

# The Reinforcing and Subjective Effects of Morphine in Post-Addicts: A Dose-Response Study

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## ABSTRACT

The reinforcing and subjective effects of morphine were determined in five human volunteers with histories of i.v. heroin abuse. Subjects responded under a second-order schedule of i.m. injection. Under this schedule, every 100 lever presses produced a brief stimulus light [fixed ratio (FR) 100:s]; the 30th completion of the FR 100 requirement turned on the light for 15 min and the subject received an i.m. injection of morphine [FR 30 (FR 100:s)]. Once each weekday morphine or placebo was available under this schedule. Each drug dose was available for 1 week. Under these conditions placebo did not maintain responding; 3.75 mg of morphine maintained responding in four of five subjects, and higher morphine doses (7.5, 15 and 30 mg) maintained responding in all five subjects. Subjective effects were measured concurrently: these included measures of drug liking, the Morphine

Benzedrine Group scale of the Addiction Research Center Inventory, drug detection and identification. Subjects did not report subjective effects different from placebo for the lowest dose of morphine; the intermediate doses of morphine produced inconsistent effects, and the highest dose of morphine occasioned reports of drug liking and "dope" identifications. These results indicate that there can be a significant dissociation of the reinforcing and the subjective effects of opioids, which has implications for theories of opioid abuse, particularly those assuming that the reinforcing effects are causally related to the euphoric effects of opioids. Furthermore, these results confirm that measures of reinforcing effects and measures of subjective effects do not necessarily lead to identical predictions when used to assess the liability for abuse of a substance.

To estimate the liability for abuse of new analgesics, a number of measures of pharmacological similarity to morphine have been developed (*cf.* Jasinski, 1977; Himmelsbach, 1988; Brady and Lukas, 1984; U.S. Department of Health and Human Services, 1988). For example, the extent to which new analgesics share certain physiologic and subjective effects with morphine is generally used as an indication of whether these drugs have a morphine-like liability for abuse. Techniques for the direct laboratory assessment of the reinforcing effects of opioids have also been devised (*e.g.*, Headlee *et al.*, 1955; Nichols *et al.*, 1956; Weeks, 1962; Weeks and Collins, 1964; Thompson and Schuster, 1964). By using these techniques, completion of a specified sequence of behaviors by the subject (*e.g.*, pressing a lever 100 times) is followed immediately by drug injection. Maintenance of that behavior at levels exceeding those main-

tained by vehicle indicates that the drug has reinforcing effects, which contribute to its abuse liability.

Although there have been few formal comparisons, several authors have indicated a relatively good agreement between results obtained with measures of pharmacological similarity to morphine in humans and measures of reinforcing effects in animals (*cf.* Griffiths and Balster, 1979; Woods *et al.*, 1982; Woolverton and Schuster, 1983). Nevertheless, direct comparisons are needed. Such comparisons would be useful for at least two reasons: 1) determining if use of a particular pharmacological effect to predict the reinforcing effects of opioids leads to an accurate prediction and 2) determining the extent to which certain pharmacological effects may covary with the reinforcing effects of opioids. Because the reinforcing effects of drugs are frequently assumed to be due to their pleasant or euphoric subjective effects, it is particularly important to assess agreement among measures of these effects.

In the present experiments, the reinforcing effects of various morphine doses were examined in human volunteers with histories of heroin addiction; additionally, the physiologic and

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**ABBREVIATIONS:** ARCI, Addiction Research Center inventory; MBG, Morphine Benzedrine Group; PCAG, Pentobarbital Chlorpromazine Alcohol Group; LSD, lysergic acid diethylamide; FR, fixed-ratio.

subjective effects of the self-administered morphine were measured. A single i.m. morphine injection was available after the completion of a long sequence of responses during each daily experimental session. This schedule allowed for the assessment of the reinforcing, physiologic and subjective effects of morphine without the complications of multiple drug injections within the session. Additionally, a range of morphine doses was studied in the present experiments, allowing an assessment of the extent to which the physiologic and subjective effects of morphine paralleled its reinforcing effects.

## Materials and Methods

**Subjects.** Five subjects participated in this study. Subjects were males greater than 21 years of age with histories of daily i.v. heroin use who had used opioids during the 14 days preceding study recruitment. Subjects were not currently physiologically dependent on opioids or other drugs as determined by self-report and by observation for withdrawal signs for several days while subjects resided on the Addiction Research Center Research Ward before beginning the study. Subjects were not currently seeking treatment for their drug abuse, or had they been in treatment in the last 6 months. Other than their drug abuse, subjects were in good health as determined by history, physical examination, routine clinical chemistries and standardized psychological tests and interviews.

Written informed consent was obtained from all subjects, and subjects were free to leave the study at any point. Subjects were informed that the purpose of the study was to learn why people abuse opioid drugs (e.g., heroin, morphine and pentazocine), and that placebo (a blank) as well as opioid drugs might be administered during the study. Subjects were also informed that at the end of the study they would be given a naloxone test in order to ensure that they were not physiologically dependent upon opioids. Subjects were paid for their participation in the study.

Subjects participated in this study while residing on the Residential Research Ward of the Addiction Research Center. This research ward consisted of subject bedrooms, a nursing station, study and examination rooms and a central day room that had various recreational facilities (e.g., television, pool table, crafts, etc.), a small kitchen and dining area. Nursing staff were present 24 hr/day. Physician coverage was provided around the clock.

