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ORIGINAL INVESTIGATION

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High-dose methadone produces superior opioid blockade and comparable withdrawal suppression to lower doses in opioid-dependent humans

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Abstract *Rationale:* The efficacy of methadone for treating heroin dependence derives, in part, from suppression of opiate withdrawal and attenuation of the effects of heroin. *Objectives:* The purpose of this double-blind, within-subject, inpatient study was to determine whether larger doses of methadone, which are more effective in the treatment of opioid dependence, produce greater or longer-lasting blockade of the effects of heroin in addition to adequate withdrawal suppression. *Methods:* Participants were maintained on 30, 60, and 120 mg methadone (ascending order) for approximately 3 weeks at each dose. During each maintenance period, heroin challenges were administered at 4, 28, and 52 h after the last methadone dose. Opioid agonist effects and opioid withdrawal symptoms were assessed prior to heroin challenge. Challenge sessions consisted of three doses of heroin (0, 10, and 20 mg/70 kg; ascending order) 45 min apart. *Results:* All three methadone maintenance doses produced similar agonist effects. Participants tested 4 h after receiving 120 mg methadone showed complete suppression of withdrawal symptoms and full attenuation of the effects of heroin. Thirty and 60 mg methadone suppressed withdrawal for up to 52 h, but failed to block completely the effects of heroin. The effects of heroin increased slightly at longer post-methadone intervals. *Conclusions:* Heroin use may persist during methadone treatment because low to moderate doses of methadone suppress withdrawal, but fail to eliminate the effects of heroin. These results provide a mechanism for the clinical observation that higher methadone doses are more effective at reducing heroin use.

Keywords Tolerance · Opioid · Methadone · Heroin · Withdrawal

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Introduction

The long-acting mu-opioid agonist, methadone, has been used as a maintenance medication in the treatment of heroin dependence since the mid-1960s (Dole and Nyswander 1965). Although a number of studies have demonstrated its efficacy in reducing illicit opioid use (Strain and Stitzer 1999), many patients continue to use opiates during treatment. One-year follow-up data from the Drug Abuse Treatment Outcome Study (DATOS) indicated that 27.8% of patients assigned to outpatient methadone treatment continued to use heroin either weekly or daily (Hubbard et al. 1997). Recent evidence suggests that the rate of illicit opioid use in methadone-maintained patients is inversely related to methadone dose (see, for example, Strain et al. 1993a, 1999; Hartel et al. 1995; Ling et al. 1996; Schottenfeld et al. 1997).

Methadone serves multiple functions in the treatment of illicit opioid abuse: it relieves opioid withdrawal, attenuates the subjective and reinforcing effects of continued opioid use, reduces craving for opiates, and normalizes physiological functioning. The degree to which opioid-dependent patients continue to use heroin while being maintained on methadone may reflect a failure in one of these functions of methadone treatment. The primary purpose of the present study is to investigate methadone dose-related reductions in the effects of heroin (i.e., blockade).

Dole and colleagues (1966) first reported that methadone reduced the effects of heroin. Seven patients maintained on 80–100 mg methadone for between 20 and 150 days were challenged with intravenous heroin (5–160 mg) approximately 5 h after methadone dosing. The reduction in the effects of heroin was greatest in pa-

tients who had been in methadone treatment for a longer period of time. However, even after 150 days of methadone treatment, the attenuation could be overcome by large doses of heroin (80 mg). Although this study provided an important demonstration that methadone reduced the effects of heroin, it did not examine the relative reduction in the effects of heroin produced by different doses of methadone.

Dose dependency in the reduction of the effects of concurrent opioids was later demonstrated by Volavka et al. (1978) in a group of recently detoxified postaddicts. The dose of methadone was increased to either 40 or 80 mg daily methadone over 18–22 days. Participants were challenged with 15 mg/70 kg heroin or placebo prior to methadone maintenance, between the 8th and 12th day of induction (at 25 or 50 mg methadone), and at the end of the 18- to 22-day period. 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.

Subsequent studies confirmed that doses of 100 mg or more may be necessary to completely eliminate the effects of moderate doses of opioids (Jones and Prada 1975; Zaks et al. 1971). Jones and Prada (1975) allowed six participants to work for intravenous injections of 4 mg hydromorphone during induction onto and maintenance on 100 mg methadone. As the dose of methadone was gradually increased, the rate of opioid self-administration declined, indicating that the reinforcing effects of opioids may be dose-dependently attenuated by methadone. Maintenance on 100 mg eliminated responding for hydromorphone in five of the six patients. In contrast, studies of doses of 80 mg or less have found that patients continue to experience the subjective effects of opioids (McCaul et al. 1983; Volavka et al. 1978). However, it is difficult to compare the effectiveness of different doses of methadone across studies due to differences in the timing of methadone administration, the duration of methadone treatment, the specific opioid and dose used in challenge sessions, and the history of the participants.

Relatively little is known about the duration of methadone-induced blockade of the effects of concurrent opioids. With a half-life of 15–40 h (Reisine and Pasternak 1996), daily administration of methadone produces peak plasma levels 2–4 h after dosing followed by a gradual reduction over a 24-h period (Foster et al. 2000; Kreek 1973). However, patients may periodically miss one or more scheduled doses. A study by Zaks and colleagues (1971) found that participants maintained on 100 mg methadone were completely tolerant to up to 75 mg heroin 6 h after dosing, but that the effects of heroin became greater with each additional 24-h period. By 72 h all participants could detect 25 mg heroin. This study indicated that even relatively high doses of methadone (i.e., 100 mg) may fail to eliminate completely the effects of heroin following one or more missed doses. However, it was limited by a small sample size (n=5–6/interval), a brief assessment of the effects of heroin, and a complete time course analysis that was restricted to a single dose of methadone.

