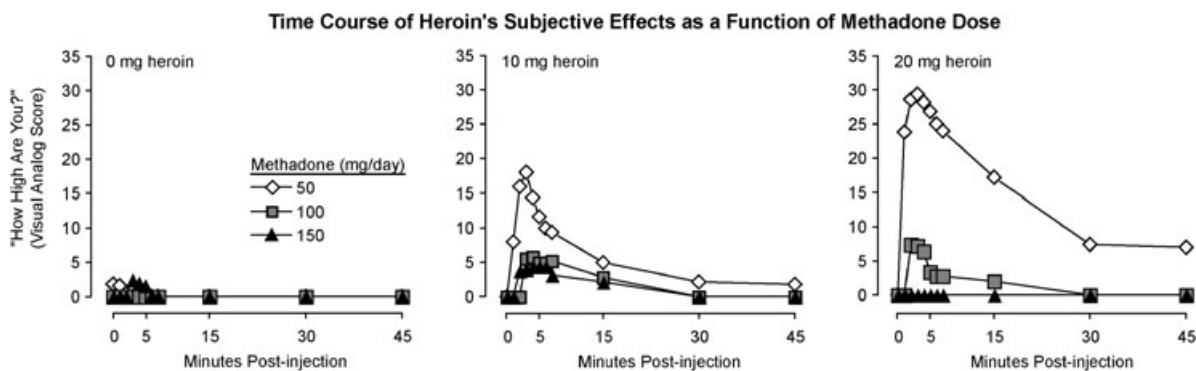


Figure 1 Visual analog ratings of 'How High Are You?' after 0, 10 and 20 mg heroin while participants were maintained on 50, 100 and 150 mg methadone. All participants had baseline ratings of 0 'High'; therefore, the raw data are shown. The critical difference ($P < 0.05$) between points was 12.54. Heroin (10 mg) produced a significantly lower rating of 'high' during maintenance on 100 (2 min post-injection) and 150 (3 min post-injection) compared to 50 mg methadone. Heroin (20 mg) produced a significantly lower rating of 'high' from minutes 1–15 post-injection during maintenance on 100 and 150 compared to 50 mg methadone. Symbols denoting significant pairwise comparisons were omitted for clarity

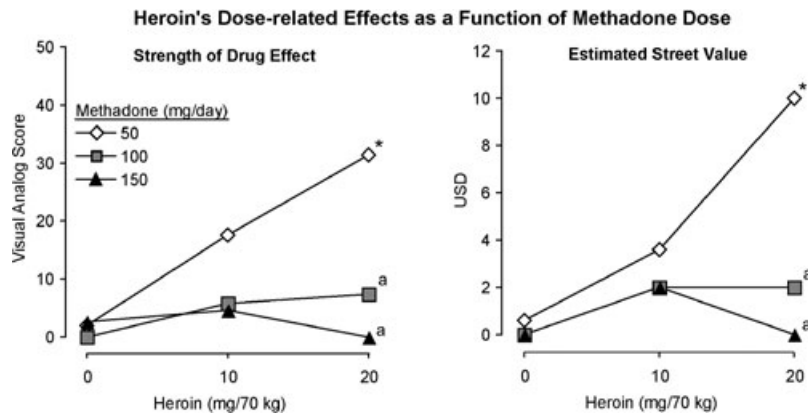


Figure 2 Mean change from baseline visual analog rating of 'How strong is the drug effect?' and the estimated street value of heroin after 0, 10 and 20 mg heroin administered during the sample session while participants were maintained on 50, 100 and 150 mg methadone. For ratings of 'drug effect', there was a significant main effect of Methadone Dose ($F_{2,8} = 9.2, P < 0.05$) and a Methadone Dose by Heroin Dose interaction ($F_{4,16} = 5.0, P < 0.05$). For street value, there was a significant main effect of Methadone Dose ($F_{2,8} = 20.75, P < 0.005$) and a Methadone Dose by Heroin Dose interaction ($F_{4,16} = 7.66, P < 0.05$). The critical differences ($P < 0.05$) between points were 18.49 (Drug Effect) and \$4.93 (street value). a indicates a significant difference ($P < 0.05$; Tukey HSD) compared to 50 mg methadone (within heroin dose). *indicates a significant difference ($P < 0.05$; Tukey HSD) compared to placebo heroin (within methadone dose)