**Apparatus.** Experimental sessions were conducted in rooms which housed the subject, the operant panel, a personal computer and the physiologic monitoring equipment. The nurse sat in an adjacent room (for subject 943 the nurse sat in the same room as the subject). Control and recording equipment for the operant panels were housed separately. The operant panels (Micro Lab Services) consisted of two or three Lindsay levers above which were white Plexiglas panels that could be transilluminated by colored stimulus lights, and another white Plexiglas panel that was centered and could be illuminated. The operant panels were controlled by a PDP/8 compatible computer running SKED software. Heart rate, blood pressure and oral temperature were collected using an IVAC Vital Check model 4000AEE. Pupil diameter was measured using a stationary close-up pupillometer (Marquardt *et al.*, 1961). Subjective effects measures were collected using an IBM compatible personal computer.

**Procedures.** Subjects 1041 and 1055 participated concurrently in this study as did subjects 1199 and 1204. No other subject in this study was present on the ward during subject 943's participation. Subjects 1041, 1055, 1199 and 1204 received the following morphine dose sequence: 15 mg, 15 mg, placebo, 7.5 mg, 3.75 mg, 30 mg of morphine and placebo; and subject 943 received the following morphine dose sequence: 15 mg, placebo, placebo, 7.5 mg, 3.75 mg, 30 mg and placebo. Each dose condition was in effect for 1 week. Drug administration was double-blind.

Experimental sessions were conducted each weekday. Each session was preceded by physiological and subjective measures. Pretest meas-

ures were started at 1:00 P.M. Operant sessions started from 30 to 60 min after the pretest. Post-test measures were collected 90 min after the operant sessions. Subjects returned to the day area between these three periods. The exact start time for the operant sessions was determined by the subject, who could ask the nurse to begin the session at anytime between 30 and 60 min after the pretest. It was hoped that this variable (time to begin the operant session) might function as a measure of the reinforcing effects of morphine, but instead starting time became entrained with ward routine and did not vary across conditions.

The physiologic measures collected were heart rate, blood pressure, oral temperature and pupil diameter.

The subjective effects measures collected before each session were a version of the ARCI, and a computerized analog rating scale that could be resolved into 50 points. The ARCI scales that were collected were the MBG scale, the PCAG scale, the LSD scale (Martin *et al.*, 1971) and a group of items related to opiate withdrawal (opiate withdrawal scale, Higgins *et al.*, 1988). On the analog scale subjects were asked to rate how well they liked the drug they had received yesterday.

The subjective effects measures collected after each session were the same ARCI items as in the pretest session and in addition the single dose questionnaire (Fraser *et al.*, 1961; Martin and Fraser, 1961), a series of analog rating scales and several additional questions and ratings. Subjects used analog scales to rate drug liking, good and bad effects and drug strength. They were also asked to rate drug strength in dollars and bags, and were questioned about whether they thought they had received drug today. The Single-Dose-Questionnaire consisted of four scales. The first asked subjects if they felt the medicine. The second required subjects to categorize the drug received as most like one of the following: 1) blank; 2) dope; 3) cocaine; 4) marijuana; 5) Valium; 6) downers; 7) alcohol; 8) speed; 9) LSD; 10) Thorazine; 11) glue; 12) PCP; 13) tobacco; and 14) other. The third asked subjects to rate on a five point Likert scale how much they liked the drug (0 = not at all and 4 = an awful lot). The fifth asked subjects to indicate which if any of the following symptoms they experienced: 1) normal; 2) skin itchy; 3) relaxed; 4) coasting; 5) nodding; 6) high; 7) sleepy; 8) drunken; 9) nervous; 10) drive; 11) soap box; 12) turning stomach; 13) pleasant sick; and 14) other.

During the experimental session subjects were required to remain sitting in the study room for 1 hr after a response on the left lever that started the session. The start of the session was indicated by illumination of a green light over the right lever (starting the session was the sole consequence of any response on the left lever). Subjects were then free to respond or not respond on the right lever. Intramuscular injections were available under a second-order schedule of responding on the right lever. Under this schedule, each response on the right lever resulted in a brief flash of white light, and each 100th response turned off the green light and turned on a red stimulus light for 1 sec (FR 100:s); the 30th such completion of the FR 100 requirement turned on the red light for 15 min and subjects received an i.m. injection [FR 30 (FR 100:s) schedule of morphine injection]. When subjects did not complete the response requirements within 45 min the green light over the lever was turned off, responding had no further consequences and subjects were required to remain in the room an additional 15 min.

Subjects were given the following instructions about responding:

"To start the session press the left lever. During the session you are free to press the right lever as often as you like. Only presses on the right lever will have an effect; any responses on the left lever once the session has begun will have no effect. However you need not press either lever. When the red light comes on and stays on the nurse will give you an injection. If this does not happen before the session ends, then you will not get an injection on this day. You must remain seated in this room for 1 hr from the beginning of the session. The drug available will remain the same during each week, but may change from week to week."

A naloxone test was conducted on the last study day after the last measures were collected. Subjects were administered 0.8 mg of naloxone

i.m., and observed for withdrawal signs. No withdrawal signs were observed, nor were any symptoms reported.

**Drugs.** Each day the Addiction Research Center Pharmacy prepared the predetermined solution for drug self-administration: 0, 3.75, 7.5, 15 and 30 mg of morphine sulfate. Drug solutions were dissolved in bacteriostatic saline and injected i.m. in a volume of 0.5 ml. For the naloxone test, naloxone hydrochloride (0.8 mg) was prepared in bacteriostatic saline and injected i.m. in a volume of 1.0 ml. Drug doses were calculated on the basis of the salt.