The purpose of this within-subject study was to determine whether larger doses of methadone (60 and 120 mg) resulted in a greater or longer-lasting reduction in the effects of heroin compared to doses that are believed to produce minimal blockade (i.e., 30 mg). The study employed an intravenous heroin challenge to simulate use in the natural environment and a cumulative dose challenge procedure to obtain a heroin dose-effect function efficiently within each study session. The methadone doses are relevant to modern general clinical practice (D'Aunno et al. 1999), and heroin doses are representative of current street doses in Baltimore (NIDA 1996). An extensive battery of assessment techniques was used to document both the physiological and subjective effects of heroin challenge. In addition, we report a simultaneous evaluation of spontaneous withdrawal as a first attempt to understand the dose- and time-dependency of opioid withdrawal during methadone maintenance under controlled laboratory conditions.

Materials and methods

Participants

Eleven male community volunteers were recruited through local newspaper advertisement and word-of-mouth. Seven African-American and three Caucasian males [average age (± SD): 31.4±7.59 years] completed the protocol. The first participant received higher doses of heroin than are reported here, and therefore his data are excluded. All participants reported using opioids at least five times per week and provided two opioid-positive urines prior to admission. Any potential participant 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 to research participation. They were paid for their time and inconvenience.

All participants met DSM-IV criteria for current opioid dependence (SCID; First et al. 1995). Participants reported using opiates for an average of 12.1 years (±8.54) and spending $26.8 (±5.09) on heroin on 27.7 (±4.96) of the last 30 days. Participants reported an average of 13.2 days (±12.84) of cocaine use and 5.1 days (±6.32) of alcohol use in the last 30 days.

Overview of the study design

This inpatient study used a multidose, within-subject design. Research personnel and study participants were blind to methadone dose, methadone dose omissions, and heroin dose. The study design and experimental procedures were approved by the Johns Hopkins Bayview Medical Center Institutional Review Board and were in accordance with the 1964 Declaration of Helsinki. The protocol consisted of approximately 9.5 weeks of methadone maintenance. Patients were maintained on three ascending doses of methadone, receiving each dose daily for approximately 3 weeks. The physiological and subjective effects of heroin were assessed using a cumulative dosing procedure during the 2nd and

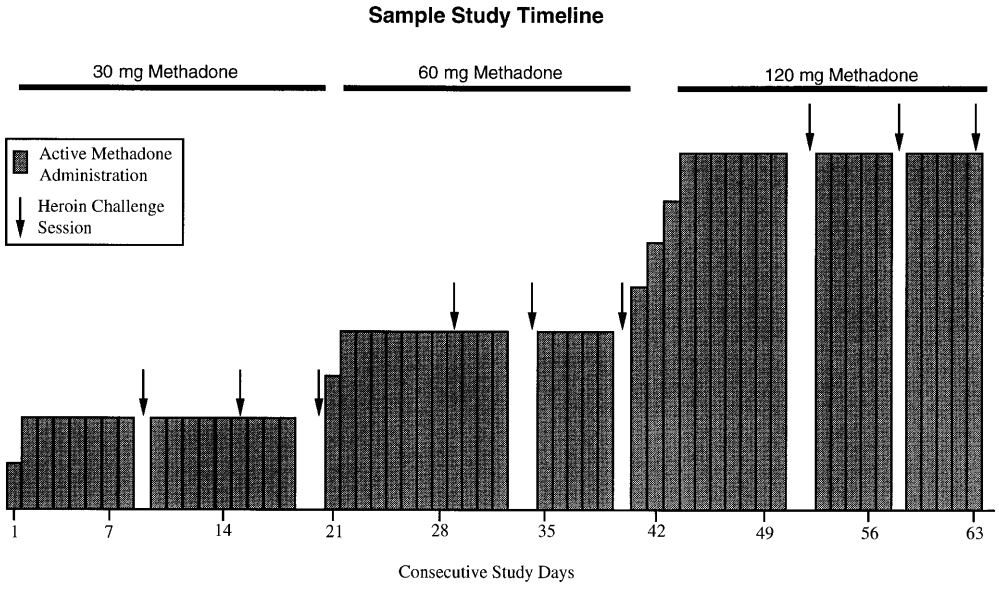

Fig. 1 Representative example of the study design and timeline. Participants were maintained on 30, 60, and 120 mg methadone (ascending order) for approximately 3 weeks at each dose. Participants were stabilized on each dose for a minimum of 1 week prior to heroin challenge. Heroin challenge sessions were conducted following zero, one, or two methadone dose omissions in random order to assess the effects of heroin 4, 28, and 52 h after the last dose of methadone. Methadone dose was increased from 30 to 60 mg and from 60 to 120 mg in increments of 15 mg/day. The study was approximately 9.5 weeks in duration

3rd week of maintenance on each methadone dose. Participants received intravenous heroin at three different post-methadone intervals during maintenance on each of the three methadone doses (i.e., a total of nine challenge sessions). Figure 1 provides an overview of the study design and timeline.

Methadone maintenance

All participants were administered 15 mg oral methadone upon admission. Beginning the following day, participants were maintained on 30 mg/day p.o. for approximately 21 days. The dose of methadone was subsequently increased to 60 and then 120 mg/day with each dose in effect for approximately 3 weeks. Methadone dose was increased by 15 mg/day between maintenance doses. Thus, the transition from 30 to 60 mg took 2 days, while the transition from 60 to 120 mg took 4 days. The first 7 days at each methadone maintenance dose served as a stabilization week, and heroin challenge sessions took place after this 7-day period. Methadone was administered in capsule form at 8:30 a.m. each day.

The effects of heroin were assessed at 4, 28, and 52 h after administration at each methadone maintenance dose to assess the duration of opioid blockade. In order to conduct heroin challenges at 28 h post-methadone, placebo was substituted for methadone on the morning of heroin challenge. Similarly, for the 52-h condition, placebo was substituted for methadone on the day before and the morning of the heroin challenge session. Because of the potential for withdrawal symptoms following methadone dose omission, participants in the 28- and 52-h post-methadone interval conditions received 50% of the current methadone dose 3 h after completing the heroin challenge session (7:00 p.m.). Participants in the 4-h condition received a placebo capsule for their evening dosing to maintain the study blind. Evening methadone doses were only given on the day of a heroin challenge session. Methadone dose conditions were presented in ascending order, and post-methadone interval conditions were presented randomly within each methadone dose. Starting the morning after each heroin challenge session, participants were re-stabilized on the current methadone maintenance dose for a minimum of 3, 4, or 5 days in the 4-, 28-, and 52-h post-methadone conditions, respectively, before the next heroin challenge session.

