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Effects of Flupenthixol and Quadazocine on Self-Administration of Speedball Combinations of Cocaine and Heroin by Rhesus Monkeys

Nancy K. Mello, Ph.D. and S. Stevens Negus, Ph.D.

The simultaneous i.v. administration of heroin and cocaine, called "speedball," is often reported clinically, and identification of effective pharmacotherapies for polydrug abuse is a continuing challenge. This study compared the effects of treatment using combinations *of dopamine and opioid antagonists with each antagonist alone on speedball self-administration by rhesus monkeys. Speedballs (0.01 mg/kg/inj cocaine and 0.0032 mg/kg/inj heroin) and food (1 g banana pellets) were available in four daily sessions on a second-order schedule of reinforcement [FR4 (VR16:S)]. Monkeys were treated for 10 days with saline or ascending 1:10 dose combinations of the dopamine antagonist flupenthixol and the opioid antagonist quadazocine. The combination of flupenthixol (0.018 mg/kg/day) + quadazocine (0.18 mg/kg/day) significantly reduced speedball self-administration in comparison to the saline treatment baseline ($p < .05$), whereas, the same doses of each antagonist alone had no significant effect on speedball-maintained responding. Treatment with 0.018 mg/kg/day flupenthixol + 0.18 mg/kg/day quadazocine produced a 3-fold rightward shift in the speedball (3:1 cocaine-heroin combination) dose-effect curve. Food-maintained responding was similar during treatment with saline and with flupenthixol + quadazocine combinations. These findings suggest that medication mixtures designed to target both the stimulant and opioid component of the speedball combination, may be an effective approach to polydrug abuse treatment.* ***[Neuropsychopharmacology 21:575–588, 1999]*** *© 1999 American College of Neuropsychopharmacology. Published by Elsevier Science Inc.*

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It is increasingly recognized that drug abusers tend to use multiple drugs rather than a single drug (NIDA, 1998). Polydrug abuse often involves the concurrent abuse of cocaine and heroin, and both cocaine and continued opiate abuse have been reported in methadone-maintained patients (Condelli et al. 1991; Kosten et al. 1989b; Schottenfeld et al. 1993, 1997). One common form of polydrug abuse is called the speedball, which usually refers to the simultaneous intravenous administration of cocaine and heroin (NIDA, 1998; Schütz et al. 1994). Currently approved pharmacotherapies for opiate abuse have been only moderately effective in reducing polydrug abuse, and there is no consistently effective pharmacotherapy for either abuse of cocaine alone or combinations of cocaine and heroin "speedball" (Mendelson and Mello 1996).

Preclinical evaluation of medications for reducing

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polydrug abuse has been greatly facilitated by the development of animal models of speedball self-administration (Hemby et al. 1996, 1999; Mello et al. 1995; Mello and Negus 1998; Rowlett et al. 1998; Rowlett and Woolverton 1997) and speedball discrimination (Negus et al. 1998a). Combinations of cocaine and heroin produce robust reinforcing and discriminative stimulus effects in these animal models, and cocaine and heroin may enhance each other's reinforcing and discriminative stimulus effects under some conditions (Negus et al. 1998a; Rowlett and Woolverton 1997).

Similarly, neurochemical evidence suggests that self-administration of cocaine and heroin in combination has synergistic effects on extracellular dopamine release at the nucleus accumbens in rats (Hemby et al. 1999). Dopamine levels measured by microdialysis remained at baseline levels during heroin self-administration, increased by 400% during cocaine self-administration, and increased by 1000% during speedball self-administration, even though cocaine levels measured in dialysate samples were equivalent during cocaine and speedball self-administration (Hemby et al. 1999). Interestingly, however, the synergistic increases in dopamine levels during speedball self-administration were not accompanied by differences in operant responding maintained by cocaine and heroin alone and in combination (Hemby et al. 1999). Moreover, several other studies found that co-administration of cocaine and opioids produced discrimination stimulus and reinforcing effects that were additive or less than additive and resembled the effects of cocaine or heroin alone (Mello et al. 1995; Negus et al. 1998b; Lamas et al. 1998; Rowlett and Spealman 1998).