**Data analysis.** The data reported for 15 mg of morphine are from the 2nd week of availability, and the data reported for placebo are from the 1st week of placebo availability. Response rate data are the average of the last 2 days of drug availability. Other data are from the 1st day of drug administration. Change scores for pupil diameter and the MBG scale were calculated by subtracting the value obtained before the session from the value obtained after the session.

In order to examine the utility of various measures in predicting reinforcement a measure, percentage of agreement was calculated to assess the extent to which the effects of morphine on the preceding day predicted the maintenance of behavior. Percentage of agreement was calculated as follows. For the liking-Likert scale, feel drug scale and change score on the MBG scale: increases on days preceding a day that drug was received and no change or a decrease on days that preceded a day drug was not received were scored as agreement. Then, the total number of agreements was divided by the total number of possible agreements, and multiplied by 100 to calculate a percentage. The "liking yesterday" scale was scored similarly except that data from the pretest immediately preceding the drug self-administration session were used. Percentage of agreement for the change score on the opiate withdrawal scale and change in pupil diameter were scored similarly, except that decreases on the day before drug was received, and no change or increases on the day before drug was not received, were scored as agreement. In other words, if yesterday's drug was liked or produced euphoria we expected self-administration; if not, we expected no self-administration. Similarly, if the drug relieved withdrawal signs or produced pupillary constriction, we expected self-administration; but if not, we expected no self-administration.

## Results

**Reinforcing effects.** Morphine-maintained responding occurred at a high rate and continued until reinforced; only occasionally did subjects pause briefly before beginning to respond. The pattern of steady-state responding during morphine availability is typical of ratio-schedule responding (Fester and Skinner, 1957). On the other hand, no responding occurred at steady state when placebo was available; on the middle 2 days of placebo availability (*i.e.*, after the 1st and before the last 2), responding maintained by placebo was all or none, either occurring at a high rate or not at all. There was no indication that brief stimulus presentations exerted any independent control of responding, that is there was no tendency to pause between the brief stimulus presentations and beginning another ratio. Rather, responding continued during brief stimulus presentations.

Figure 1 shows the dose-response relationship for responding on the last 2 days of availability of each dose for individual subjects, as well as the group mean; 3.75 mg of morphine maintained high response-rates in four of five subjects, and higher morphine doses maintained high response rates in all subjects. For the group there was a significant effect of dose ( $F = 26.7$ ,  $dF = 5.45$ ,  $P < .05$ ) and the response rate for all morphine doses was greater than the response rate for placebo (for 3.75 vs. 0 mg:  $t = 4.52$ ,  $dF = 9$ ,  $P < .05$ ; for 7.5 vs. 0 mg:  $t = -57.39$ ,  $dF = 9$ ,  $P < .05$ ; for 15 vs. 0 mg:  $t = -26.09$ ,  $dF = 9$ ,  $P < .05$ ; and for 30 vs. 0 mg:  $t = -62.13$ ,  $dF = 9$ ,  $P < .05$ ) At

these response rates it typically took subjects between 10 and 14 min to complete 3000 responses. Placebo did not maintain responding in any of the five subjects.

In the left panel of figure 2 are shown the response rates across days maintained by 15 mg of morphine (circles) and by placebo (squares). Morphine responding occurred at a high constant rate across days (for an effect of day:  $F = 2.29$ ,  $dF = 1.38$ ,  $P > .05$ ), whereas placebo responding occurred in every subject on the 1st day, but decreased across days until no subject responded on the last 2 days of placebo availability (for an effect of day:  $F = 34.15$ ,  $dF = 1.38$ ,  $P < .05$ ). The graded decline in responding seen in figure 2 reflects decreases in the number of subjects responding, rather than a graded decline in response rate by individual subjects. Both placebo and 15 mg of morphine were available on two occasions; the left panel of figure 2 shows the response rate data from both of these replications: results from both the first (open symbols) and the second (filled symbols) substitutions were quite similar (for an effect of replication:  $F = 2.25$ ,  $dF = 1.78$ ,  $P > .05$ ).

**Physiological effects.** Figure 3 illustrates the effects of morphine on the change in pupil diameter after the first administration of each morphine dose or placebo for individual subjects, as well as the group mean. All morphine doses produced pupillary constriction (for an effect of dose:  $F = 7.10$ ,  $dF = 4.24$ ,  $P < .05$ ; for 3.75 vs. 0 mg:  $t = 3.37$ ,  $dF = 8$ ,  $P < .05$ ; for 7.5 vs. 0 mg:  $t = 2.50$ ,  $dF = 8$ ,  $P < .05$ ; for 15 vs. 0 mg:  $t = 4.42$ ,  $dF = 8$ ,  $P < .05$ ; and for 30 vs. 0 mg:  $t = 5.22$ ,  $dF = 8$ ,  $P < .05$ ) and, generally, larger morphine doses produced greater pupillary constriction; although in some subjects (1199 and 943) the degree of pupillary constriction was relatively constant across the doses tested. No tolerance developed to the pupillary constricting effects of morphine (fig. 2). Furthermore, the results obtained in both the first (open symbols) and the second (filled symbols) substitutions were quite similar. In contrast, morphine had no clear dose-related or consistent effects on the other physiological measures that were collected (data not shown).