Heroin challenge sessions

Challenge sessions were conducted from 12:00 noon to 4:00 p.m. in a testing room designed to provide a constant environment. The participant was seated in a comfortable chair throughout the session in front of a personal computer (Apple IIGS; Apple Computer, Cupertino, Calif., USA) that recorded subjective and physiological responses. A slow drip i.v. line remained in place throughout each session. Heroin (0, 10, and 20 mg/70 kg, i.v.) was administered at 12:30 p.m., 1:15 p.m. and 2:00 p.m., respectively, via an indwelling catheter. Supplemental oxygen was available at all times, although it was not needed.

During each heroin challenge 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.

Physiological measurements

Physiological measures, including skin temperature, systolic and diastolic blood pressure, heart rate, pupil diameter, respiration rate, and oxygen saturation, were monitored throughout the 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 first injection and at 5, 10, 15, 25, and 35 min following each injection. Skin temperature, systolic and diastolic blood pressure, and heart rate were collected every minute via an automatic physiologic monitoring device (Noninvasive Patient Monitor model 506; Criticare Systems, Waukesha, Wis., USA) that was interfaced with the Macintosh computer. Photographs of the eye were taken using a camera (Polaroid, Cambridge, Mass., USA) 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 first injection and at 5, 10, 15, 25, and 35 min after each injection.

Participant-rated measurements

Participant-rated measurements during session included visual analog scales, the Addiction Research Center Inventory (ARCI) short form (Martin et al. 1971), a street value question, and adjective checklists (Opioid Agonist Scale, Withdrawal Scale). The participants responded to the visual analogs, the ARCI, and the adjectives using a computer mouse to select the most appropriate response on the computer screen. 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 were presented at baseline, once each minute for 6 min after the start of each injection, and at 10, 15, 25, and 35 min after each injection. The participants responded by positioning an arrow along a 100-point line labeled with "not at all" at one end and "an awful lot" at the other. The ARCI short form presented 49 true/false questions at 20 min before the first injection and 25 min after each 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 35 min after each injection. The participant-rated adjective checklist consisted of 37 items that the participants rated from 0 (indicating "not at all") to 4 (indicating "extremely"). Subsets of these items were summed to derive the Opiate Agonist Scale and the Withdrawal Scale as described previously (Houtsmuller et al. 1998). Participant-rated adjectives were presented 20 min prior to the first injection and at 15 and 35 min after each injection.

Observer-rated measurements

Observer ratings included a modified version of the Himmelsbach withdrawal rating scale (Eissenberg et al. 1996; Himmelsbach 1941) and an adjective rating scale. The Modified Himmelsbach included ratings on a scale of 0 to 2 for lacrimation, rhinorrhea, perspiration, gooseflesh, bowel sounds, yawning, and restlessness. The observer-rated opioid adjective scale included nodding, scratchy, magnitude of drug effect, restlessness, talkative, sleepy/sedated, energetic, irritable, friendly, vomiting, drunken, and nervous. Observer-rated adjectives were rated on a scale of 0 to 4. Observer-rated measurements were taken 20 min before the first injection, and at 15 and 35 min after each injection.

Aftercare

Participants were offered assistance and encouraged to seek continuing treatment at the end of the study. All participants were offered a 90-day outpatient detoxification on site.

Drugs

All doses of methadone HCl USP (Mallinckrodt, St. Louis, Mo., USA) and matched placebo were measured by the weight of the salt and placed into a single lactose-filled capsule. Heroin HCl (Macfarlan Smith, 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.

Data analysis

The direct agonist and withdrawal-suppressing effects of methadone were assessed by analyzing data collected at baseline immediately prior to heroin challenge. The subjective and physiological effects of heroin were assessed using two different data analytic strategies: difference score (as compared to baseline) analyses were used to determine the time course of the effects of heroin, and peak change from baseline. The strategy of adjusting all analyses for baseline was employed to address specifically the effects of heroin during methadone maintenance in light of possible baseline shifts due to the direct effects of methadone and/or withdrawal effects after dose omission.

All data were analyzed using ANOVA with two or more of the following factors: Methadone Dose, Post-Methadone Interval, Heroin Dose (challenge sessions only), and Time (time course analyses only). All repeated measures data were adjusted for sphericity using Huynh-Feldt corrections. Post hoc comparisons were made using Tukey's Honestly Significant Difference (HSD). Graphs are presented with error bars representing half the critical difference value, such that non-overlapping bars indicate significant differences. Differences with a probability of $P<0.05$ were considered statistically significant.

Results

Direct opioid agonist effects of methadone maintenance

Participant-rated and observer-rated measures

Analyses at baseline immediately prior to heroin challenge revealed no effect of methadone dose and minimal evidence for an effect of post-methadone interval on ratings of opioid agonist effects. Visual analog scales, the ARCI, the Opiate Agonist Scale (Fig. 2), and observer-rated adjectives all failed to reveal a significant effect of methadone dose. A significant effect of post-methadone interval was found for the Opiate Agonist Scale (Fig. 2), participant ratings of the individual items, relaxed (Fig. 2) and drive ($F=3.61$, $P<0.05$), and observer ratings of sleepy/sedated (Fig. 2). These findings were consistent with a slight loss of methadone's effects over time. Although not reported here, additional assessment of the direct effects of methadone that were collected over multiple time points in the 2 days prior to heroin challenge revealed similar findings.

Physiological measures

Methadone's physiological effects were generally mild and did not produce any safety concerns. Analysis of the effects of methadone dose at baseline prior to heroin challenge (i.e., 12:15 p.m.) revealed no significant effects on heart rate, blood pressure, respiratory rate, oxygen saturation (Fig. 2), or pupil diameter (Fig. 2). Only skin temperature (Fig. 2) was significantly affected by methadone dose; 60 and 120 mg methadone tended to produce a greater increase in skin temperature at the 4 h post-methadone time point. Pupils also tended to be smaller 4 h after administration of 60 and 120 mg compared to 30 mg methadone. Both oxygen saturation and pupil diameter increased as the time since methadone dosing elapsed.

