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# Butorphanol and nalbuphine in opioid-dependent humans under a naloxone discrimination procedure

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**Abstract**

Opioid-maintained volunteers were trained to distinguish between a low dose of the opioid antagonist naloxone (0.15 mg/70 kg, im; i.e., Drug A) and placebo (i.e., Drug B) under an instructed novel-response drug-discrimination procedure in which subjects identify the drug condition as "A," "B," or "N" (neither A nor B—'novel'). Once the discrimination was acquired, doses of naloxone (0–0.15 mg/70 kg, im) and the mixed-action opioid agonist/antagonists butorphanol (0–1.5 mg/70 kg, im) and nalbuphine (0–3.0 mg/70 kg, im) were tested. Naloxone produced dose-related increases in naloxone-appropriate responding with little or no 'novel'-appropriate responding. Butorphanol produced a dose-related increase in naloxone- and 'novel'-appropriate responding, occasioning approximately 70% and 29%, respectively, at the highest dose tested. Nalbuphine produced 40–65% naloxone-appropriate responding at all doses tested and 33% 'novel'-appropriate responding at the highest doses. Self-reported effects produced by each agent differed only slightly. These results suggest that mixed-action opioid agonist/antagonists may be distinguished from the opioid antagonist naloxone based on their discriminative-stimulus effects under a novel-response naloxone discrimination procedure. 

*Keywords:* Naloxone; Butorphanol; Nalbuphine; Opioid dependence; Humans; Drug discrimination; Instructed novel response

## 1. Introduction

In the drug-discrimination procedure, a subject is trained to make one type of response after administration of drug A (e.g., naloxone) and another type of response after administration of drug B (e.g., placebo). Once the subject has learned to discriminate between drugs A and B, other doses or compounds are administered to determine whether their interceptive stimulus effects are similar to drug A. The greater their similarity in effects to drug A, the greater the amount of drug A-appropriate responding. Many drugs have been differentiated in this manner, and this paradigm has become a standard assay in nonhuman behavioral pharmacology due to the high concordance between drug discrimination and receptor binding studies, as well as the paradigm's high pharmacological specificity (e.g., Colpaert, 1986). These procedures have also been adapted for use in humans. The results of human discrimination studies are similar to those with nonhumans, demonstrate pharmacological specificity, and generally show a high concordance with self-reports (e.g., see reviews by Kamien et al., 1993; Preston and Bigelow, 1991; Schuster and Johanson, 1988).

One limitation of the drug-discrimination procedure, however, is that placebo-appropriate responding is occasioned not only by the absence of drug effects but also by drug effects pharmacologically dissimilar to the training drug stimulus; that is, placebo-appropriate responding is not specific and is interpreted as a default option (Overton, 1984; Young, 1991a). This lack of specificity has made phenomena such as partial generalization and functional antagonism difficult to interpret (e.g., see Colpaert, 1991; Stolerman, 1991; Young, 1991b). A methodological advance in the human drug-discrimination procedure has been

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the addition of an instructed novel-drug effects response option to a triazolam vs. placebo discrimination (e.g., Bickel et al., 1993; Kamien et al., 1994; Oliveto et al., 1994). In the Bickel et al. (1993) study, dose–effect curves for triazolam and for the CNS stimulant D-amphetamine were determined with and without the addition of the instructed novel-drug response in humans trained to discriminate triazolam from placebo. Triazolam produced dose-related increases in triazolam-appropriate responding under both conditions. In contrast, D-amphetamine produced placebo- or some triazolam-appropriate responding without the novel-response addition, but placebo- or novel-appropriate responding when the novel-drug response was added. These results indicate that the novel response drug-discrimination procedure enhances the pharmacological specificity of the training drug stimulus, as well as the selectivity of the placebo stimulus. A subsequent review of several triazolam novel response discrimination studies has indicated that this procedure can increase the selectivity of both placebo- and drug-appropriate responding, allowing for finer distinctions to be made among sedatives than a standard two-response procedure (Smith and Bickel, 1999a).

The novel-response discrimination procedure has been employed by our laboratory to investigate the discriminative-stimulus effects of the opioid antagonist naloxone in opioid-dependent participants. In one study (Oliveto et al., 1998b), methadone-maintained (25–55 mg/day) participants were trained to distinguish between a low dose of naloxone and placebo. Once the discrimination was acquired, doses of naloxone alone, the opioid agonist hydromorphone alone and hydromorphone in combination with the naloxone training dose were tested. Naloxone alone produced dose-related increases in naloxone-appropriate responding, with some 'novel'-appropriate responding at low doses, and increases in self-reported opioid antagonist adjective ratings. Hydromorphone alone produced dose-related increases in 'novel'-appropriate responding, little or no naloxone-appropriate responding, and self-reported opioid agonist adjective ratings. When combined with naloxone, hydromorphone produced dose-related decreases in naloxone-appropriate responding without significantly increasing 'novel'-appropriate responding and decreases in antagonist adjective ratings without significantly increasing agonist adjective ratings. These results indicate that the naloxone stimulus is pharmacologically specific and that a competitive antagonism can be discerned under an instructed novel response discrimination procedure.

The present study examined further the pharmacological specificity of the naloxone discriminative-stimulus effects in this paradigm by examining the behavioral effects of the mixed-action agonist/antagonists butorphanol and nalbuphine. Previously in opioid-maintained humans trained to discriminate among naloxone, hydromorphone and saline, butorphanol and nalbuphine each produced dose-related increases in naloxone-appropriate responding and self-reported effects similar to naloxone, suggesting that these agents have antagonist-like stimulus effects in opioid-dependent participants (Preston et al., 1990). The purpose of the present study was to determine whether the actions of these mixed-action opioid agonist/antagonists could be differentiated from naloxone in opioid-dependent individuals under the novel response procedure.