**Self-reported subjective effects.** A measure of the presence of any drug effect, yes-no responses to the question "Do you feel the drug?", is shown in table 1; morphine occasioned a dose-related increase in yes-responses. Placebo occasioned only no responses; 3.75 mg of morphine occasioned yes-responses only 38% of the time; 7.5 and 15 mg of morphine occasioned similar numbers of yes and no responses (59 and 44% yes-responses, respectively), and 30 mg of morphine occasioned yes-responses 96% of the time. The confidence intervals for the proportions of no-responses to the question "Do you feel the drug?" all overlapped that obtained for placebo except at the highest dose tested.

After each drug administration, subjects identified which drug the administered drug's effects were most like from a list of possible choices; these identifications produced a graded measure of the effects of morphine. Table 2 shows these identifications. Placebo occasioned only blank identifications; 3.75 mg of morphine occasioned blank identifications 81% of the time; 7.5 and 15 mg of morphine occasioned similar numbers of blank and drug identifications (32 and 52% blank-identifications, respectively). Of the drug identifications only 18% after 7.5 mg of morphine and 8% after 15 mg of morphine were dope, whereas 30 mg of morphine occasioned dope identifications 92% of the time.

Figure 4 shows the effects of morphine on analog ratings of

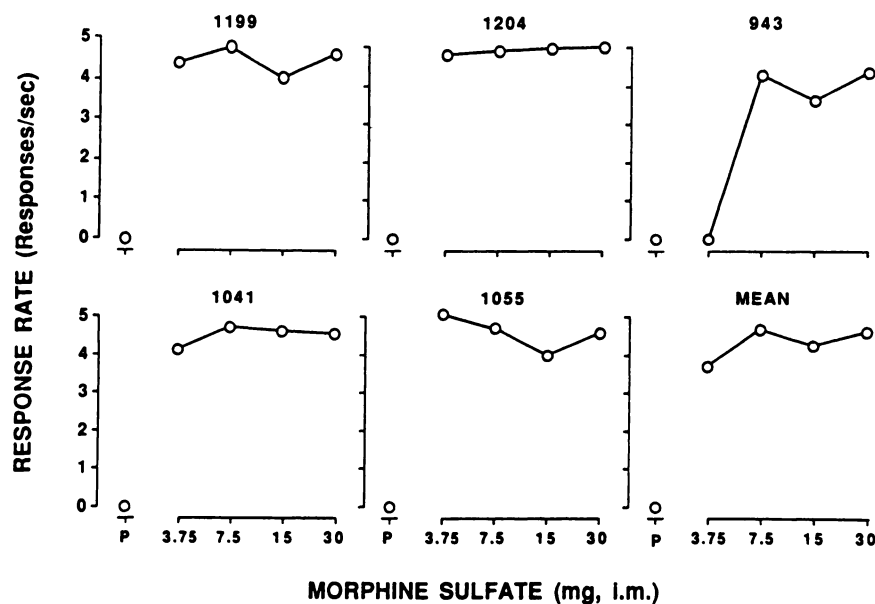


Fig. 1. Mean response-rate for the last 2 days of each substitution under a FR 30 (FR 100:s) schedule of i.m. injection. Individual data for each subject and mean data for the group are presented. The vertical axes represent response rate in responses per second. The horizontal axes represent drug dose in milligrams per injection plotted on a log scale. The points above "P" represent the data obtained during placebo substitution.

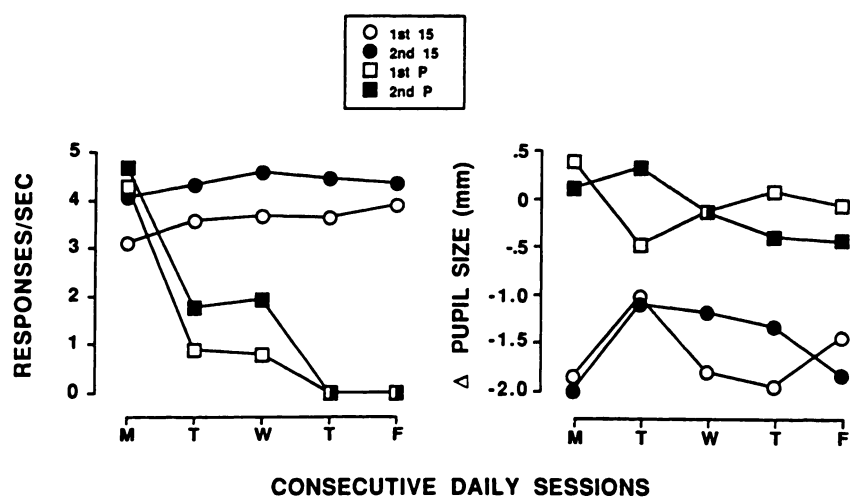


Fig. 2. Mean response-rate (left panel) and mean change in pupil diameter (right panel) across days for the first (○; □) and second (●; ■) substitutions of 15 mg of morphine (○; ●) and placebo (□; ■). The horizontal axes represent sequential days (M, Monday; T, Tuesday; W, Wednesday; T, Thursday; F, Friday). Left vertical axis represents responses rate in responses per second; and right vertical axis represents change (pre-post) in pupil diameter in millimeters. Data for subject 943 are excluded from the 15 mg of morphine points, because these points were only determined once in subject 943. P, placebo.

drug-liking for each subject after the first administration of each morphine dose and placebo; 30 mg of morphine occasioned ratings of drug-liking in all subjects, and 7.5 mg of morphine occasioned ratings of drug-liking in most subjects. But, placebo and other morphine doses did not occasion ratings of drug liking. For the grouped data there was a significant effect of morphine dose ( $F = 7.34$ ,  $dF = 4, 20$ ,  $P < .05$ ), but only the 30-mg dose was significantly different from placebo ( $t = -2.84$ ,  $dF = 4$ ,  $P < .05$ ). Similar results were obtained with Likert scale ratings of drug-liking, analog ratings of drug-liking taken 1 day later and analog ratings of drug-produced good effects administered on the same day (table 3). Ratings of drug-produced bad effects were not increased (table 3).