Taken together, these findings are consistent with behavioral reports that the abuse-related effects of cocaine and heroin appear to be relatively independent of each other, and speedball combinations usually produce a compound drug stimulus that includes aspects of both component drugs (Foltin and Fischman 1992; Mello et al. 1995; Negus et al. 1998a). These findings also suggest that successful treatment of speedball abuse may require pharmacotherapies that are directed at *both* the stimulant and opioid components. For example, in polydrug abuse involving both cocaine and heroin, the combination of a dopamine antagonist and an opioid antagonist might be more effective than treatment with either type of medication alone. However, there is a paucity of information about the effects of combinations of treatment medications on polydrug abuse in animal models or clinical studies. Only a few preclinical studies have examined the effects of single medications on speedball self-administration (Hemby et al. 1996; Mello and Negus 1998; Rowlett et al. 1998).

One of these studies examined the effectiveness of *chronic* treatment with the opioid mixed agonist-antagonist buprenorphine in reducing speedball self-administration by rhesus monkeys (Mello and Negus 1998). Buprenorphine was selected for study because it has been shown to reduce heroin abuse in inpatient and outpatient clinical studies (Johnson et al. 1992; Mello and Mendelson 1980), and to reduce cocaine abuse by persons dually dependent on cocaine and opioids (Gastfriend et al. 1993; Kosten et al. 1989a, b; Schottenfeld et al. 1993). In rhesus monkeys, *chronic* treatment with buprenorphine selectively reduced self-administration of cocaine alone (Mello et al. 1989, 1990), heroin alone, and some speedball combinations (Mello et al. 1983; Mello and Negus 1998). However, the effectiveness of buprenorphine varied as a function of the unit dose of cocaine in the speedball. Buprenorphine (0.237 mg/kg/day) was most effective when heroin was combined with a low (0.001 mg/kg/inj) or a high (0.10 mg/kg/inj) unit dose of cocaine on the ascending or descending limb of the cocaine dose-effect curve. These findings are consistent with our earlier reports that buprenorphine (0.237–0.70 mg/kg/day) reduced self-administration of relatively high unit doses of cocaine (0.05 and 0.10 mg/kg/inj) by rhesus monkeys (Mello et al. 1989, 1990, 1992, 1993a, b). Buprenorphine was least effective when heroin was combined with an intermediate unit dose of cocaine (0.01 mg/kg/inj) that was at the peak of the cocaine alone dose-effect curve (Mello and Negus 1998).

The effects of *acute* treatment with the opioid antagonist naltrexone on cocaine (100 μg/kg/inj), heroin (6.4 or 13 μg/kg/inj), or speedball self-administration by rhesus monkeys was studied by Rowlett and co-workers (Rowlett et al. 1998). Naltrexone had no effect on cocaine self-administration (Rowlett et al. 1998), a finding that was consistent with earlier reports in rhesus monkeys (Mello et al. 1993b, 1990) and in rats (Corrigall and Coen 1991). Naltrexone (3.2–1600 μg/kg, i.m.) dose-dependently decreased self-administration of heroin alone and speedball combinations, but these effects were surmounted by increasing doses of heroin (Rowlett et al. 1998). The effects of naltrexone alone and a dopamine antagonist alone on self-administration of speedball combinations of cocaine and heroin were examined in rats (Hemby et al. 1996). Naltrexone (3.0–30 mg/kg) antagonized the rate-suppressant effects of the cocaine and heroin speedball combination, but the resulting speedball dose-effect curve was not significantly different from that for cocaine alone (Hemby et al. 1996).

Acute administration of the dopamine D_2 receptor antagonist eticlopride (0.03–0.3 mg/kg) resulted in a downward shift in the speedball dose-effect curve that was more pronounced at high (18 μg) than low (5.4 μg) doses of heroin in combination with cocaine (Hemby et al. 1996). The authors concluded that antagonism of both dopamine and opioid receptors may be necessary to significantly reduce speedball self-administration (Hemby et al. 1996).