## 2. Materials and methods

### 2.1. Subjects

Nineteen opioid-dependent volunteers (ages 28–49 years) gave written informed consent to participate in this study. All subjects had to have no significant medical or psychiatric disorder; no prescribed use of psychoactive drugs; no current diagnosis of other drug dependence (except tobacco); no current pregnancy; and no medical contraindication to or prior serious adverse effects from naloxone. Three subjects participated on an inpatient basis; they had to have confirmation of opioid dependence via urine toxicology screen and Narcan challenge, were admitted to an inpatient unit (see below), and stabilized on methadone. The other 16 subjects participated on an outpatient basis. They had to be currently in a methadone or LAAM maintenance program in good standing, be on a stable dose of opioid agent, and submit a urine sample negative for illicit drugs. Eligibility was ascertained through a comprehensive evaluation including complete physical, neurological, and clinical psychiatric examinations, routine laboratory studies, and electrocardiogram. Subjects were compensated monetarily for their participation at a rate of US$20 per session for inpatient subjects and at a rate of US$10 per session during Phase 1, US$15 per session during Phase 2, and US$20 per session during Phase 3 for outpatient subjects (described below). All subjects were also compensated for their performance on the drug-discrimination procedures (see below). Additional compensation of US$100 (inpatient) or US$200 (outpatient) was awarded upon participation in the final session of the study. This protocol was approved by the Yale University Human Investigations Committee, the VA CT Healthcare System Human Studies Committee, and the APT Foundation Community Board.

Thirteen subjects were white, three were African American and three were Hispanic. Subjects reported using opiates for a mean of 13.1 years (range: 3–39 years). The primary route of administration was nasal insufflation (7/19), intravenous injection (9/19), intramuscular injection (1/19), or oral (1/19).

### 2.2. Setting

Those who participated on an inpatient basis were admitted to the Yale Medications Development Research Center at the Connecticut Mental Health Center, which is in a locked ward for patients with psychiatric and substance abuse

problems. Subjects remained on the ward and were encouraged to participate in the ongoing inpatient substance abuse treatment program when not participating in the experimental sessions. Once subjects' participation in the experiment was terminated, subjects were offered referrals to other treatment programs, if desired. Those who participated on an outpatient basis attended sessions at the Outpatient Behavioral Pharmacology Laboratory located at the VA CT Healthcare System. For each experimental session, subjects were escorted to and from the laboratory, which consisted of a four- or six-station room with automated blood pressure equipment. The outpatient laboratory also had an adjacent lounge, where subjects could relax after the experimental portion of the session while waiting for drug effects to subside. At both sites, a research nurse administered all medications and was present for the entire session, while a physician was available by pager during each session.

### 2.3. Opioid maintenance schedule

Subjects participating on an inpatient basis were first placed on a 25-mg/day dose of methadone. This dose was increased in 5-mg/day increments until withdrawal symptoms subsided. These three subjects were maintained on methadone doses ranging between 30 and 60 mg/day. After study participation was completed, subjects underwent detoxification from methadone over a 5–10-day period and were referred to outpatient treatment programs, if desired.

Subjects participating on an outpatient basis were maintained on either methadone hydrochloride at 45–100 mg/day ($N$=14) or on methadyl acetate (LAAM) at either 45, 45, 55 or 80, 80, 100 mg/MWF ($N$=2) by the opioid maintenance clinic that they were attending. Subjects continued attending their respective opiate maintenance treatment facility during and after their participation in the study.

### 2.4. Experimental procedure

Subjects were trained to discriminate 0.15 mg/70 kg naloxone, im, from placebo (vehicle) under an instructed novel-response (i.e., active dose, placebo dose, 'novel') discrimination procedure (Bickel et al., 1993; Kamien et al., 1994; Oliveto et al., 1994, 1998b). An initial nondrug session was conducted to familiarize subjects with the procedures. The study then proceeded in three phases.

#### 2.4.1. Training (Phase 1)

Subjects were exposed to both naloxone (0.15 mg/70 kg, im) and placebo twice each in alternating order and were informed of the drug's letter code (e.g., Drug A or Drug B) at the time of drug administration. Subjects were never informed of the actual identities of the drugs, but were given a list of drugs that they might receive during the course of the study. Letter codes associated with the training drug stimuli were varied across subjects.

#### 2.4.2. Tests of acquisition (Phase 2)

Stimulus control by the training conditions was tested by administering the naloxone training dose and placebo at least twice in random order. The drug letter code associated with the drug administration was not revealed until the end of the experimental session. Subjects had to meet an accuracy criterion of $\geq$80% correct responding on four consecutive sessions in order to enter the testing phase. If this criterion was not met within 15 sessions, subjects were dismissed from the study.

#### 2.4.3. Testing (Phase 3)

Dose–effect curves were determined for naloxone (0, 0.0375, 0.075, 0.15 mg/70 kg, im), butorphanol (0, 0.375, 0.75, 1.5 mg/70 kg, im), and nalbuphine (0, 0.75, 1.5, 3.0 mg/70 kg). After each session was completed, subjects were informed only that it was a test and that the drug code would not be revealed. During this phase, subjects were informed that if they received a drug not precisely like either of the training conditions, only novel-appropriate responses would be reinforced (see Bickel et al., 1993); however, in actuality, subjects' bonus earnings during all test sessions were equal to the average earned on the preceding four test-of-acquisition sessions. Earnings were not contingent upon discriminative performance.

Test-of-acquisition sessions (i.e., administration of the training dose of naloxone or placebo) were interspersed among the test sessions to ensure that the training conditions still appropriately controlled responding. If the training drug stimuli failed to control the appropriate response in one of these tests of acquisition or if more than 6 days occurred between sessions, two more test-of-acquisition sessions were conducted. If the training drug stimuli did not control the appropriate response in two sessions, additional test-of-acquisition sessions were added until the criterion for acquisition of the discrimination (i.e., four consecutive correct) was met again. The ratio of test to test-of-acquisition sessions was approximately 3:2. The training dose of naloxone, doses of butorphanol and nalbuphine, and timing of postdrug assessments were selected based on those employed by Preston et al. (1990) in order to compare results more easily.