Subject ratings of drug strength, drug amount (bags) and dollar value of the injection received were similar to the ratings obtained with drug-liking measures (table 3). That is, ratings of 30 mg of morphine were clearly different from placebo on these measures, but ratings of lower morphine doses were not.

Responses to items on the ARCI scales were relatively unaffected by morphine administration. Table 3 shows that only 30 mg of morphine produced any change in MBG responses, and these were of borderline significance. Table 3 also shows

that there were no significant effects of morphine administration on change in the opiate withdrawal scale, the PCAG scale and the LSD scale subsequent to the first administration of each morphine dose and placebo.

**Relationship between reinforcing and other effects.** Figure 5 shows the percentage of agreement between MBG-score-predicted self-administration (upper left panel) and actual self-administration; that is, when an increase in MBG scale on the day before was followed by drug self-administration on the following day, or when no change or a decrease in MBG scale was followed by no self-administration. The MBG scale change was predictive of drug self-administration 57% of the time, and the rate of agreement was a function of morphine dose inasmuch as there was less agreement at lower morphine doses and more agreement at higher morphine doses. Figure 5 also shows percentage of agreement obtained with liking yesterday's drug (upper center panel) and the Likert scale measure of liking (upper right panel). Overall agreement with these ratings was around 70%, and agreement varied with morphine dose; at 3.75 mg, agreement was only 25 to 35% on these measures. Thus, at low morphine doses neither increased MBG scale nor drug-liking were predictive of the reinforcing effects of morphine in these experiments.

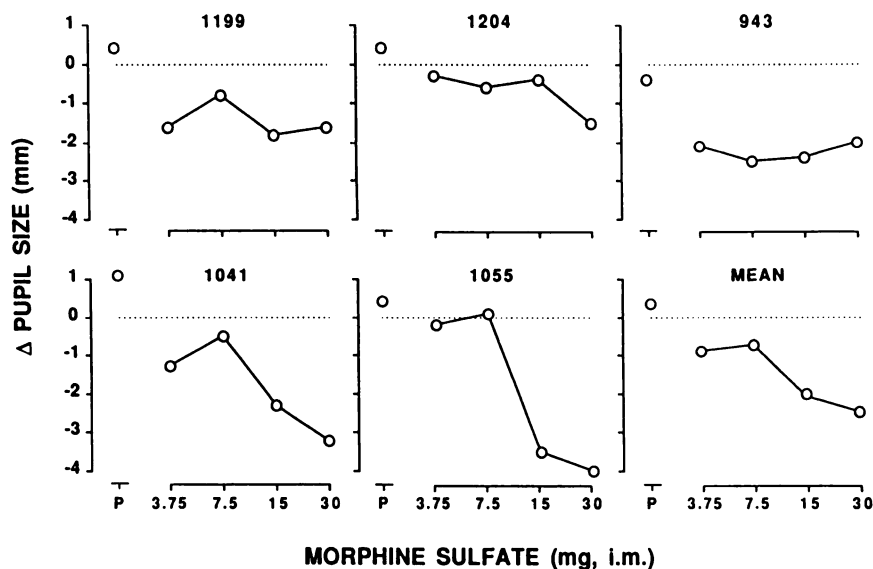


Fig. 3. Change (pre-post) in pupil diameter subsequent to the first injection of each dose. Individual data for each subject and mean data for the group are presented. The vertical axes represent change in pupil diameter in millimeters. The horizontal axes represent drug dose in milligrams per injection plotted on a log scale. The points above "P" represent the data obtained during placebo substitution.

Figure 5 (lower left panel) shows the agreement between the pattern of self-administration predicted by the opiate withdrawal scale (left bottom panel) and the actual pattern of self-administration; overall agreement was relatively low (42%) and agreement was lower at lower morphine doses.

In this experiment, reports of feeling the drug predicted drug self-administration 69% of the time. This predictive ability ranged from 50% (15 mg of morphine) to 95% (30 mg of morphine) and was one of the best predictors at the lowest morphine dose (53%). Pupillary constriction was the best predictor of the reinforcing effects of morphine (fig. 5, bottom right panel). Overall agreement was 85%, and agreement increased with morphine dose.

## Discussion

The reinforcing effects of morphine were assessed in the present experiments by making i.m. injection of morphine dependent upon completion of a long sequence of lever-press responses. Over the dose range studied, morphine injections maintained response rates of several responses per second; when placebo saline injections were substituted for morphine, responding ceased within a few sessions. Physiological and self-reported subjective effects of morphine or placebo injections were measured concurrently. The reinforcing effects of morphine and its subjective effects such as euphoria, drug-liking and drug-identification were separable, inasmuch as reinforcing effects of morphine were observed at much lower doses than reports of these subjective effects.