$P < 0.05$) and a methadone by heroin dose interaction ($F_{4,16} > 4.6, P < 0.05$). The main effect of heroin dose generally failed to reach significance, although trends ($P < 0.10$) were observed for ratings of 'High', 'Drug Effect', 'Good Effect' and 'Liking.' Consistent with the visual analog ratings, larger methadone doses (100 and 150 mg) also reduced the estimated street value of heroin (Fig. 2) as indicated by a main effect of methadone dose ($F_{2,8} = 20.8, P < 0.01$) and a methadone by heroin dose interaction ($F_{4,16} = 7.7, P < 0.05$). The ARCI and the composite participant-rated agonist scale failed to reveal either a methadone or heroin dose effect. Analysis of the individual adjectives revealed only a main effect of heroin dose on 'sleepy' ($F_{2,8} = 5.0, P < 0.05$) and an interaction between heroin and methadone dose on 'friendly' ($F_{4,16} = 3.3, P < 0.05$). Observer-rated measures revealed significant main effects of methadone and heroin dose on scratching ($P < 0.05$), and methadone by heroin dose interactions for nodding, scratchy, magnitude of drug effect, and talkative ($F_{4,16} > 3.2, P < 0.05$). In general, larger methadone doses decreased observer ratings of opioid agonist effects. Ratings of nodding after 10 mg heroin increased when participants were maintained on 150 compared to 50 mg methadone; however, this difference was not present after 20 mg heroin.

Physiological measures failed to reveal a main effect of heroin or an interaction of methadone by heroin dose. The lack of an effect of heroin in producing prototypic mu opioid agonist effects, such as a decrease in O₂ saturation and pupil diameter, may have been due to overshadowing by the effects of methadone.

Heroin self-administration. The total number of participants choosing to take an injection over money is

displayed in Fig. 3. The choice to take an injection was related to the dose of heroin available, the magnitude of the alternative reinforcer and the current methadone maintenance dose. Regardless of methadone dose, when placebo was available injection choices were infrequent even when the alternative reinforcer was small. When active heroin was available injection choices were greater for the larger heroin dose and lower at higher methadone doses. Larger magnitudes of monetary alternatives were more effective in reducing heroin use; however, lower methadone doses required larger monetary alternatives to achieve the same reduction in heroin self-administration.

Analysis of the four summary measures of heroin self-administration revealed significant main effects of methadone dose ($F_{2,8} > 10.0, P < 0.01$) and heroin dose ($F_{2,8} > 4.9, P < 0.05$) as well as an interaction between methadone and heroin dose ($F_{2,8} > 4.3, P < 0.05$; Fig. 4). The availability of 10 and 20 mg heroin compared to placebo increased the total number of injections taken, the maximum amount paid for an injection and the minimum monetary alternative chosen over an injection, and decreased the total amount of money earned (20 mg heroin only), when participants were maintained on 50 mg methadone ($P < 0.05$). In contrast, the total number of injections, total earnings, and maximum amount paid for an injection were not significantly related to heroin dose when participants were maintained on 100 or 150 mg methadone. Furthermore, only 20 mg heroin increased the minimum amount chosen over an injection compared to placebo when participants were maintained on 100 mg methadone ($P < 0.05$). None of the measures of heroin reinforcement revealed significant differences

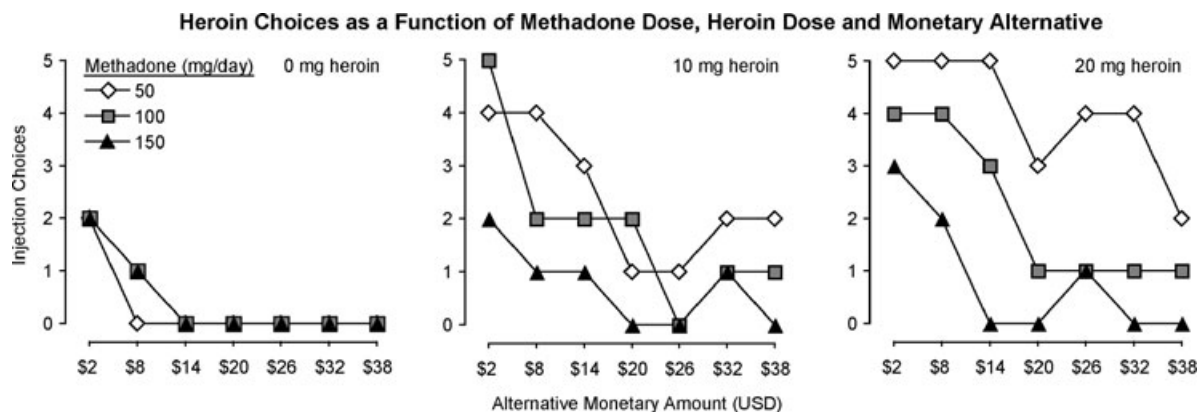


Figure 3 Number of participants choosing to take an injection of heroin or placebo over varying amounts of money (represented on the ordinate)