Opioid withdrawal during methadone maintenance

Ratings of withdrawal tended to be greatest 52 h after the last dosing of 120 mg. Although the participant-rated composite Withdrawal Scale failed to reveal significant main or interaction effects, scores increased at the longest post-methadone interval when participants were maintained on 120 mg methadone (Fig. 3). Participant ratings of the individual adjectives "hot and cold flashes" (Fig. 3)

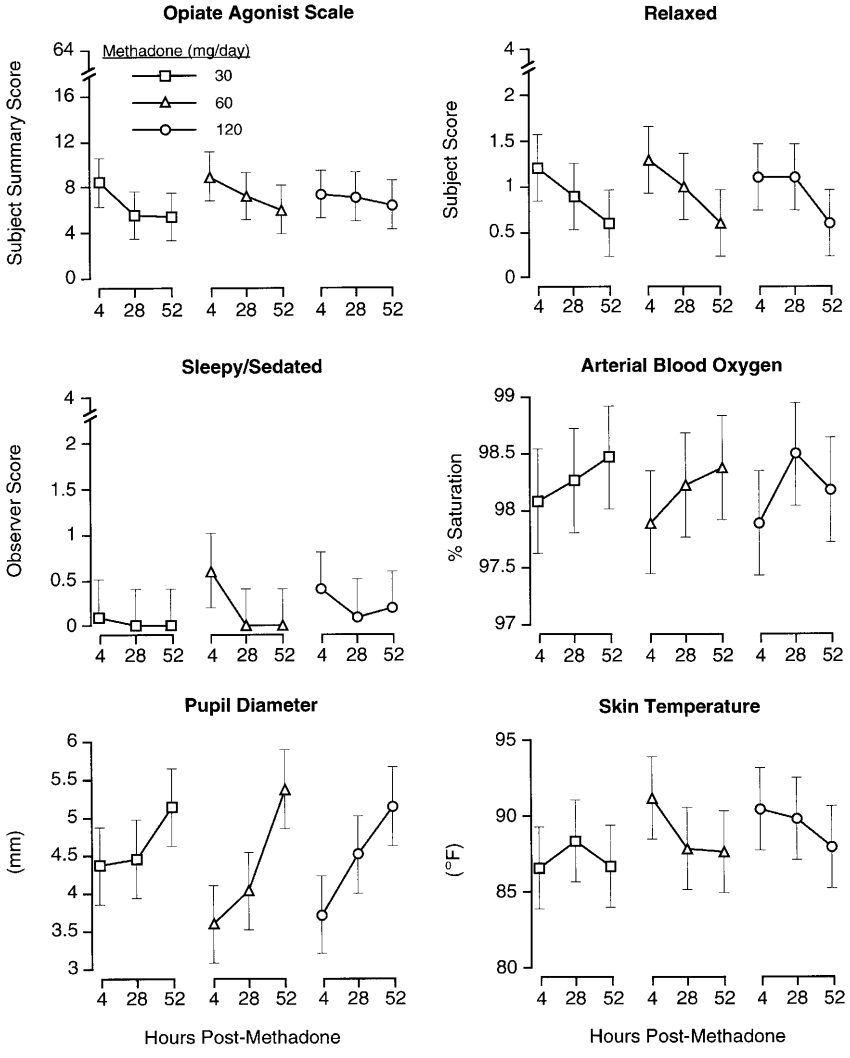

Fig. 2 Direct agonist effects of chronic methadone 20 min prior to heroin challenge. Each set of three connected data points represents change in the effects of that dose of methadone as the time since active methadone dosing elapsed (i.e., across post-methadone interval conditions). Statistical analyses revealed the following effects: methadone dose [skin temperature: $F(2,18)=3.77$, $P<0.05$] and post-methadone interval [Opiate Agonist Scale: $F=3.67$, $P<0.05$; relaxed: $F=6.91$, $P<0.01$; sleepy/sedated: $F(2,18)=5.15$, $P<0.05$; blood oxygen: $F(2,18)=5.14$, $P<0.05$; pupil diameter: $F=12.69$, $P<0.001$]. *Error bars* represent half the critical difference; *non-overlapping bars* indicate a ignificant difference ($P<0.05$; Tukey HSD); $n=10$