In substance abuse treatment, there has been relatively little use of drug combinations to increase the effectiveness of pharmacotherapies. Rather, the primary emphasis has been on designing drug combinations to decrease the risk for illicit diversion of the treatment medications. For example, several investigators have examined the feasibility of combining naloxone with either buprenorphine or methadone to prevent intravenous abuse of these opioid agonist medications (Fudala et al. 1998; Loimer et al. 1991; Mendelson et al. 1996, 1997, 1999; Preston et al. 1989; Weinhold et al. 1992). Naloxone has poor bioavailability by oral and sublingual routes of administration and much higher bioavailability by intravenous route. Consequently, appropriate doses of naloxone have little impact on the therapeutic effects of sublingual buprenorphine or oral methadone. However, they are sufficient to antagonize the effects of these medications after intravenous administration and precipitate withdrawal signs in opioid-dependent persons.

The purpose of the present study was to examine the effects of chronic treatment with the non-selective dopamine antagonist flupenthixol and the opioid antagonist quadazocine alone and in combination on speedball self-administration by rhesus monkeys. The potential ability of this antagonist combination to reduce speedball self-administration was suggested by our recent study of speedball discrimination (Negus et al. 1998a). Combined pretreatment with flupenthixol and quadazocine dose-dependently antagonized the discriminative stimulus effects of a speedball more effectively than pretreatment with either antagonist alone (Negus et al. 1998a). We now report that a combination of flupenthixol and quadazocine reduced self-administration of a speedball combination of 0.01 mg/kg/inj cocaine + 0.0032 mg/kg/inj heroin more effectively than the same doses of either quadazocine or flupenthixol alone. Moreover, a combination of flupenthixol and quadazocine produced a rightward shift in the speedball self-administration dose-effect curve. Our results suggest that medication combinations may be a useful approach to enhancing treatment efficacy in the pharmacotherapeutic management of polydrug abuse.

METHODS

Subjects

Subjects were one male (606.5) and three female (R800, 89B211, and 89B157) rhesus monkeys *(Macaca mulatta)* that weighed between 6 and 12 kg. All monkeys had self-administered cocaine for at least one year before cocaine-heroin speedball combinations were made available. Speedball-maintained responding was studied for at least six months before these studies began. Monkeys were maintained at *ad libitum* weight and given multiple vitamins, fresh fruit, and vegetables and Lab Diet Jumbo Monkey Biscuits (PMI Feeds Inc., St. Louis, MO) to supplement a banana pellet diet. Food supplements were given between 5:00 and 5:30 p.m. Water was continuously available. A 12-hr light-dark cycle was in effect (lights on from 7 a.m. to 7 p.m.), and the experimental chamber was dark during food and drug self-administration sessions.

Animal maintenance and research were conducted in accordance with the guidelines provided by the Institute of Laboratory Animal Resources (ILAR-NRC 1996). The facility is licensed by the US Department of Agriculture, and protocols were approved by the Institutional Animal Care and Use Committee. The health of the monkeys was periodically monitored by consultant veterinarians trained in primate medicine. Operant food and drug acquisition procedures provided an opportunity for enrichment and for monkeys to manipulate their environment (Line 1987). Monkeys had visual, auditory and olfactory contact with other monkeys throughout the study.

Surgical Procedures

Double lumen Silicone® rubber catheters (I.D. 0.028 in, O.D. 0.088 in) were surgically implanted in the internal jugular or femoral vein and exited in the mid-scapular region. All surgical procedures were performed under aseptic conditions. Monkeys were initially sedated with ketamine (5–10 mg/kg, i.m.), and anesthesia was induced with sodium thiopental (10 mg/kg, i.v.). Atropine (0.05 mg/kg, s.c. or i.m.) was administered to reduce salivation. An endotracheal tube was inserted and anesthesia was maintained with isofluorane (1–2% mixed with oxygen). After surgery, monkeys were given procaine penicillin G at 20,000 units/kg, i.m. or cephalexin 20 mg/kg, p.o. twice daily for five days. An analgesic dose of buprenorphine 0.032 mg/kg, i.m. was administered twice daily for three days.