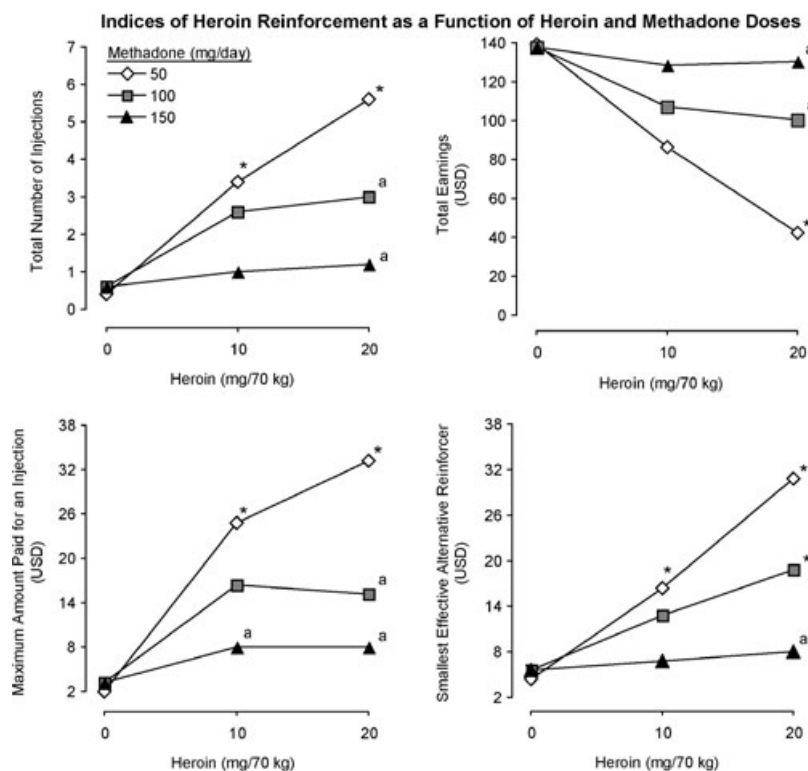


Figure 4 Mean values for four summary measures of choice behavior during the self-administration sessions. There were significant main effects of Methadone Dose and Heroin Dose, as well as an interaction between Methadone and Heroin Dose for all four summary measures ($P < 0.05$). The critical differences ($P < 0.05$) between points were 2.58 (Total number of injections), \$55.52 (Total earnings), \$15.03 (Maximum amount paid for an injection) and \$12.01 (Minimum effective alternative reinforcer). ^aindicates a significant difference ($P < 0.05$; Tukey HSD) compared to 50 mg methadone (within heroin dose). *indicates a significant difference ($P < 0.05$; Tukey HSD) compared to placebo heroin (within methadone dose)

between placebo and active heroin when participants were maintained on 150 mg methadone.

Direct comparison of the different methadone doses (within each heroin dose condition) revealed significant differences between 50 and 100 mg methadone in the maximum amount paid for an injection, the total number of injections taken, and the amount of money earned when 20 mg heroin was available ($P < 0.05$). Compared to 50 mg, 150 mg methadone reduced the reinforcing effects of both 10 mg (as indicated by the maximum amount paid for an injection; $P < 0.05$) and 20 mg heroin (as indicated by all four summary measures of choice; $P < 0.01$).

DISCUSSION

The results of this study show that larger doses of methadone are more effective in reducing heroin self-administration and suggest that the mechanism of this increased efficacy is by reduction of the positively reinforcing/euphoric effects of heroin (i.e. cross-tolerance) and not by reduction of opioid withdrawal discomfort. We summarize these findings below and then focus on methodological and clinical considerations in interpreting these data.

Heroin self-administration was dose-dependent, related to the magnitude of the alternative reinforcer, and strongly influenced by methadone dose. Active (10 and

20 mg/70 kg) heroin increased the number of injection choices compared to placebo. Small alternative reinforcers (e.g. \$2) were generally ineffective at suppressing active heroin use, while large alternative reinforcers (e.g. \$38) suppressed use under most methadone dose conditions. Most importantly, the choice to take active heroin injections over money was greatest when the dose of methadone was low (50 mg) and was nearly abolished when participants were maintained on 150 mg. The percentage of choices for heroin over money decreased from 80% to 43% to 17% as the dose of methadone was increased from 50 to 100–150 mg. Further, compared to when participants were maintained on 50 mg, the maximum amount participants were willing to pay for an injection of 20 mg/70 kg heroin decreased by 54% and 76% during maintenance on 100 and 150 mg methadone, respectively. These data indicate that the reinforcing effects of heroin decrease substantially when heroin dependent individuals are maintained on larger doses of methadone.