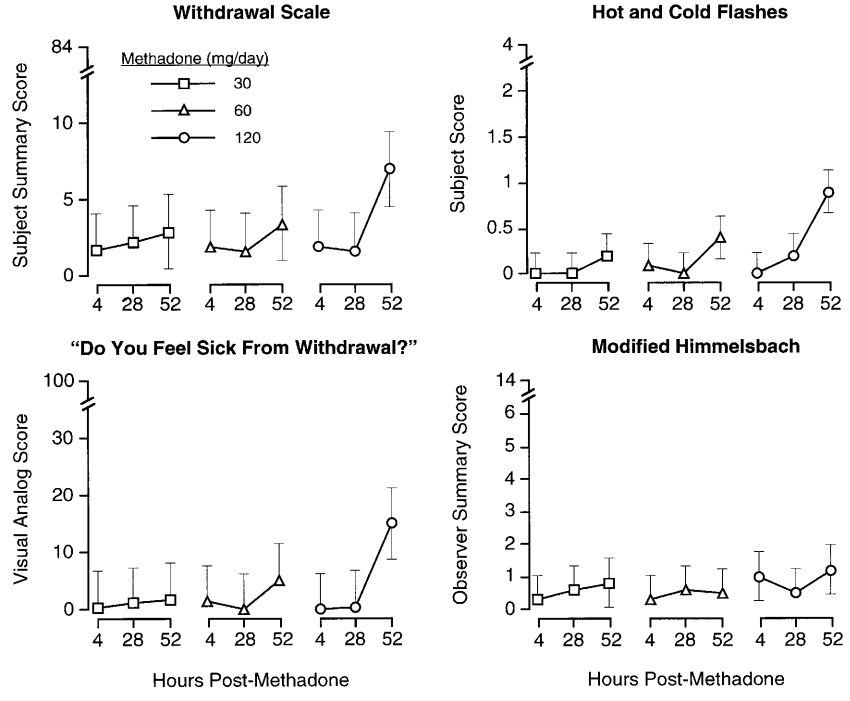

Fig. 3 Signs and symptoms of withdrawal 20 min prior to heroin challenge. Each set of three connected data points represents change in the effects of a dose of methadone as the time since methadone elapsed (i.e., across post-methadone interval conditions). Statistical analyses revealed the following main and interaction effects for "hot and cold flashes": methadone dose ($F=4.85$, $P<0.05$), post-methadone interval [$F(2,18)=6.17$, $P<0.05$], and methadone dose by post-methadone interval [$F(4,36)=3.63$, $P<0.05$]. No other main or interaction effects were statistically significant. *Error bars* represent half the critical difference; *non-overlapping bars* indicate a significant difference ($P<0.05$; Tukey HSD); $n=10$

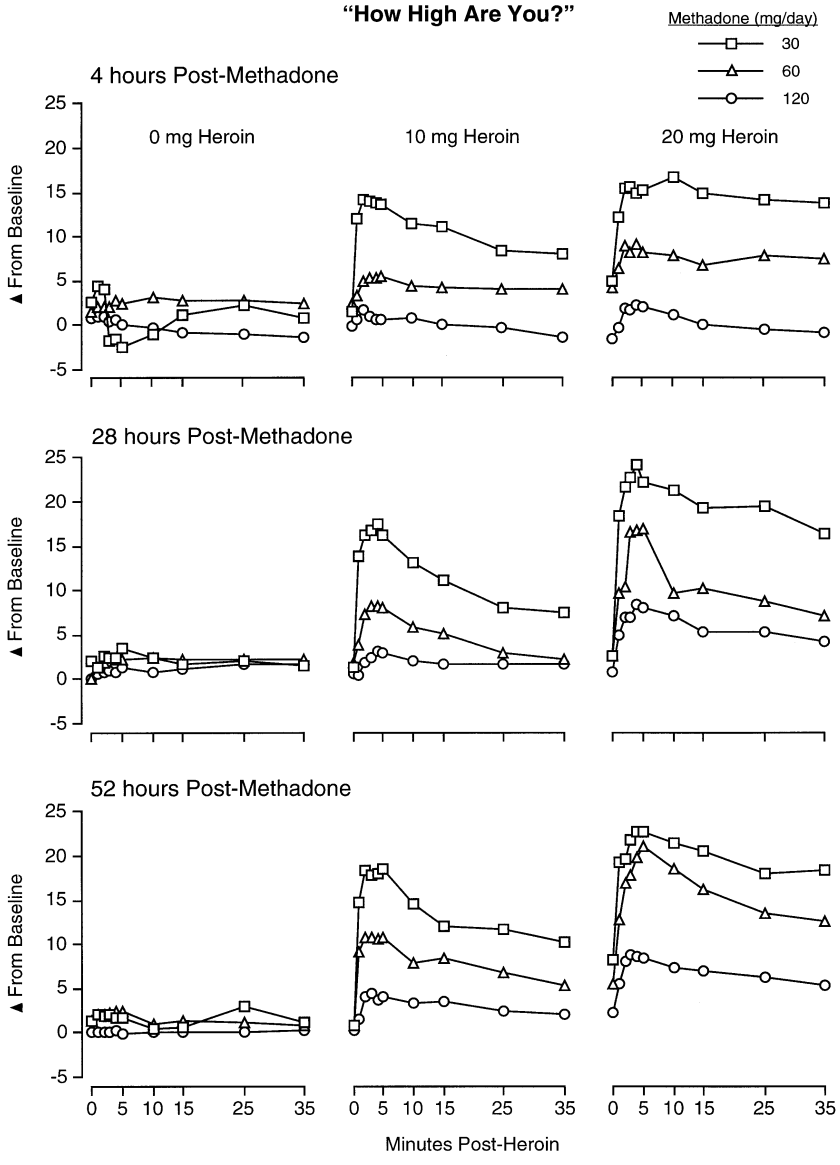

Fig. 4 Time-course of the effects of heroin on the visual analog question "How high are you?" after subtracting out baseline values. Statistical analyses revealed the following significant effects: methadone dose [$F(2,18)=6.65$, $P<0.05$], heroin dose [$F(2,18)=10.17$, $P<0.01$], time [$F(9,81)=8.54$, $P<0.001$], methadone dose by heroin dose [$F(4,36)=4.73$, $P<0.05$], post-methadone interval by heroin dose [$F(4,36)=3.60$, $P<0.05$], heroin dose by time [$F(18,162)=6.60$, $P<0.001$], and methadone dose by heroin dose by time [$F(36,324)=2.84$, $P<0.05$]; $n=10$

and "sweating" (data not shown) were related to methadone dose in a similar orderly fashion (main effect of methadone dose for "sweating": $F=6.88$, $P<0.05$; all other statistics shown in figure caption). Likewise, ratings of "Do you feel sick from withdrawal?" (Fig. 3) increased in the 120 mg/52 h condition only. However, all ratings of withdrawal were mild. For example, average ratings of hot and cold flashes were between 0 (i.e., none at all) and 1 (i.e., a little bit). Furthermore, analysis of the observer-rated Modified Himmelsbach failed to reveal any significant withdrawal effects (Fig. 3).