### 2.5. Experimental session

Sessions were conducted 3–5 days/week, depending upon subject and staff availability, and typically began between 8:30 and 10 AM. The time at which sessions were begun remained consistent within subjects. Subjects remained at the laboratory for approximately 2.5 h. After subjects who were participating on an outpatient basis submitted a urine and all subjects passed a sobriety test, a predrug assessment cycle occurred, which consisted of baseline self-report questionnaires (see below). Vital signs (blood pressure, heart rate) were taken. Immediately afterwards, one injection was administered into the muscle of the

upper arm. Subjects completed tasks during two postdrug assessment cycles, conducted 20 and 40 min after injection (Oliveto et al., 1998b; Preston et al., 1987). Each assessment cycle lasted approximately 15 min and consisted of discrimination measures, self-report measures and vital signs (see below). After the second postdrug assessment cycle was completed, a sealed envelope was opened for each subject, informing subject and experimenter either of the letter code identity of the administered drug or that the session had been a test day.

Subjects were monitored for 2 h postinjection, with vital signs taken every 20 min during the first hour and once more at the end of the second hour (see below). During this time, subjects were offered food. After passing the sobriety test, subjects participating on an inpatient basis were then allowed to reenter the ward and subjects participating on an outpatient basis were allowed to leave the laboratory.

Subjects were instructed to abstain from caffeine and solid food for at least 4 h before each session. Smokers participating inpatient were required to smoke a cigarette from their regular brand about 10 min prior to the session. Smokers participating outpatient were asked to smoke a cigarette at least 1/2 h prior to the session. No smoking was permitted from this time until after completion of the experimental portion of the session. Otherwise, subjects were instructed to maintain a regular pattern of smoking for the duration of the study.

#### 2.5.1. Dependent measures

For those participating on an inpatient basis, discrimination and self-report assessments were administered on paper completed with a pen; for those participating on an outpatient basis, these assessments were administered via computer in a predetermined timed sequence.

#### 2.5.2. Discrimination measures

Data were collected during each assessment cycle using two procedures in subjects using paper and pencil. A third procedure was also presented to those subjects using the computer (Preston et al., 1987, 1989a; Bickel et al., 1989). In each procedure, only correct responses during training or test-of-acquisition sessions were converted to monetary reinforcement for subjects. In the first procedure, subjects made a discrete choice response that indicated by letter code (e.g., A or B) the drug that they received. Each correct identification was worth either US$2.00 or US$3.00. In the second procedure, subjects distributed 50 points among the two drug codes depending upon how certain they were of the identity of the drug administered. Each point on the correct code was worth US$0.02 or US$0.03. In the third procedure, the results of which will not be presented here because it was not completed by all subjects, subjects responded on either of three keys corresponding to training drug, placebo, and 'novel' according to a FI 1-s schedule of point presentation. Under this schedule, the first response made after each elapsed 1-s interval increased the total number of points accumulated on a given key by one. This schedule lasted 3 min, and the number of points earned on each of the three letter codes and the overall rate of responding were recorded. Each point on the correct letter code was worth US$0.012. Subjects completing two procedures earned up to US$8.00 per session or US$4.00 per procedure for maximal correct responding, while subjects completing three procedures earned up to US$9.00 per session or US$3.00 per procedure for maximal correct responding.

#### 2.5.3. Self-report measures

Three questionnaires were administered: the shortened version of the Addiction Research Center Inventory (ARCI), an adjective rating scale, and visual analog scales (VAS). The ARCI consisted of 49 true/false questions that were scored as five subscales: morphine–benzedrine group (MBG), a measure of "euphoria"; pentobarbital–chlorpromazine–alcohol group (PCAG), a measure of "sedation"; lysergic acid diethyl amide (LSD), a measure of "dysphoria"; and the benzedrine group (BG) and amphetamine (A) scales, which are sensitive to D-amphetamine-like effects (Jasinski, 1977; Martin et al., 1971).

The adjective rating scale listed 32 adjectives that were rated on a five-point scale from 0 (not at all) to 4 (extremely). The items in the list were grouped into three subscales: (1) Agonist Scale, consisting of the adjectives carefree, coasting or spaced out, drive, dry mouth, drunken, energetic, flushing, good mood, heavy or sluggish feeling, nodding, pleasant sick, relaxed, skin itchy, sleepy, sweating, talkative, tingling, and turning of stomach; (2) Antagonist Scale, consisting of the adjectives agitated, chills, goose flesh, restless, runny nose, shaky, tired, and watery eyes; and (3) Mixed Agonist/Antagonist Scale, consisting of the adjectives confused, depressed, floating, headache, lightheaded, and numb (Preston et al., 1987).

The VAS consisted of eight 100-point horizontal lines anchored with "not at all" on one end and "extremely" on the other. On these scales, subjects marked the part of the line that represented the extent to which they experienced any drug effect, effects similar to each training condition (identified by letter code) or dissimilar to either condition (identified by the letter "N"), drug-liking, "good" drug effects, "bad" drug effects, and drug-induced high.

At the end of the second postdrug assessment cycle, subjects also completed a pharmacological drug class questionnaire, in which they indicated which type of drug they thought they had received from the following list: placebo (blank or nothing), opiates (heroin, methadone, etc.), phenothiazines (haldol, major tranquilizers), barbiturates and sleeping medications, antidepressants (desipramine, imipramine), opiate antagonists (Narcan, naloxone, naltrexone), hallucinogens (marijuana, mushrooms, etc.), benzodiazepines (Xanax, Halcion, Valium, etc.), stimulants (cocaine, amphetamines, etc.), or phencyclidine (PCP, angel dust) (Preston et al., 1987).

*2.5.4. Physiological measures*

Heart rate and blood pressure were taken prior to and at 20, 40, 60, and 120 min postinjection. Heart rate and blood pressure were measured with a blood pressure cuff automated through a Dinamap vital signs monitor. For those participating on an outpatient basis, body temperature was measured tympanically prior to and at 10, 20, 30, 40, and 60 min postinjection using Thermoscan Pro-1 Instant Thermometer.