The subjective effects of heroin were also dose-dependently reduced by methadone. Heroin produced moderate increases in euphoric subjective effects and ratings of street value when participants were maintained on 50 mg methadone, but these effects were largely undetectable when participants were maintained on 100 and 150 mg methadone. These findings are similar to those reported by Donny *et al.* (2002). In that study, daily administration of 120 mg of methadone, but not 30 or 60 mg, provided complete blockade of the subjective effects of 20 mg/70 mg heroin as assessed by adjective rating scales and visual analog scale questions identical to those in the present study.

The heroin detection test failed to reveal any significant change in the discriminative stimulus effects of heroin when participants were maintained on different methadone doses. In 10 of 15 sessions (67%), participants reported that they did not detect heroin. Three of the five sessions when heroin was detected occurred while participants were maintained on 50 mg methadone. These trends are consistent with the subjective data collected during the sample sessions indicating larger ratings of drug effects during maintenance on 50 mg methadone.

The present data are more concordant with the view that heroin self-administration during methadone maintenance is controlled by the availability of positively rewarding heroin effects than with the view that it is controlled by relief from withdrawal discomfort. Heroin use tended to be higher when participants were maintained on 50 mg methadone both when participants were assessed by urinalysis in the clinic setting and during the choice procedure in the inpatient setting. In contrast, withdrawal tended to be greater while participants were

maintained on 50 mg methadone compared to both 100 and 150 mg in the outpatient setting, but there was no relationship between dose and withdrawal symptoms during the inpatient assessments. This discordance could be due to a number of factors, including differences in the duration of methadone dosing at the time of assessment, differences in the time since the last methadone dose, additional concurrent outpatient opioid use, and the presence of environmental cues that elicit withdrawal symptoms that are not part of the residential environment. Regardless of the mechanism, larger methadone doses may have the additional benefit of greater withdrawal suppression in the natural environment.

Relatively limited research has examined heroin self-administration in human volunteers. Early work (Altman *et al.* 1976; Meyer *et al.* 1976) utilized an operant procedure in which participants earned heroin injections by pressing a button. Mello and colleagues incorporated an alternative reinforcer by allowing participants to choose to work for either heroin or a modest monetary reinforcer (\$1.50) (Mello *et al.* 1981; Mello, Mendelson & Kuehnle 1982). In each of these early studies, participants chose to take almost all the available heroin. Recent work by Comer and colleagues used a progressive ratio schedule of reinforcement in which participants could earn 1/10 of the amount of a sampled heroin injection or 1/10 of a single monetary reinforcer over 10 consecutive trials. The total amount of heroin and money earned was then given at the end of the task. Using this method, the largest ratio completed was dose-dependent; however, increasing the magnitude of the monetary alternative (e.g. \$40) did not reduce heroin self-administration (Comer *et al.* 1998). Subsequent work showed that self-administration was sensitive to the route of administration (i.e. intranasal vs. intravenous; Comer *et al.* 1999) and that intravenous heroin self-administration was suppressed by pretreatment with 16 compared to 8 mg buprenorphine (Comer, Collins & Fischman 2001).

The model of heroin self-administration used here was adapted from our recent cocaine research (Walsh *et al.* 2001; Donny, Bigelow & Walsh 2003, 2004) and was modified for the longer duration of action produced by heroin by presenting each choice between drug and money in a separate session. The reinforcing effects of heroin were quantified by varying the magnitude of the alternative reinforcer across seven sessions at each heroin dose. This procedure allowed us to scale the reinforcing effects of heroin in terms of the amount of money a participant was willing to forego in order to take an injection. An advantage of this model is that it captures the essential feature of progressive ratio schedules of reinforcement (i.e. measuring the magnitude of reinforcement and/or the degree of motivation) using a face valid metric (i.e. how much someone is willing to pay) without

requiring an operant response that could be disrupted by the psychomotor effects of opioids. In addition, participants were allowed to choose between the full sample dose of heroin and money (as opposed to a fraction of each reinforcer). A clear disadvantage, however, is that the present procedure is more labor intensive; seven choice sessions were required to generate a single 'break point' measure of the reinforcing effects of heroin.