Heroin challenge sessions

Participant-rated and observer-rated measures

Heroin produced dose-dependent subjective effects typical of a mu agonist. Methadone's attenuation of the subjective effects of heroin was related to both the dose of methadone and the post-methadone interval. The time course of the effects of heroin on the visual analog question "How high are you?" is shown in Fig. 4 (ANOVA results are presented in the figure caption). Subjective ratings of "high" after 10 and 20 mg 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. Longer post-methadone intervals yielded slightly greater ratings of "high" after heroin. By 52 h there were no longer any differences in the effects of heroin on the "high" rating between the 30 and 60 mg methadone conditions, however, 120 mg methadone continued to produce significant attenuation of drug-induced "high" relative to the other methadone dose conditions. Although 120 mg was more effective than 30 or 60 mg methadone at attenuating the heroin-induced "high" regardless of the time since dosing, 20 mg heroin still produced a significant increase in

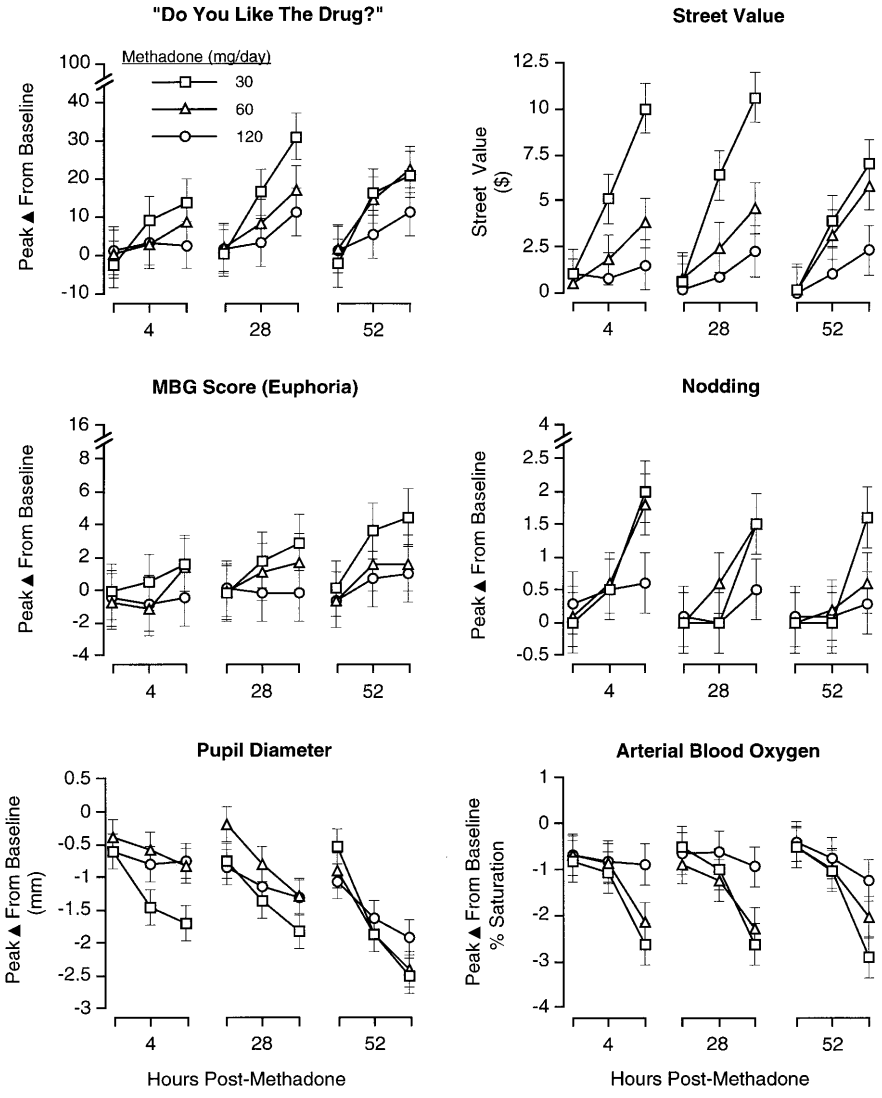

Fig. 5 Peak change from baseline for participant ratings of the visual analog question "Do you like the drug?," the estimated street value, the MBG scale of the ARCI, observer ratings of nodding, pupil diameter, and blood oxygen in response to heroin challenge. Each set of three connected data points represents the dose-effect curve for ascending doses of heroin (0, 10, and 20 mg/70 kg). Statistical analyses for "Do you like the drug?," street value, the MBG scale, pupil diameter, and blood oxygen are reported in Table 1. Nodding revealed the following statistical results: methadone dose [$F(2,18)=4.85$, $P<0.05$], heroin dose ($F(2,18)=32.46$, $P<0.001$), and methadone dose by heroin dose ($F(4,36)=8.36$, $P<0.001$). *Error bars* represent half the critical difference; *non-overlapping bars* indicate a significant difference ($P<0.05$; Tukey HSD); $n=10$

ratings of "high" at 52 h (compared to placebo heroin; $P<0.05$ at 2–5 min post-heroin) after 120 mg methadone. Time course analyses of the visual analog questions "Do you feel any drug effect?", "Does the drug have good effects?", and "Do you like the drug?" also revealed significant increases following 20 mg heroin compared to placebo heroin 28 and 52 h after 120 mg methadone ($P<0.05$; data not shown).

Peak change from baseline analyses of heroin's euphoric effects were generally concordant with the time course analysis described above. Statistical results for heroin's subjective effects are reported in Table 1. Heroin produced dose-dependent increases in maximal ratings of effects such as high, liking (Fig. 5), good effects, and good mood. As can be seen in Fig. 5, higher doses of methadone tended to flatten the dose-effect curves for heroin. Measures of the euphoric effects of heroin (for example, liking, street value, MBG scale; Fig. 5) were dose-dependently attenuated by methadone; higher doses produced significantly greater attenuation. Similar effects were observed for other participant-ratings of the agonist effects of heroin. Heroin produced mild agonist effects that were inversely related to methadone dose and/or positively correlated with post-methadone interval (Table 1). Although some measures appeared to be heroin-dose related (for example, liking and street value), heroin administration to participants maintained on 120 mg methadone, regardless of the interval condition, failed to change peak subjective ratings of opioid agonist effects significantly (compared to placebo heroin, $P>0.05$).