The all-or-none nature of changes in response rate with changes in dose in the present experiments is characteristic of extended second-order schedules with a single injection of drug occurring only after completion of long sequences of drug-seeking behavior (Katz and Goldberg, 1990). For example, in studies with monkeys, there are dose-related changes in response rate when drug injections are available every 6 min under second-order schedules of i.v. cocaine injection, but not when drug is injected only at the end of each daily session (Goldberg *et al.*, 1981). In the present experiments there also tended to be an all-or-none response to changes in dose in positive ratings of subjective drug effects. Strikingly, a mark-

edly lower dose of morphine functioned as a reinforcer relative to the dose that occasioned positive reports of subjective drug effect.

The reinforcing effects of morphine are well documented, and the present laboratory demonstration of this in humans was not unexpected. Morphine and its derivative, heroin, have long been drugs of abuse. Also, there have been numerous experimental demonstrations in animals of the reinforcing effects of morphine under conditions similar to those used in the present experiments with humans (Goldberg *et al.*, 1976; Goldberg and Tang, 1977a,b). Finally, there have been a number of experimental laboratory demonstrations in humans of the reinforcing effects of other drugs of abuse, including opioids other than morphine (*e.g.*, Griffiths *et al.*, 1979; Fischman and Schuster, 1982; Henningfield *et al.*, 1983; Mendelson and Mello, 1984; Jones and Prada, 1975).

Previous self-administration studies with experimental animals are consistent not only with morphine serving as a reinforcer but, also, with morphine and other opioids serving as reinforcers at very low doses that do not result in measurable development of physical dependence despite repeated daily injections (Woods and Schuster, 1968). Furthermore, consistent with the results of the present study, reports of euphoria, drug-liking and dope-identification by human subjects generally do not occur until doses of morphine greater than 8 mg are administered (*e.g.*, Jasinski and Preston, 1986; Johnson and Jasinski, 1987; Martin *et al.*, 1974; Preston *et al.*, 1987). Thus, the present findings that relatively small morphine doses can serve as a reinforcer and that relatively larger morphine doses are needed to occasion self-reports of euphoria, drug-liking and dope identifications are consistent with previous studies.

Another example of a dissociation of the reinforcing and subjective effects of opioids is provided in a study of hydromorphone self-administration by post-addict human volunteers before and during chronic methadone administration (Jones and Prada, 1975). In this study before chronic methadone administration, all subjects reported liking hydromorphone, and hydromorphone injections maintained responding. During chronic methadone administration, however, subjects did not report liking hydromorphone but, in some subjects, hydromorphone continued to maintain responding (Jones and Prada,

TABLE 1

Subjects' self-report to the prompt "Do you feel the medicine?" across consecutive session and at each morphine dose

Y, yes response; N, no response; —, no session; blank space, drug not earned that session.

Subjects	Days				
	M	T	W	T	F
Placebo					
943	N		N		
1041	N				
1055	N	N			
1199	N				
1201	N				
% Yes	0	0	0		
3.75 mg of Morphine					
943	N		N		
1041	N	Y	Y	Y	Y
1055	N	N	N	N	N
1199	Y	Y	Y	Y	N
1204	N	N	N	N	N
% Yes	20	50	40	67	25
7.5 mg of Morphine					
943	—	Y	Y	Y	Y
1041	—	Y	Y	Y	N
1055	—	Y	N	N	N
1199	Y	Y	Y	Y	N
1204	Y	N	N	N	N
% Yes	100	80	60	60	20
15 mg of Morphine					
943	N	N	Y	N	N
1041	N	Y	Y	N	N
1055	N	Y	Y	N	N
1199	Y	Y	Y	Y	Y
1204	N	Y	N	N	N
% Yes	20	80	80	20	20
30 mg of Morphine					
943	Y	Y	Y	Y	Y
1041	Y	Y	Y	Y	Y
1055	Y	Y	Y	Y	Y
1199	Y	Y	Y	N	Y
1204	Y	Y	Y	Y	Y
% Yes	100	100	100	80	100

1975). The processes observed in this experiment and the present experiment may be analogous to the continued self-administration of drugs observed in patients at the same time that the patient reports that the drug no longer gets them "high."

The human subjects in the present experiments were post-dependent addicts; thus, they had histories of drug-seeking behavior being reinforced and of social reinforcement of their verbal reports of drug effects that undoubtedly influence their self-reports of the effects of morphine and their drug seeking behavior in this experiment. This history may also have altered their physiological state, *e.g.*, produced a protracted withdrawal syndrome, in a way that would influence the self-reported and reinforcing effects of morphine under these conditions as compared to individuals without this history (*e.g.*, Dole, 1988; Martin and Jasinski, 1969). These possible differences in physiological responses to opiates, and in sensitivity to their reinforcing and subjective effects, do not affect the importance of the present findings. What is important is that these two

TABLE 2

Subjects' self-report on which drug the effects of the administered injection were most similar to across consecutive daily session and for each morphine dose