*2.6. Drugs*

Methadone hydrochloride (Mallinkrodt Specialty Chemicals, St. Louis, MO) was dissolved in distilled water at a concentration of 10 mg/ml and administered orally to those participating on an inpatient basis. The active compounds and placebo were administered via intramuscular injection in a mean volume of 0.9 ml (range: 0.65–1.2). Injection volumes remained consistent within individuals, unless a subject's weight changed by more than 5 lb, in which case, injection volumes were adjusted. For those participating on an inpatient basis, injections were prepared by the Connecticut Mental Health Center Pharmacy for naloxone hydrochloride (Dupont-Merck Pharmaceuticals, Manati, Puerto Rico), butorphanol tartrate, and nalbuphine hydrochloride. For those participating on an outpatient basis, injections were prepared by the VA CT Healthcare System Research Pharmacy for these compounds (Amerisource, Springfield, MA). Active naloxone, butorphanol and nalbuphine were each prepared in a NaCl 0.9% solution. Naloxone placebo consisted of dextrose 5% solution and NaCl 0.9% solution in a ratio of 1:1. Naloxone, butorphanol, and nalbuphine were each injected 20 min prior to the first postdrug assessment cycle (Preston et al., 1990). Each drug was administered in a double-blind fashion. Order of dose–effect curve determinations and of dose presentation within dose–effect curve determinations varied nonsystematically across subjects.

*2.7. Data analyses*

Discrimination data within each session were averaged across the two postdrug assessment cycles. Results from the ARCI, VAS, and adjective scales are reported as the mean change from predrug scores. Physiological measures are reported as mean scores.

Repeated-measures analyses of variance (ANOVAs) were used to evaluate the significance associated with differences between the naloxone training dose and placebo on self-report and physiological measures during training/test-of-acquisition phases. Factors for self-report and physiological measures included training condition (naloxone and placebo), session (four sessions each with placebo and naloxone), and time (20 and 40 min postdrug for self-reports; 0, 20, 40, 60, and 120 min postdrug for vitals signs; 0, 10, 20, 30, 40, 60 min postdrug for temperature).

During the testing phase, the significance of dose effects on self-reports and physiological measures were evaluated for naloxone (0, 0.0375, 0.075, 0.15 mg/70 kg), nalbuphine (0, 0.75, 1.5, 3.0 mg/70 kg), and butorphanol (0, 0.375, 0.75, 1.5 mg/70 kg), using repeated-measures ANOVA with dose and time (20 and 40 min postdrug for self-reports; 0, 20, and 40 min postdrug for physiological measures) as the within-subjects factors. Pearson correlation coefficients were determined between naloxone- or novel-appropriate responding and self-report ratings for naloxone, butorphanol, and nalbuphine. For all statistical analyses, $P \leq .05$ was used to infer statistical significance. Analyses were performed using SPSS statistical software.

## 3. Results

*3.1. Discrimination performance during training/test of acquisition*

Because performance under both the discrete choice and point distribution discrimination tasks was similar, only data collected under the point distribution procedure will be presented. Eleven of 19 subjects did not complete enough sessions to determine whether they met the criterion for discrimination (i.e., $\geq 80\%$ correct drug code identification across four consecutive sessions). Reasons for discontinuing participation include not liking the effects of the drug ($N=5$), finding a job ($N=2$), having child care issues ($N=1$), finding the study boring ($N=1$), becoming ill ($N=1$), and being discontinued from the methadone program ($N=1$). Of the eight subjects continuing through the test-of-acquisition phase, six met the discrimination criterion within a mean of 5.83 sessions (range: 4–13). Two (S5, S6) of these six subjects participated on an inpatient basis and the rest (S1–S4) on an outpatient basis.

*3.2. Self-reports and physiological measures during training/test of acquisition*

On the ARCI, the training dose of naloxone produced significantly higher ratings on the LSD subscale relative to placebo [$2.94 \pm 1.14$ vs. $0.38 \pm 0.36$; $F(1,5)=9.6$, $P=.03$]. The effects of naloxone and placebo did not differ on the PCAG, MBG, A, and BG subscales.

On the VAS, naloxone produced significantly lower ratings on the 'similar to placebo' [$4.17 \pm 4.17$ vs. $74.85 \pm 17.04$; $F(1,5)=14.32$, $P=.01$] scales than placebo. The naloxone training dose also significantly increased ratings of any drug effect [$32.0 \pm 8.72$ vs. $10.12 \pm 4.48$; $F(1,5)=12.7$, $P=.02$] and 'similar to naloxone' [$97.27 \pm 1.69$ vs. $0.04 \pm 0.04$; $F(1,5)=3236.1$, $P<.0001$] relative to placebo. Naloxone showed no difference in ratings of good effects, bad effects, liking, high, and 'similar to novel' relative to placebo.

On the adjective ratings, no significant differences between naloxone and placebo occurred on the opioid antagonist, agonist, and agonist/antagonist scales.

On the pharmacological drug class questionnaire, placebo was identified primarily as "placebo" on 15 of 24 occasions (62.5%) and "barbiturate/benzodiazepine" on five occasions (20.8%). On four other occasions (16.7%), placebo was identified as either "antidepressant" or "phenothiazine." In contrast, the training dose of naloxone was identified as "opiate antagonist" on 15 of 24 occasions (62.5%), "stimulant" on two occasions (8.3%),"phenothiazine " on three occasions (12.5%), "barbiturate/benzodiazepine" on one occasion (4.2%), and "placebo" on four occasions (16.7%).

Regarding physiological measures, naloxone increased while placebo decreased systolic [$F(1,5)=20.16$, $P=.006$] and diastolic blood pressure [$F(1,5)=8.13$, $P=.04$; data not shown]. Heart rate and temperature did not differ across training conditions.