The heroin detection test failed to produce reliable differences between methadone dose conditions in the discriminative effects of heroin. It is important to recognize that the detection test used here differed substantially from standard tests of drug discrimination in which participants are trained over repeated sessions to discriminate drug from placebo. That methodology may have yielded a different pattern of results. The present approach may have failed to detect methadone dose effects on the discriminative effects of heroin for several reasons. First, although unlikely, it is possible that 30 mg/70 kg heroin was inadequate to produce opioid agonist effects in methadone-maintained individuals. However, during maintenance on 50 mg methadone, all five participants reported an increase in ratings of 'drug effect' after the 20 mg sample injection (compared to placebo). Furthermore, pupil diameter data taken during the detection sessions showed a mean decrease of 0.7 mm from baseline to 5 min after the tenth injection in sessions in which participants reported being unable to detect heroin. This effect was greater when participants were maintained on 50 mg methadone (1.4 mm) compared to the 100 and 150 mg methadone conditions (0.2 and 0.5 mm, respectively). A related possibility is that heroin's subjective effects, in particular, were reduced by dividing the 30 mg/70 kg heroin dose into 10 injections spaced over 100 min. Previous research suggests that the rate of increase in plasma drug levels is related to the subjective effects of other drugs of abuse (de Wit, Bodker & Ambre 1992; de Wit, Duder & Ambre 1993). Although small changes in injection speed (2–60 s) did not affect the subjective response to the opioid agonist hydromorphone in a previous study (Abreu *et al.* 2001), changes in a drug stimulus that occur over a more prolonged period of time may be difficult to detect and/or may be attributed to causes other than the injection (e.g. boredom). A third possibility is that participants may have discovered the dosing schema and failed to report detecting the effects of heroin in order to receive additional injections. However, no spontaneous reports of this were given and it is unlikely that this could explain the failure of two participants to report detecting heroin during the first test (i.e. at 50 mg). Finally, the failure to detect a significant methadone dose effect on heroin detection may be due to the limited sensitivity and/or statistical power of the dichotomous (detected vs. not detected) outcome measure.

The self-administration data indicate that methadone doses of 100 mg or larger may be more efficacious in the treatment of heroin dependence. It should be noted, however, that these data were derived from non-treatment seekers and that patients seeking treatment may differ from the participants reported here. Furthermore, clinical recommendations regarding dosing must take into account numerous factors, including the relationship between methadone dose and cross-tolerance to heroin, the range of street doses used, the use of concurrent behavioral therapies such as contingency management and the potential risks of maintenance on high doses of methadone. These issues are discussed below.

Substantial gains in opioid cross-tolerance occur when methadone dose is increased from 30 to 60 mg to 100–150 mg. For the most part, we observed only limited differences between 100 and 150 mg methadone in terms of suppression of heroin's subjective and physiological effects and no differences in outpatient opioid use. There was a trend for heroin to continue to produce detectable reinforcing effects when participants were maintained on 100 mg methadone; however, direct comparisons of the 100 and 150 mg methadone dose conditions failed to reach statistical significance. These findings are consistent with those reported by Jones & Prada (1975) in which 100 mg methadone suppressed hydromorphone self-administration in the majority of participants and suggesting the gains in cross-tolerance may diminish as doses greater than 100 mg are employed. It is important to note, however, that differences between moderate (e.g. 100 mg) and larger (150 mg or more) doses of methadone may have been revealed with a larger sample size or larger doses of heroin (see below).

The degree of cross-tolerance is related to the available dose of heroin. The heroin dose used here was relatively small compared to the doses available in many major metropolitan cities. Larger doses of heroin may continue to produce opioid agonist effects that can support self-administration. Indeed, the relatively high levels of opiate-positive urines in this study compared to low rates of self-administration in the laboratory may have been related to the fact that participants could use large doses of 'street' heroin that continue to reinforce behavior. In localities where heroin has become inexpensive and relatively pure, larger doses of methadone may be necessary to produce adequate blockade.