Subjects	Days				
	M	T	W	T	F
Placebo					
943	Blank		Blank		
1041	Blank				
1055	Blank	Blank			
1199	Blank				
1204	Blank				
% Blank	100	100	100		
% Dope	0	0	0		
3.75 mg of Morphine					
943	Blank		Blank		
1041	Blank	Other	Blank	Other	Other
1055	Blank	Blank	Blank	Blank	Blank
1199	Blank	Valium	Blank	Blank	Blank
1204	Blank	Blank	Blank	Blank	Blank
% Blank	100	50	100	67	75
% Dope	0	0	0	0	0
7.5 mg of Morphine					
943	— <sup>a</sup>	Dope	Dope	Dope	Dope
1041	—	Valium	Valium	Valium	Valium
1055	—	Blank	Other	Blank	Blank
1199	Marijuana	Marijuana	Marijuana	Valium	Downers
1204	Marijuana	Blank	Blank	Blank	Blank
% Blank	0	40	20	40	40
% Dope	0	20	20	20	20
15 mg of Morphine					
943	Blank	Blank	Dope	Blank	Blank
1041	Valium	Valium	Valium	Valium	Valium
1055	Blank	Blank	Blank	Blank	Blank
1199	Other	Valium	Marijuana	Alcohol	Other
1204	Blank	Dope	Blank	Blank	Blank
% Blank	60	40	40	60	60
% Dope	0	20	20	0	0
30 mg of Morphine					
943	Dope	Dope	Dope	Blank	Dope
1041	Dope	Dope	Dope	Dope	Dope
1055	Dope	Dope	Dope	Dope	Dope
1199	Dope	Dope	Dope	Dope	Dope
1204	Marijuana	Dope	Dope	Dope	Dope
% Blank	0	0	0	20	0
% Dope	80	100	100	80	100

<sup>a</sup> No session.

measures of behavior do not covary and can give different answers about the liability for abuse of a compound.

One implication in the finding that the reinforcing effects of opioids can occur at doses lower than those that produce clear subjective effects is that opioid partial agonists may have reinforcing effects that would be unexpected based upon measures of their subjective effects. This implication argues for directly measuring the reinforcing effects of opioids when assessing their abuse liability. Higher drug doses are generally chosen over lower drug doses when both are available, and higher drug doses often maintain greater response requirements than lower drug doses (Bickel *et al.*, 1986; McLeod and Griffiths, 1983; Johanson and Schuster, 1975; Hoffmeister, 1979; Lemaire and Meisch, 1985). Thus, to the extent that full agonists are able to produce greater effects than partial ago-

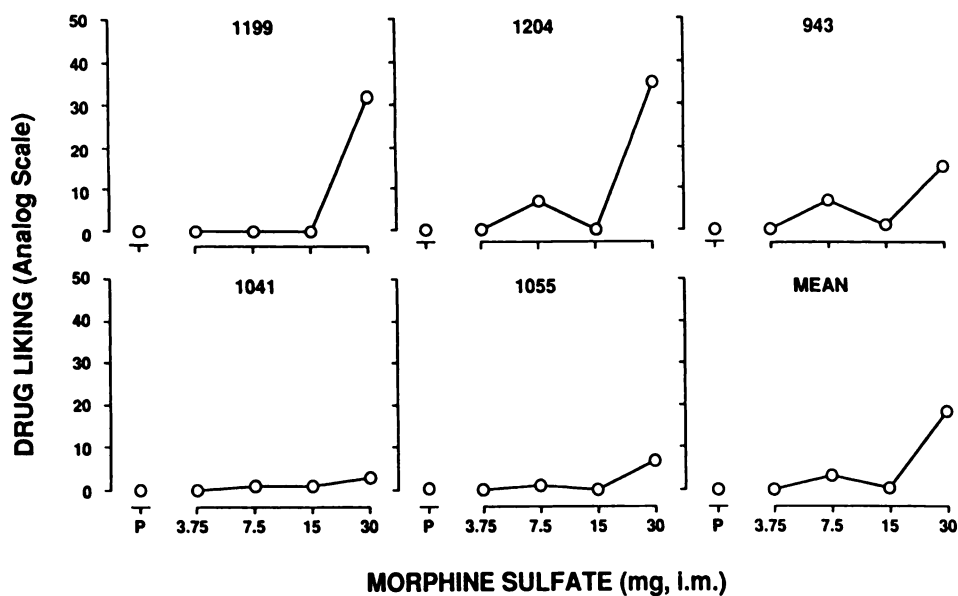


Fig. 4. Ratings of drug-liking subsequent to the first injection of each dose. Individual data for each subject and mean data for the group are presented. The vertical axes represent ratings of drug liking on an analog scale that had a 50-point resolution. The horizontal axes represent drug dose in milligrams per injection plotted on a log scale. The points above "P" represent the data obtained during placebo substitution.

TABLE 3  
Scores on several self-report measures after the first injection of each morphine dose

	Morphine Dose (mg)				
	0	3.75	7.5	15	30
Drug liking					
Likert	0.0 (0)*	0.0 (0)	1.0 (0.3)	0.4 (0.2)	2.6 (0.2)
Yesterday	0.0 (0)	0.0 (0)	3.0 (1.8)	2.0 (0.8)	20 (4.4)
Good effects	0.0 (0)	0.0 (0)	4.6 (2.9)	0.2 (0.2)	19 (6.4)
Bad effects	0.4 (0.4)	0.4 (0.4)	0.0 (0)	0.0 (0)	2.2 (2.0)
Strength of drug effect	0.0 (0)	0.0 (0)	2.6 (1.2)	0.4 (0.2)	14 (5.4)
Amount of drug (bags)	0.0 (0)	0.0 (0)	0.2 (0.2)	0.0 (0)	2.4 (1.7)
Dollar value of drug	0.0 (0)	0.0 (0)	4.6 (3.9)	0.4 (0.2)	15 (5.0)
Change scores ARCI measures					
MBG scale	-2.2 (1.7)	-3.0 (1.9)	0.6 (1.7)	0.0 (0.8)	3.0 (1.9)
PCAG scale	1.2 (0.7)	0.6 (0.4)	-0.4 (0.7)	0.2 (0.2)	2.8 (1.0)
LSD scale	0.2 (0.5)	1.0 (0.3)	-0.8 (0.9)	0.2 (0.4)	2.0 (0.7)
Opioid withdrawal scale	1.0 (0.5)	0.4 (0.5)	-0.4 (0.5)	-0.2 (0.4)	0.4 (1.1)