### 3.3. Discrimination performance during testing

All six subjects who met the criterion for discrimination completed the entire test phase. For these subjects, the mean percentage of correct responding ranged from 75% to 100% for the training dose of naloxone and from 93.3% to 100% for placebo during the testing phase (Fig. 1).

The effects of naloxone, butorphanol, and nalbuphine on discrimination performance are shown in Fig. 1. Naloxone produced dose-related increases in the percentage of naloxone-appropriate responding such that the lowest dose (0.0375 mg/70 kg) and the highest dose (0.15 mg/70 kg) produced 16.7% and 100% naloxone-appropriate responding, respectively (Fig. 1, top left panel). Naloxone occasioned no 'novel'-appropriate responding at the lowest and highest doses and only 16.7% 'novel'-appropriate responding at the middle dose tested (Fig. 1, bottom left panel).

Butorphanol also produced a dose-related increase in naloxone-appropriate responding, such that the lowest dose (0.375 mg/70 kg) and the highest dose (1.5 mg/70 kg) produced 33.3% and 70.8% naloxone-appropriate responding, respectively (Fig. 1, top middle panel). In addition, butorphanol produced 29% 'novel'-appropriate responding at the two highest doses (Fig. 1, bottom middle panel).

Nalbuphine produced naloxone-appropriate responding that ranged from 40% to 65% across all doses (Fig. 1, top right panel). Nalbuphine also produced dose-related increases in 'novel'-appropriate responding, such that the two highest doses produced 33.3% 'novel'-appropriate responding (Fig. 1, bottom right panel).

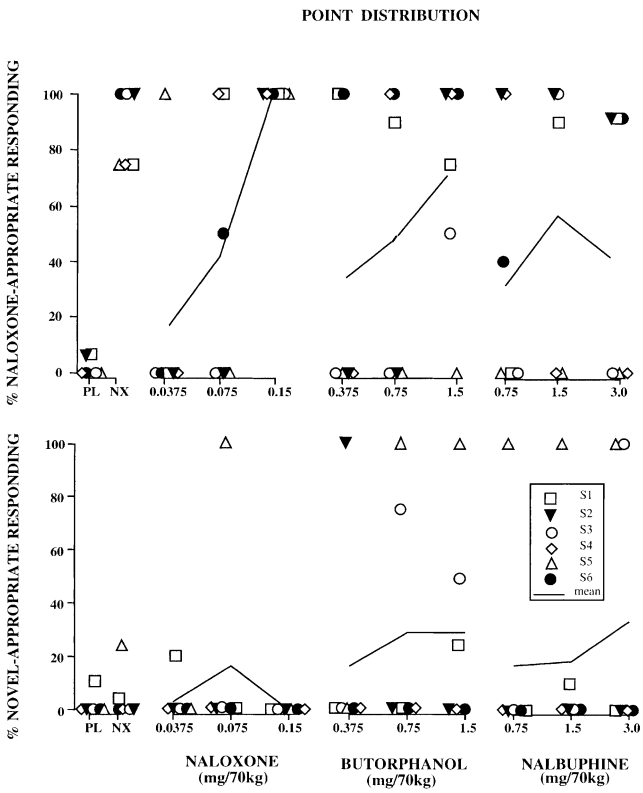


Fig. 1. Effects of naloxone (left panels), butorphanol (middle panels), and nalbuphine (right panels) on naloxone-appropriate (top panel) and 'novel'-appropriate (bottom panel) responding under the point distribution discrimination procedure. Ordinate: Discrimination performance expressed as percentage appropriate responding. Abscissa: Dose of drug, expressed as mg/70 kg body weight. Each point on the dose–effect curves represents one observation in an individual. Each line represents the mean of six subjects. The points above "PL" and "NX" represent mean performance within each subject during test-of-acquisition sessions in the testing phase, in which placebo and the training dose of naloxone (0.15 mg/70 kg), respectively, were administered.