Contingency management, in which drug abstinence is reinforced with monetary and/or other reinforcers, has been shown to reduce illicit opioid use during both methadone detoxification (McCaul *et al.* 1984; Robles *et al.* 2002) and maintenance (Stitzer, Bigelow & Liebson 1980; Silverman *et al.* 1996). For example, McCaul and colleagues found that patients who could earn \$10 and take home methadone doses contingent on opioid-free

urines during a six-week detoxification provided a higher percentage of opioid-negative urines. Similarly, patients maintained on methadone reduce their illicit opioid use when abstinence contingencies are in effect (e.g. Silverman *et al.* 1996; Stitzer *et al.* 1980). However, the relationship between methadone dose and the effectiveness of contingency management has not been thoroughly evaluated. A meta-analysis of the relationship between methadone dose (<50 mg vs. >50 mg) and effect size in contingency management studies failed to find an effect of methadone dose (Griffith *et al.* 2000). Likewise, in a recent study by Preston, Umbricht & Epstein (2000) examining the efficacy of voucher-based contingency management in participants receiving 50 or 70 mg methadone, there were no significant differences in the percentage of opioid-positive urines between the two doses. Abstinence incentives and increasing the methadone dose both increased the percentage of opioid negative urines; however, larger doses of methadone did not add to the beneficial effects of abstinence incentives. However, as discussed by Preston and colleagues, the dose range tested in this study was narrow and larger methadone doses may have revealed a greater effect of combining the therapies. Indeed, both past research (Donny *et al.* 2002) and the current findings suggest that the methadone doses tested in the Preston study were likely inadequate for producing cross-tolerance to the reinforcing effects of heroin. In the present study, alternative monetary reinforcers were more effective at suppressing the choice to take heroin when participants were maintained on 100 and 150 mg methadone. Approximately \$31 was required to suppress the choice to take 20 mg/70 kg heroin when participants were maintained on 50 mg methadone, compared to only \$8 when participants were maintained on 150 mg methadone. While the absolute value of alternative reinforcement necessary to suppress heroin use in methadone maintained patients is likely to be different in the clinic than in the laboratory, we believe the process by which money substitutes for heroin generalizes to the clinical setting. In both environments, participants are aware of the effects of available effects of heroin (although the actual dose is unknown) and their use behavior can be readily altered by alternative reinforcement. If generalizable, the present results suggest that contingency management may be more effective at reducing persistent illicit heroin abuse when patients are maintained on doses of methadone that block the reinforcing effects of heroin.

Recent data suggest that larger doses of methadone may induce changes in cardiac conductance (e.g. prolonging the QT interval) and may be related to an increased risk of ventricular arrhythmias. Retrospective case studies suggest that maintenance on very high doses

of methadone (e.g. 300–400 mg/day) may increase the risk of torsade de pointes (i.e. a potentially fatal ventricular arrhythmia; Gil *et al.* 2003). Other case reports suggest that doses of less than 150 mg may prolong the QT interval (Decerf *et al.* 2004; Piguet *et al.* 2004; also see subset of patients in Krantz *et al.* 2002). In a recent prospective study, the ECGs from 132 heroin dependent patients were examined before and after induction and maintenance on 30–150 mg methadone (Martell *et al.* 2003). Methadone maintenance significantly increased the QT interval by approximately 10.8 ms (to 428 ms) regardless of the methadone dose. Because the magnitude of this change was far less than the changes that typically raise clinical concerns (an increase of 40 ms and/or a QT interval of >500 ms), the clinical significance of these findings is unclear (see Martell *et al.* 2003). However, it is important to note that the risk of a cardiac event may be exacerbated by concurrent use of other medications that inhibit methadone metabolism and/or have their own effects on cardiac function. Although larger methadone doses may function to reduce persistent heroin use, the risk of cardiac complications should be carefully considered and monitored especially during the induction to larger doses in patients with other risk factors (Krantz *et al.* 2002; Decerf *et al.* 2004).

These and other data suggest that relatively larger doses of methadone may be required to produce the full range of therapeutic effects. Small doses of methadone (i.e. 30–60 mg) are often effective at suppressing opioid withdrawal symptoms; however, larger doses (100–150 mg) may be required to produce adequate cross-tolerance to the reinforcing effects of heroin. Many patients also continue to abuse other drugs of abuse during methadone treatment; increasing the dose of methadone may not aid in reducing use of non-opiate drugs. Although recent trends in treatment practices indicate that the percentage of patients receiving >80 mg/day methadone has increased from 5.8% in 1988 to 32.4% in 2000 (D'Aunno & Pollack 2002), the majority of patients may still be receiving methadone doses that produce incomplete cross-tolerance to the euphoric and reinforcing effects of heroin.

Acknowledgements

These findings were presented in part at the 2004 annual meeting of the College on Problems of Drug Dependence, Scottsdale, AZ, USA. The authors gratefully acknowledge the contributions of the staff at BPRU for their time and effort, especially Shirley Savage, Abigail Yuscavage, Abigail Roberts, Jackie Smith, Mike Sklar, Kellie Lawson, Tiffany Tomlin, Paul Nuzzo, Lisa Schade and John Yingling. Supported by NIDA P50 DA05273, T32 DA07209, K05 DA00050.