\* Mean (S.E.M.).

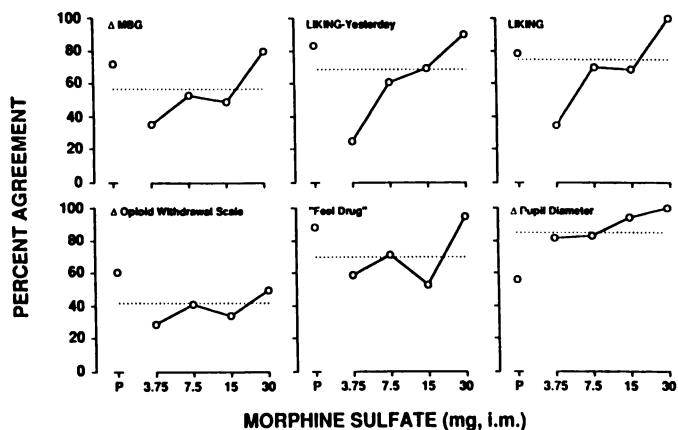
nists, full agonists may have a greater liability for abuse than partial agonists.

Because of the separation of their dose-response curves, measuring the reinforcing and subjective effects of opioids under certain conditions may provide a crude ordering of the efficacy and liability for abuse of  $\mu$  opioids, *i.e.*, from low to high, those producing neither reinforcing effects nor subjective effects, those producing reinforcing but only limited subjective effects and those producing both reinforcing and clear subjective effects. Subjective effects measures may also supplement direct assessments of the reinforcing effects of opioids by providing information on possible non- $\mu$  opioid actions produced by the compound. It is possible that non- $\mu$  actions could modify the abuse liability of a compound in ways that are not easily predictable. Thus, assessments of the reinforcing and subjective effects of opioids can be usefully combined in examining their abuse liability.

Responses to subjective effects scales are complexly and multiply determined by such things as the verbal textual stimuli provided by the scale itself and the private events produced by the drug. Subjective effects produced by drug administration are often tacitly considered to be the underlying causes of drug taking behavior. For example, it has been suggested that drugs

have reinforcing effects because they produce euphoria. In the present study terms such as euphoria and drug-liking were defined as particular results obtained from the subjective effects scales. Because of these definitions it was possible to assess the subjective and reinforcing effects simultaneously, and thus show that whereas certain doses were effective in producing euphoria and drug-liking, those doses were relatively high compared to the minimal doses effective as reinforcing stimuli. Therefore, these subjective effects of morphine are not necessary for the reinforcing effects to be manifest under these conditions. Of course, the present study does not rule out an etiological role for these effects in the natural history of drug abuse. However, the present study and others (*e.g.*, Jones and Prada, 1975; *cf.* Schuster *et al.*, 1981) suggest that these effects are not necessary in the maintenance of opioid abuse.

Experimental conditions might be found which bring the reinforcing and subjective effects of morphine into greater concordance, *e.g.*, larger response requirements, prior drug discrimination training of the subjects or changes in instructions that might influence both drug-seeking behavior and subjective reports. It may be that having sensitive models of reinforcement of behavior by drug injection may help in the refinement of more sensitive measures of subjective response. This would not



**Fig. 5.** Percentage of agreement between the actual self-administration behavior and the self-administration behavior predicted by change in MBG score (left top panel), analog ratings of liking-yesterday's-drug (center top panel), Likert scale ratings of drug-liking (right top panel), change in opiate withdrawal scale score (left bottom panel), reports of feeling the drug (center bottom panel) and change in pupil diameter (left bottom panel). The vertical axes represent percentage of agreement between predicted and actual self-administration. The horizontal axes represent drug dose in milligrams per injection plotted on a log scale. The points above "P" represent the data obtained during placebo substitution. Dashed horizontal lines represent mean overall percentage of agreement for the measure.

invalidate the basic finding of the present study that the reinforcing effects of morphine can occur in the absence of self-reported subjective effects and thus, do not appear to be causally related to drug-liking or euphoria.

In summary, morphine functioned as a reinforcer in the present study. This study did not directly assess the determinants of the reinforcing effects of morphine, but it did demonstrate that the measured pleasant subjective effects of morphine are not critical for these reinforcing effects, at least in subjects with histories of heroin addiction. It also indicates that reports of drug effects by addict or postaddict subjects do not substitute for well controlled laboratory studies of drug-taking behavior with concurrent measurements of the physiological and subjective drug effects. Experimental analysis of drug taking in human subjects with concurrent physiological and subjective report measurements should further our understanding of both the pharmacological and behavioral determinants of the reinforcing effects of drugs of abuse.

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