Observer-ratings of opioid agonist effects were similar to participant-ratings. Analysis of the peak change from baseline for observer-rated measures revealed a significant interaction between methadone dose and heroin dose for nodding (Fig. 5), scratchy, magnitude of drug effect, restlessness, talkative, and sleepy/sedated ($P<0.05$). The interactions between post-methadone interval and heroin dose for nodding, magnitude of drug effect, and talkative were marginal ($P<0.10$) with the effects of heroin tending to increase as the time since methadone elapsed.

Table 1 Statistical results for peak change from baseline analyses in response to heroin. There were no significant three-way interactions. Individual observer and participant-rated adjectives are not shown

	Methadone dose (MD) *df*=2,18	Methadone interval (MI) *df*=2,18	Heroin dose (HD) *df*=2,18	MD×MI *df*=4,36	MD×HD *df*=4,36	MI×HD *df*=4,36
Visual analog scales						
High	**		***		**	
Drug effect	**		***		***	
Good effect	***		***		***	
Bad effect						
Liking			***		***	
Sick						
Desire						
Withdrawal						
Adjective scales						
Withdrawal scale		*				*
Opiate agonist scale	***		***		***	
ARCI						
PCAG		*				
BENZ						**
AMPH			**			
MBG			**			
LSD						
SED	*					
Street value	***		***	*	***	
Physiological						
Respiratory rate			***		*	
Oxygen saturation	**		***		***	
Heart rate			***			
Skin temperature			*			
Systolic blood pressure			*			
Diastolic blood pressure						
Pupil diameter		**	***		***	**

*P<0.05; **P<0.01; ***P<0.001

Peak change from baseline analyses of items indicative of opioid withdrawal revealed significant main effects of methadone dose (sweating), post-methadone interval (flushing, hot and cold flashes, Withdrawal Scale), and the interactions between post-methadone interval and heroin dose (yawning, hot and cold flashes, Withdrawal Scale). Post hoc comparisons revealed that both 10 and 20 mg heroin significantly reduced peak ratings of withdrawal symptoms observed during the 120 mg/52 h condition compared to the placebo heroin injection [sweating, hot and cold flashes, "Do you feel withdrawal?" (20 mg only); P<0.05].

Physiological measures

Heroin produced dose-dependent decreases in respiratory rate, oxygen saturation, and pupil diameter, and increases in heart rate and skin temperature. Larger doses of methadone resulted in a greater attenuation of the effects of heroin on oxygen saturation, respiratory rate, pupil diameter, and skin temperature. Longer post-methadone intervals increased the effects of heroin on pupil diameter, but generally failed to alter systematically other physiological effects of heroin. The two lower panels of Fig. 5 illustrate the peak change from baseline for pupillary constriction and oxygen saturation after each dose of heroin (statistical results are presented in Table 1). Maintenance on 60 or 120 mg methadone eliminated additional pupillary constriction by heroin when the heroin challenge was conducted at 4 h post-methadone administration. However, heroin-induced pupillary constriction could clearly be seen at the longer post-methadone intervals (Fig. 5), conditions under which methadone itself produced only partial constriction (see Fig. 2 for baseline). Heroin-induced decreases in oxygen saturation were evident in both the 30 and 60 mg methadone condition under all post-methadone intervals. In contrast, there was little relationship between heroin dose and oxygen saturation when participants were maintained on 120 mg methadone daily. Time course analyses revealed a similar pattern of results.

Individual differences in response to heroin

Ratings of street value were used as a marker for individual differences in the ability of different doses of

methadone to completely attenuate the effects of heroin. Any increase in ratings of street value from placebo to either active dose of heroin was taken as evidence that the participant detected an effect of heroin. All ten participants reported that active doses of heroin had a greater value than placebo heroin while they were maintained on 30 mg methadone regardless of the post-methadone interval. Seven participants detected the effects of heroin given 4 h after 60 mg methadone. The number of participants detecting the effects of heroin during maintenance on 60 mg methadone increased to eight and nine in the 28 and 52 h post-methadone conditions, respectively. In contrast, only one participant reported an increase in the value of active compared to placebo heroin when tested 4 h after receiving 120 mg methadone. The number of participants reporting an increase in street value after active doses of heroin increased to six and five, 28 and 52 h after 120 mg methadone, respectively.

Discussion

Methadone maintenance attenuated the physiological and subjective effects of i.v. heroin in a dose-dependent fashion. Heroin administration to participants maintained on 30 or 60 mg methadone produced subjective effects indicative of euphoria. This observation is consistent with early reports that low-to-moderate doses of methadone fail to eliminate the discriminative (Preston et al. 1987) and subjective effects of other opioids (see, for example, McCaul et al. 1983; Strain et al. 1992). The largest dose of methadone, 120 mg, attenuated the effects of heroin relative to the other methadone dose conditions. The effects of heroin were generally not detectable 4 h after dosing with 120 mg, and only mild opioid agonist effects emerged in response to heroin challenge 28 and 52 h after dosing with 120 mg methadone. These findings indicate that methadone reduces the effects of heroin and reveal a potential mechanism for the increased therapeutic benefit produce by higher methadone maintenance doses (Strain et al. 1993a, 1999).

The direct effects associated with chronic methadone administration were mild and largely unrelated to methadone dose. These participants were likely partially tolerant to the effects of methadone as they were opioid dependent and stabilized on each methadone dose for a minimum of 1 week before testing. Opioid agonist effects declined 52 h after methadone dosing, suggesting that methadone continued to produced some agonist activity that dissipated over time. Daily administration of 30, 60, or 120 mg methadone was equally effective at suppressing withdrawal (Fig. 3). This is consistent with early studies indicating that 30 mg or less can suppress opiate withdrawal (Isbell et al. 1948; Strain et al. 1993b). Substituting placebo for active methadone produced only a modest increase in withdrawal in participants maintained on 120 mg methadone, while having little effect during maintenance on 30 or 60 mg methadone. Similarly, Martin et al. (1973) showed that abstinence symptoms emerged 24–48 h and peaked 3 days following the last dose of 100 mg methadone. Importantly, no participant in the present study ever requested or received symptomatic treatment for the relief of withdrawal.