References

- Abreu, M. E., Bigelow, G. E., Fleisher, L. & Walsh, S. L. (2001) Effect of intravenous injection speed on responses to cocaine and hydromorphone in humans. *Psychopharmacology*, **154**, 76–84.
- Altman, J. L., Meyer, R. E., Mirin, S. M. & McNamee, H. B. (1976) Opiate antagonists and the modification of heroin self-administration behavior in man: an experimental study. *International Journal of the Addictions*, **11**, 485–499.
- American Psychiatric Association (1994) *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn. Washington, DC: American Psychiatric Association.
- Comer, S. D., Collins, E. D. & Fischman, M. W. (2001) Buprenorphine sublingual tablets: effects on IV heroin self-administration by humans. *Psychopharmacology (Berl)*, **154**, 28–37.
- Comer, S. D., Collins, E. D., MacArthur, R. B. & Fischman, M. W. (1999) Comparison of intravenous and intranasal heroin self-administration by morphine-maintained humans. *Psychopharmacology (Berl)*, **143**, 327–338.
- Comer, S. D., Collins, E. D., Wilson, S. T., Donovan, M. R., Foltin, R. W. & Fischman, M. W. (1998) Effects of an alternative reinforcer on intravenous heroin self-administration by humans. *European Journal of Pharmacology*, **345**, 13–26.
- D'Aunno, T. & Pollack, H. A. (2002) Changes in methadone treatment practices: results from a national panel study, 1988–2000. *JAMA*, **288**, 850–856.
- Decerf, J. A., Gressens, B., Brohet, C., Liolios, A. & Hantson, P. (2004) Can methadone prolong the QT interval? *Intensive Care Medicine*, **30**, 1690–1691.
- Dole, V. P. & Nyswander, M. E. (1965) A medical treatment for diacetylmorphine (heroin) addiction: a clinical trial with methadone hydrochloride. *JAMA*, **193**, 80–84.
- Dole, V. P., Nyswander, M. E. & Kreek, M. J. (1966) Narcotic blockade. *Archives of Internal Medicine*, **118**, 304–309.
- Donny, E. C., Bigelow, G. E. & Walsh, S. L. (2003) Choosing to take cocaine in the human laboratory: effects of cocaine dose, inter-choice interval, and magnitude of alternative reinforcement. *Drug and Alcohol Dependence*, **69**, 289–301.
- Donny, E. C., Bigelow, G. E. & Walsh, S. L. (2004) Assessing the initiation of cocaine self-administration in humans during abstinence: effects of dose, alternative reinforcement, and priming. *Psychopharmacology (Berl)*, **172**, 316–323.
- Donny, E. C., Walsh, S. L., Bigelow, G. E., Eissenberg, T. & Stitzer, M. L. (2002) High-dose methadone produces superior opioid blockade and comparable withdrawal suppression to lower doses in opioid-dependent humans. *Psychopharmacology (Berl)*, **161**, 202–212.
- First, M., Spitzer, R., Gibbon, M. & Williams, J. (1995) *Structured Clinical Interview for DSM-IV Axis I Disorders Biometrics*. New York: Research Department, New York State Psychiatric Institute.
- Gil, M., Sala, M., Anguera, I., Chapinal, O., Cervantes, M., Guma, J. R. et al. (2003) QT prolongation and torsades de pointes in patients infected with human immunodeficiency virus and treated with methadone. *American Journal of Cardiology*, **92**, 995–997.
- Griffith, J. D., Rowan-Szal, G. A., Roark, R. R. & Simpson, D. D. (2000) Contingency management in outpatient methadone treatment: a meta-analysis. *Drug and Alcohol Dependence*, **58**, 55–66.
- Jones, B. E. & Prada, J. A. (1975) Drug-seeking behavior during methadone maintenance. *Psychopharmacologia*, **41**, 7–10.
- Krantz, M. J., Lewkowicz, L., Hays, H., Woodroffe, M. A., Robertson, A. D. & Mehler, P. S. (2002) Torsade de pointes associated with very-high-dose methadone. *Annals of Internal Medicine*, **137**, 501–504.
- Martell, B. A., Arnsten, J. H., Ray, B. & Gourevitch, M. N. (2003) The impact of methadone induction on cardiac conduction in opiate users. *Annals of Internal Medicine*, **139**, 154–155.
- Martin, W. R., Sloan, J. W., Sapira, J. D. & Jasinski, D. R. (1971) Physiologic, subjective, and behavioral effects of amphetamine, methamphetamine, ephedrine, phenmetrazine, and methylphenidate in man. *Clinical Pharmacology and Therapeutics*, **12**, 245–258.