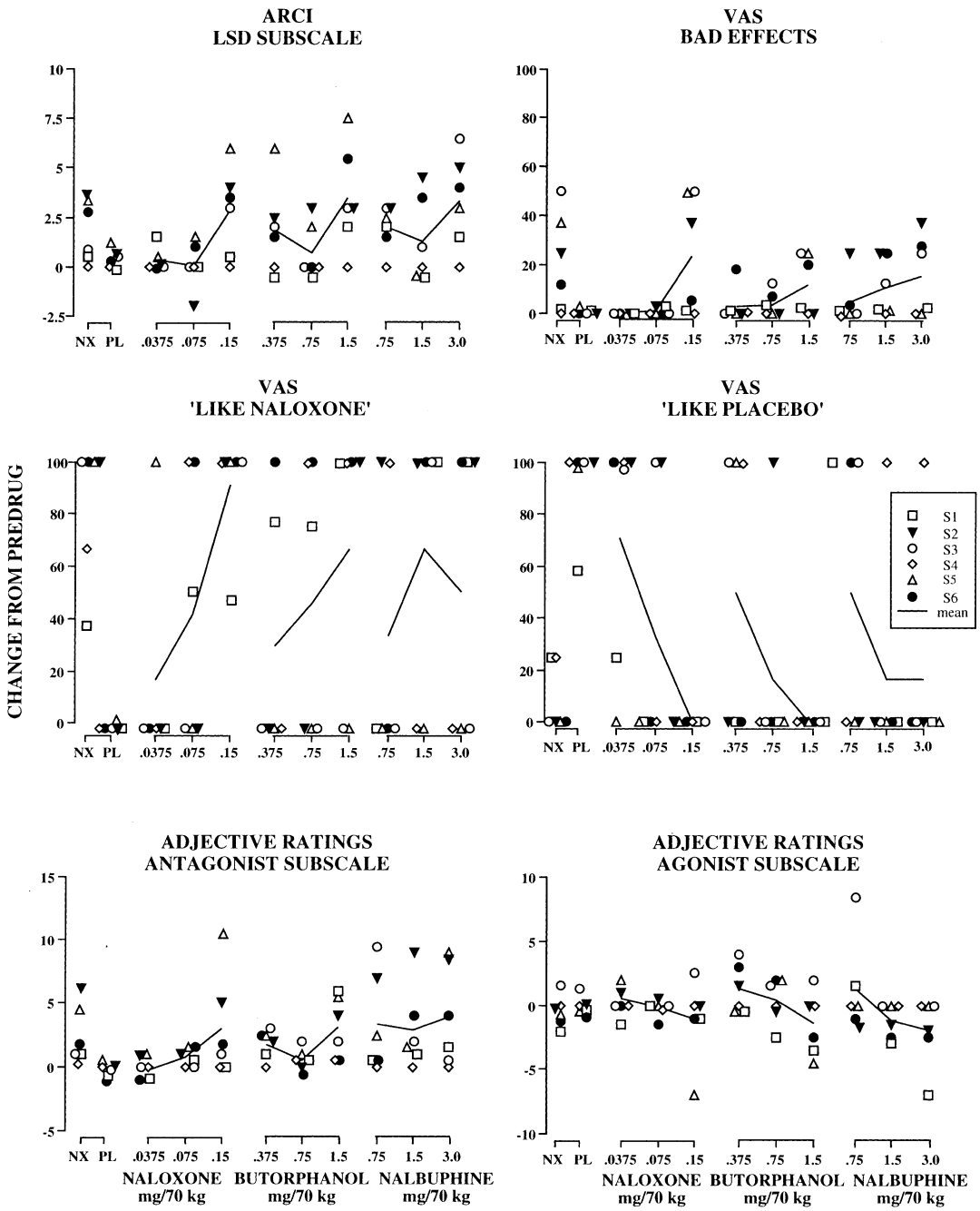


Fig. 2. Effects of naloxone (left panels), butorphanol (middle panels), and nalbuphine (right panels) on selected self-report measures. Ordinate: Change from predrug score. Abscissa: Dose of drug, expressed as mg/70 kg body weight. Each point on the dose–effect curves represents one observation in an individual. Each line represents the mean of six subjects. The points above "PL" and "NX" represent mean performance within each subject during test-of-acquisition sessions in the testing phase, in which placebo and the training dose of naloxone (0.15 mg/70 kg), respectively, were administered.

### *3.4. Self-report and physiological measures during testing*

Because only two measures showed a Dose×Time interaction for one of the test compounds, these data will not be reported. Those self-report measures that showed a main effect of drug dose for naloxone, butorphanol or nalbuphine are shown in Fig. 2. Naloxone [$F(3,15)=5.2$, $P=.01$], butorphanol [$F(3,15)=8.9$, $P=.001$], and nalbuphine [$F(3,15)=5.3$, $P=.01$] each significantly increased ratings on the LSD subscale of the ARCI (Fig. 2, top left panel). No other ratings on the ARCI showed a main effect of dose for any of the compounds tested.

On the VAS, nalbuphine [$F(3,15)=4.0$, $P=.03$], but not naloxone [$F(3,15)=2.4$, $P=.1$] or butorphanol [$F(3,15)=3.1$, $P=.06$], produced statistically significant increases in ratings of bad effects (Fig. 2, top right panel).

Table 1
Subject ratings on the pharmacological drug class questionnaire during testing

| Drug/dose (mg/70 kg) | Placebo | Opiate | Opiate antagonist | Benzodiazepine | Barbiturate | Phenothiazine | Stimulant |
|---|---|---|---|---|---|---|---|
| *Naloxone* | | | | | | | |
| 0.0325 | 3 | 0 | 1 | 1 | 1 | 0 | 0 |
| 0.075 | 2 | 0 | 1 | 0 | 2 | 0 | 1 |
| 0.15 | 1 | 0 | 4 | 0 | 0 | 1 | 0 |
| *Butorphanol* | | | | | | | |
| 0.375 | 1 | 0 | 1 | 0 | 2 | 0 | 2 |
| 0.75 | 4 | 0 | 1 | 0 | 0 | 1 | 0 |
| 1.5 | 1 | 0 | 3 | 0 | 0 | 1 | 1 |
| *Nalbuphine* | | | | | | | |
| 0.75 | 2 | 0 | 2 | 0 | 2 | 0 | 0 |
| 1.5 | 1 | 0 | 4 | 0 | 1 | 0 | 0 |
| 3.0 | 1 | 0 | 4 | 0 | 0 | 1 | 0 |

Each value represents the number of subjects identifying each particular drug/dose as being from a particular drug class.

In contrast, naloxone [$F(3,15)=6.0$, $P=.01$] and butorphanol [$F(3,15)=4.5$, $P=.02$] produced significant increases in ratings of 'like naloxone,' whereas nalbuphine did not [$F(3,15)=1.6$, $P=.2$; Fig. 2, middle left panel]. Naloxone [$F(3,15)=11.6$, $P<.001$], butorphanol [$F(3,15)=7.4$, $P=.003$], and nalbuphine [$F(3,15)=4.8$, $P=.02$] each produced dose-related decreases in ratings of 'like placebo' (Fig. 2, middle right panel). No other VAS ratings showed a main effect of dose for any compound.

On the adjective ratings, naloxone [$F(3,15)=3.8$, $P=.03$] and butorphanol [$F(3,15)=5.3$, $P=.01$] produced significant dose-related increases in ratings on the opiate antagonist subscale, whereas nalbuphine [$F(3,15)=2.5$, $P=.1$] did not (Fig. 2, bottom left panel). On the opiate agonist subscale, neither naloxone [$F(3,15)=0.3$, $P=.8$] nor nalbuphine [$F(3,15)=2.1$, $P=.14$] significantly altered ratings; however, butorphanol [$F(3,15)=3.8$, $P=.03$] produced an increase in ratings at the lowest dose tested and a progressive decrease in ratings at higher doses (Fig. 2, bottom right panel). Ratings on the agonist/antagonist subscale showed no main effect of dose for any compound.