Attenuation of the effects of intravenous heroin was clearly incomplete during maintenance on either 30 or 60 mg methadone. In this study, it was not possible to determine whether 30 mg methadone reduced the effects of heroin because the effects of heroin were not assessed in a methadone-free condition. However, other studies suggest that 25–30 mg methadone produces little blockade (Gunne and Holmstrand 1974; Volavka et al. 1978). Most participants receiving 60 mg methadone reported euphoric effects after heroin challenge, consistent with previous studies showing that 40–80 mg methadone produces only a partial attenuation of the effects of intravenous opioids (Gunne and Holmstrand 1974; McCaul et al. 1983; Volavka et al. 1978). Daily administration of 120 mg methadone eliminated the effects of the heroin doses administered here. Although early reports indicated that the effects of heroin could be reduced with relatively high doses of methadone (Dole et al. 1966; Jones and Prada 1975; Zaks et al. 1971), the present study is the first to demonstrate the dose-dependency of blockade within a group of participants. These data illustrate the methadone-induced reduction in the effects of heroin underlying clinical observations that higher doses of methadone produce better outcomes on measures of opioid use.

There was individual variability in the dose of methadone that was required to eliminate the effects of heroin. All participants were able to detect heroin during maintenance on 30 mg methadone. Administration of 60 mg methadone 4 h before heroin challenge eliminated the effects of heroin in three of the ten participants. Increasing the methadone dose to 120 mg provided complete blockade in all but one participant. Dose omissions increased the number of participants detecting active doses of heroin during maintenance on both 60 and 120 mg methadone. These data indicate that although some individuals require a moderate dose of methadone to provide adequate blockade, most require 120 mg or more for complete and lasting blockade.

The doses of heroin used here represent small to moderate street doses in the Baltimore Metropolitan area (NIDA 1996). Larger doses of heroin (for example, 50 mg/70 kg cumulative) were not used due to concerns that respiratory depression might be severe in participants maintained on 30 mg methadone (unpublished observations). Although complete blockade of the effects of heroin was reported during maintenance on 120 mg methadone, larger doses of heroin would likely overcome this blockade. Data from Dole et al. (1966) and Zaks et al. (1971) suggest that 20–80 mg heroin is sufficient to overcome the blockade produced by 80–100 mg methadone. It is conceivable that patients maintained on 100 mg or more of methadone may increase their heroin intake to compensate for the attenuation of the effects of

heroin. However, empirical evidence suggests that self-administration of opioids is decreased, not increased, as the dose of methadone is increased to 100 mg (Jones and Prada 1975).

The effects of heroin increased slightly as the time since methadone administration elapsed. The ability of 30 mg methadone to attenuate the agonist effects of heroin were similar across the interval conditions. However, there was an increase in the magnitude and dose-dependency of the effects of heroin at later time points when patients were maintained on 60 or 120 mg methadone (see, for example, Fig. 5). These data suggest that either larger heroin doses or longer post-methadone intervals would have revealed effects of heroin even during maintenance on 120 mg methadone (see, for example, Dole et al. 1966; Zaks et al. 1971). In addition, some mild withdrawal symptoms began to emerge 52 h after dosing when participants were maintained on 120 mg methadone. These symptoms of withdrawal were eliminated by active doses of heroin. Therefore, both the opioid agonist and withdrawal-relieving effects of heroin may contribute to heroin use following one or more missed doses of methadone.

One limitation of the current study was the use of an ascending dose order for methadone. Although the results indicate that higher doses produce a greater reduction in the effects of heroin, methadone dose was confounded with duration on methadone. Greater blockade at the highest dose of methadone may have been, in part, a consequence of the 7–10 weeks of methadone treatment (Dole et al. 1966). Similarly, the relatively short duration of methadone maintenance before heroin challenge in the 30 mg condition may not have produced maximal blockade. However, patients maintained on moderate doses of methadone (50–60 mg/day) for at least 9 months also report less than complete blockade of the effects of opioids (McCaul et al. 1983).

The mechanisms by which methadone blunts the effects of opioids are not completely understood (see Trujillo and Akil 1991; Borgland 2001 for review of opioid tolerance). Both opioid cross-tolerance and competitive antagonism may play a role. Several characteristics of methadone likely contribute to its ability to produce cross-tolerance. Methadone has a long duration of action and is administered in a regimen that maintains active plasma concentrations across daily peak-to-trough variations (Foster et al. 2000). Chronic exposure to methadone may also induce adaptive changes not observed after exposure to equipotent doses of morphine, including desensitization (Blake et al. 1997; Yu et al. 1997), phosphorylation (Yu et al. 1997), and internalization (Whistler et al. 1999) of the mu receptor. Methadone may also block the effects of morphine by occupying opioid receptors and functioning as a competitive antagonist (O'Connor and Fiellin 2000). In patients maintained on an average of 62 mg/day, methadone occupied an estimated 19–32% of receptors (Kling et al. 2000). It is unknown whether this level of receptor occupancy can explain the partial reduction in the effects of heroin during maintenance on the low to moderate doses described here. However, if one assumes a half-life of 24–48 h for methadone, then the degree of blockade produced by 120 mg methadone 52 h after dosing should be roughly equivalent to the blockade produced by 30–60 mg methadone 4 h after dosing. The present results indicate a more prolonged blockade than would have been expected if the mechanism of blockade was purely competitive antagonism.

Early reports indicated that opioid self-administration could be suppressed by higher doses of methadone (Jones and Prada 1975), and recent clinical reports have shown that illicit opioid use is reduced when the maintenance dose of methadone is increased (Strain et al. 1993a, 1999). However, clinical data also reveal that persistent opioid abuse can be problematic even for patients maintained on relatively high doses of methadone. This study illustrates one reason that opioid use can persist during methadone maintenance, that is, inadequate suppression of the effects of short-acting opioids. The data also reveal that withdrawal suppression occurs at lower doses than those required for opioid blockade. Clinical selection of methadone dose based upon withdrawal suppression alone is probably inadequate. The present study suggests that methadone doses of 120 mg or more may enhance clinical benefits for patients exhibiting continued opioid use.

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