- McCaul, M. E., Stitzer, M. L., Bigelow, G. E. & Liebson, I. A. (1983) Intravenous hydromorphone: effects in opiate-free and methadone maintenance subjects. *NIDA Research Monographs*, **43**, 238–244.
- McCaul, M. E., Stitzer, M. L., Bigelow, G. E. & Liebson, I. A. (1984) Contingency management interventions: effects on treatment outcome during methadone detoxification. *Journal of Applied Behavior Analysis*, **17**, 35–43.
- Mello, N. K., Mendelson, J. H. & Kuehnle, J. C. (1982) Buprenorphine effects on human heroin self-administration: an operant analysis. *Journal of Pharmacology and Experimental Therapeutics*, **223**, 30–39.
- Mello, N. K., Mendelson, J. H., Kuehnle, J. C. & Sellers, M. S. (1981) Operant analysis of human heroin self-administration and the effects of naltrexone. *Journal of Pharmacology and Experimental Therapeutics*, **216**, 45–54.
- Meyer, R. E., Mirin, S. M., Altman, J. L. & McNamee, H. B. (1976) A behavioral paradigm for the evaluation of narcotic antagonists. *Archives of General Psychiatry*, **33**, 371–377.
- Piguot, V., Desmeules, J., Ehret, G., Stoller, R. & Dayer, P. (2004) QT interval prolongation in patients on methadone with concomitant drugs. *Journal of Clinical Psychopharmacology*, **24**, 446–448.
- Prentice, R. L. (1988) Correlated binary regression with covariates specific to each binary observation. *Biometrics*, **44**, 1033–1048.
- Preston, K. L., Bigelow, G. E. & Liebson, I. A. (1988) Butorphanol-precipitated withdrawal in opioid-dependent human volunteers. *Journal of Pharmacology and Experimental Therapeutics*, **246**, 441–448.
- Preston, K. L., Umbricht, A. & Epstein, D. H. (2000) Methadone dose increase and abstinence reinforcement for treatment of continued heroin use during methadone maintenance. *Archives of General Psychiatry*, **57**, 395–404.
- Robles, E., Stitzer, M. L., Strain, E. C., Bigelow, G. E. & Silverman, K. (2002) Voucher-based reinforcement of opiate abstinence during methadone detoxification. *Drug and Alcohol Dependence*, **65**, 179–189.
- Silverman, K., Wong, C. J., Higgins, S. T., Brooner, R. K., Montoya, I. D., Contoreggi, C. et al. (1996) Increasing opiate abstinence through voucher-based reinforcement therapy. *Drug and Alcohol Dependence*, **41**, 157–165.
- Stitzer, M. L., Bigelow, G. E. & Liebson, I. (1980) Reducing drug use among methadone maintenance clients: contingent reinforcement for morphine-free urines. *Addictive Behaviors*, **5**, 333–340.
- Strain, E. C., Bigelow, G. E., Liebson, I. A. & Stitzer, M. L. (1999) Moderate- vs high-dose methadone in the treatment of opioid dependence: a randomized trial. *JAMA*, **281**, 1000–1005.
- Strain, E. C., Stitzer, M. L., Liebson, I. A. & Bigelow, G. E. (1993) Dose-response effects of methadone in the treatment of opioid dependence. *Annals of Internal Medicine*, **119**, 23–27.

- Volavka, J., Verebey, K., Resnick, R. & Mule, S. (1978) Methadone dose, plasma level, and cross-tolerance to heroin in man. *Journal of Nervous and Mental Disease*, **166**, 104–109.
- Walsh, S. L., Geter-Douglas, B., Strain, E. C. & Bigelow, G. E. (2001) Enadoline and butorphanol: evaluation of kappa-agonists on cocaine pharmacodynamics and cocaine self-administration in humans. *Journal of Pharmacology and Experimental Therapeutics*, **299**, 147–158.
- de Wit, H., Bodker, B. & Ambre, J. (1992) Rate of increase of plasma drug level influences subjective response in humans. *Psychopharmacology (Berl)*, **107**, 352–358.
- de Wit, H., Dudish, S. & Ambre, J. (1993) Subjective and behavioral effects of diazepam depend on its rate of onset. *Psychopharmacology (Berl)*, **112**, 324–330.
- Zaks, A., Fink, M. & Freedman, A. M. (1971) Duration of methadone induced cross-tolerance to heroin. *British Journal of Addictions*, **66**, 205–208.