Results of the pharmacological drug class questionnaire during testing are shown in Table 1. As the dose of naloxone increased, the compound was identified more often as an opioid antagonist and less often as placebo or some other compound. Butorphanol produced a variety of identifications at the lowest dose, primarily placebo identifications at the middle dose and primarily opioid antagonist identifications at the highest dose. Nalbuphine was identified most often as an opioid antagonist at the two highest doses tested.

Physiological measures did not show a main effect of dose for any of the compounds tested except for heart rate and temperature. Heart rate decreased at the lowest and highest dose of naloxone relative to placebo and the middle naloxone dose [$F(3,15)=6.4$, $P=.005$]. Temperature decreased slightly at the higher doses relative to lower doses of butorphanol [$F(3,15)=4.4$, $P=.04$; data not shown].

### 3.5. Correlation between self-reports and discrimination performance during testing

Significant correlations between self-reports and naloxone-appropriate responding are shown in Table 2. For naloxone, naloxone-appropriate responding was positively associated with ARCI ratings on the LSD scale, VAS ratings of bad effects, and VAS ratings of 'like naloxone.' Increases in naloxone-appropriate responding were associated with decreases in VAS ratings of 'like placebo.'

For butorphanol, naloxone-appropriate responding was positively associated with ARCI ratings on the PCAG subscale, VAS ratings of bad effects, and VAS ratings of

Table 2
Significant correlations between self-report ratings and naloxone-appropriate responding for naloxone, butorphanol, and nalbuphine

| Measures | Naloxone | Butorphanol | Nalbuphine |
|---|---|---|---|
| *ARCI* | | | |
| A | | | |
| BG | | | |
| LSD | +.34 | | +.29 |
| MBG | | | |
| PCAG | | +.30 | |
| *VAS* | | | |
| Any drug effect | | | |
| Good | | | |
| Bad | +.41 | +.35 | +.52 |
| High | | | |
| Liking | | | |
| Similar to naloxone | +.87 | +.85 | +.82 |
| Similar to placebo | −.82 | −.57 | −.51 |
| Similar to novel | | −.32 | −.37 |
| *Adjective rating* | | | |
| Opiate antagonist | | | +.30 |
| Opiate agonist | | | −.39 |
| Agonist/antagonist | | | |

Each value represents a significant Pearson $r$ correlation ($P<.05$). Positive and negative correlations are represented by "+" and "−," respectively.

Table 3
Significant correlations between self-report ratings and novel-appropriate responding for butorphanol and nalbuphine

| Measures | Butorphanol | Nalbuphine |
|---|---|---|
| *ARCI* | | |
| A | +.31 | +.33 |
| BG | +.33 | +.35 |
| LSD | | |
| MBG | | |
| PCAG | | |
| *VAS* | | |
| Any drug effect | | |
| Good | | |
| Bad | | |
| High | | |
| Liking | | |
| Similar to naloxone | | −.42 |
| Similar to placebo | −.50 | |
| Similar to novel | +.81 | +.87 |
| *Adjective rating* | | |
| Opiate antagonist | | |
| Opiate agonist | | |
| Agonist/antagonist | | |

Each value represents a significant Pearson $r$ correlation ($P < .05$). Positive and negative correlations are represented by "+" and "−," respectively.

'like naloxone.' Increases in naloxone-appropriate responding were associated with decreases in VAS ratings of 'like placebo' and 'like novel.'

For nalbuphine, naloxone-appropriate responding was positively associated with ARCI ratings on the LSD subscale, VAS ratings of bad effects, VAS ratings of 'like naloxone,' and ratings on the opioid antagonist subscale. Naloxone-appropriate responding occasioned by nalbuphine was negatively associated with VAS ratings of 'like placebo,' VAS ratings of 'like novel,' and ratings on the opioid agonist subscale.

Significant correlations between self-reports and 'novel'-appropriate responding are shown in Table 3. 'Novel'-appropriate responding occasioned by naloxone only occurred in one subject at one dose of naloxone and so was not examined in this way. For butorphanol, increases in 'novel'-appropriate responding were associated with increases in ARCI ratings on the A and BG subscales, decreases in VAS ratings of 'like placebo,' and increases in VAS ratings of 'like novel.'

For nalbuphine, increases in 'novel'-appropriate responding were also associated with increases in ARCI ratings on the A and BG subscales, and in VAS ratings of 'like novel.' 'Novel'-appropriate responding was associated with decreases in VAS ratings of 'like naloxone.'

## 4. Discussion

The training dose of naloxone was discriminable from placebo, produced antagonist-like self-report ratings, and occasioned dose-related increases in naloxone-appropriate responding, with little or no 'novel'-appropriate responding. These results replicate previous work in our laboratory (Oliveto et al., 1998b), as well as in other studies (Preston et al., 1987, 1990). That the training conditions themselves did not show significant differences in ratings on the opiate antagonist subscale may be due to the fact that subjects who may have been more sensitive to the withdrawal-producing effects of the naloxone training dose quit the study; thus, their responses were not represented here. Nevertheless, these findings add further evidence that a low dose of naloxone can maintain stimulus control over discriminative behavior in opioid-dependent humans.

The naloxone stimulus generalized only partially to butorphanol and nalbuphine, suggesting that while butorphanol and nalbuphine each share discriminative-stimulus effects in common with naloxone, the effects are not identical. This is also indicated by the fact that these test compounds produced 'novel'-appropriate responding, suggesting that effects similar to neither naloxone nor placebo were also discerned. These results are consistent with the partial agonist activity of butorphanol (e.g., Pircio et al., 1976) and nalbuphine (e.g., Lee et al., 1997; Walker et al., 1999; Young et al., 1992), as opposed to the purely opioid antagonist activity of naloxone at the mu opioid receptor (e.g., Morgan and Picker, 1998; Oliveto et al., 1991; Preston and Jasinski, 1991), and suggest that the instructed novel-response procedure does enhance the pharmacological specificity and selectivity of the naloxone and placebo training conditions. These findings, together with a previous study in our laboratory (Oliveto et al., 1998b), extend previous work demonstrating greater pharmacological specificity and selectivity of benzodiazepine stimuli with this procedure (e.g., Bickel et al., 1993; Smith and Bickel, 1999a,b) to another drug class, namely opioid antagonists.

It should be noted, however, that one subject (S5) generated much of the novel-appropriate responding occasioned by the test compounds. This subject was maintained on the lowest dose of methadone (30 mg/day), which may have resulted in his being less opiate dependent and, thus, less sensitive to the withdrawal effects produced by naloxone. However, this subject also had the greatest increases in opiate antagonist-like ratings compared to the other participants (see Fig. 2), suggesting that this may not have been the case. Given that naloxone generated the most 'novel'-appropriate responding in this subject, S5 may simply have had a bias toward the novel option. Nevertheless, even if his discrimination data were removed, nalbuphine, if not butorphanol, would still show partial generalization to the naloxone stimulus.

Although the naloxone stimulus generalized partially to these mixed-action opioid agonist/antagonists in the present study under the novel-response procedure, it generalized fully under a naloxone–hydromorphone–saline discrimination procedure (Preston et al., 1990), suggesting that the training conditions employed greatly influence

discriminative behavior. The importance of this has been demonstrated in other human discrimination studies (Jones et al., 1999; Preston and Bigelow, 1994; Preston et al., 1989a, 1992). For instance, the hydromorphone stimulus generalized fully to butorphanol and nalbuphine in nondependent subjects responding under a two-choice saline–hydromorphone discrimination procedure (Preston et al., 1992). Yet, butorphanol and nalbuphine produced butorphanol-, but not hydromorphone-, appropriate responding in nondependent subjects responding under a butorphanol–saline–hydromorphone discrimination procedure (Preston and Bigelow, 1994). In nondependent subjects trained to discriminate among hydromorphone, saline, and the mixed-action opioid agonist/antagonist pentazocine, butorphanol produced pentazocine-appropriate responding whereas nalbuphine produced a combination of hydromorphone- and pentazocine-appropriate responding (Preston et al., 1989a). These results suggest that, especially when drugs with multiple mechanisms of action are tested, training conditions are important determinants of discriminative behavior.

Besides the discrimination procedure employed, the main difference between the present study and that by Preston et al. (1990) was that participants in the present study were generally maintained on higher doses of methadone or LAAM than in the previous report. Given that naloxone has greater antagonist-like effects during higher maintenance doses of opioid agonists (Schuh et al., 1996), this situation would potentially enhance the antagonist activity of the opioids tested here. Thus, together, these studies illustrate that the training conditions employed influence the discriminative-stimulus effects of drugs in opioid-dependent subjects.

Despite the fact that naloxone occasioned discriminative behavior that differed from butorphanol and nalbuphine, only slight differences in self-reported effects occurred among these compounds, demonstrating opioid antagonist-like self-reported effects in opioid-dependent individuals. These self-report results are generally consistent with previous reports in opioid-dependent individuals (e.g., Preston et al., 1988, 1989b, 1990) and suggest that self-reports by themselves may not necessarily be useful in differentiating mixed-action opioids from opioid antagonists in these participants. However, butorphanol and nalbuphine did not significantly increase ratings of mixed-action opioid effects on the adjective ratings scale, a result inconsistent with that reported by Preston et al. (1990). The reason for this difference is unclear, but may reflect the fact that self-report behavior, in contrast to discriminative behavior, is not explicitly trained and, therefore, subject to much greater variability.

Nevertheless, although naloxone-appropriate responding was associated with changes in similar self-reports across the three compounds, 'novel'-appropriate responding occasioned by butorphanol or nalbuphine was associated with increases in self-report ratings of stimulant-like effects, suggesting that these compounds may also produce stimulant-like effects that are not shared by naloxone. In a previous study examining the discriminative-stimulus effects of cocaine in humans, caffeine was differentiated from cocaine and D-amphetamine only when the relationship between discriminative behavior and self-reports were determined (Oliveto et al., 1998a). The present results demonstrate the utility of the instructed novel response discrimination procedure to differentiate compounds based on not only their discriminative-stimulus effects, but also the relationship between their discriminative-stimulus and self-reported effects.

It should be noted that there were methodological differences within this study, in that two study completers participated on an inpatient basis where they completed the tasks via pen and paper, whereas the other four completers participated on an outpatient basis where they completed tasks via computer. Whether these differences accounted for differences in subject responses is unclear. Human drug discrimination studies have employed both paper and pen (e.g., Chait et al., 1984; Johanson, 1991a,b; Oliveto et al., 1995, 1998b) and computers (e.g., Bickel et al., 1989, 1993; Oliveto et al., 1994, 1997, 1998a; Preston et al., 1989a, 1990; Preston & Bigelow, 1994) for data acquisition. Although both methods are not typically used within one study, similar findings have been reported across studies that employed different data acquisition strategies using caffeine (Oliveto et al., 1992, 1993, 1997), naloxone (e.g., Gonsai et al., in press; Oliveto et al., 1998b) or cocaine (Oliveto et al., 1995, 1998a) as the active training conditions. In addition, a visual inspection of the data in the present study did not indicate any consistent pattern based on inpatient or outpatient participation (see Figs. 1 and 2). That the self-report findings of this study are generally consistent with other reports (e.g., Oliveto et al., 1998b; Preston et al., 1988, 1989b, 1990) suggests that these methodological differences did not substantially affect subject responses.

In summary, the discriminative-stimulus effects of the mixed-action opioid agonist/antagonists butorphanol and nalbuphine were differentiated from naloxone under the novel-response naloxone discrimination procedure in opioid-dependent humans. This occurred despite generally similar self-reported effects; nevertheless, when the relationship between discriminative behavior and self-reports were examined, both butorphanol and nalbuphine showed an association between 'novel'-appropriate responding and stimulant-like self-reports, suggesting that compounds can also be differentiated by examining this relationship. These findings add further evidence that the novel-response discrimination procedure enhances the pharmacological specificity and selectivity of the training conditions.

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