The intravenous catheter was protected by a tether system consisting of a custom-fitted nylon vest connected to a flexible stainless-steel cable and fluid swivel (Lomir Biomedical, Inc., Malone, NY). This flexible tether system permitted monkeys to move freely. Catheter patency was evaluated periodically by administration of either a short-acting barbiturate, methohexital sodium (3 mg/kg, i.v.), or ketamine (5 mg/kg) through the catheter lumen. If muscle tone decreased within 10 sec after drug administration, the catheter was considered patent.

Behavioral Procedures and Apparatus

Monkeys were housed individually in stainless steel chambers (64 × 64 × 79 cm) equipped with a custom-

designed operant response panel (28 × 28 cm), a banana pellet dispenser (Model G5210; Gerbrands, Arlington, MA), and two syringe pumps (Model 981210; Harvard Apparatus, Inc., South Natick, MA), one for each lumen of the double-lumen catheter. During food self-administration sessions, the response key on the operant panel was illuminated with a red light, and responding under an FR4 (VR16:S) schedule resulted in presentation of a 1 g banana pellet (P.J. Noyes Co., Lancaster, NH). During drug self-administration sessions, the response key was illuminated with a green light, and responding under an FR4 (VR16:S) schedule resulted in delivery of 0.1 ml of saline or a drug solution over 0.9 sec through one lumen of the double-lumen catheter. A 10-sec time-out followed delivery of each drug or saline injection or food pellet. Schedules of reinforcement were programmed by custom-designed software and run on Apple II GS microcomputers. Additional details of this apparatus have been described previously (Mello et al. 1990).

Four food sessions and four drug sessions were conducted during each experimental day. Food sessions began at 6 a.m., 11 a.m., 3 p.m., and 7 p.m., and drug sessions began at 7 a.m., 12 noon, 4 p.m., and 8 p.m. At all other times, responding had no scheduled consequences. The experimental room was dark during all food and drug sessions. Each food and drug session lasted for one hour or until 25 food pellets or 20 injections had been delivered. Monkeys could earn a maximum of 100 food pellets per day and 80 injections per day.

Monkeys were observed at least twice every day. Any changes in general activity and responsivity to the presentation of preferred foods were noted. The observer was not blind to the treatment condition.

Drug Self-Administration Procedures

All monkeys were trained to self-administer cocaine (0.032 mg/kg/inj, i.v.) and subsequently given access to speedball combinations of cocaine and heroin. During speedball self-administration, cocaine and heroin were prepared in a single solution and delivered through one catheter lumen as in our previous studies (Mello and Negus 1998; Mello et al. 1995). The simultaneous administration of cocaine and heroin combinations was designed to simulate one type of speedball self-administration by humans (Schütz et al. 1994).

The speedball combination selected for our initial studies consisted of 0.01 mg/kg/inj cocaine in combination with 0.0032 mg/kg/inj heroin. In our previous studies, these unit doses of cocaine alone and heroin alone each maintained high rates of drug self-administration at or near the peak of the cocaine and heroin dose-effect curves (Mello and Negus 1998; Mello et al. 1995). Moreover, this reinforcing speedball combination was minimally affected by 10 days of treatment with buprenorphine (0.237 mg/kg/day) alone (Mello and Negus 1998). In subsequent studies designed to examine the complete speedball dose-effect curve, the ratio of cocaine to heroin was maintained at 3:1, and speedball combinations were examined across a dose range of 0.001 mg/kg/inj cocaine + 0.00032 mg/kg/inj heroin to 0.032 mg/kg/inj cocaine + 0.01 mg/kg/inj heroin. Our rationale for selecting a 3:1 ratio of cocaine to heroin was based on preliminary studies in which unit doses of 0.01 mg/kg/inj cocaine and 0.0032 mg/kg/inj heroin alone were the lowest doses that reliably maintained drug self-administration in all monkeys. Thus, cocaine was approximately 3-fold less potent than heroin as a reinforcer in rhesus monkeys.

Flupenthixol, Quadazocine, and Saline Administration Procedures

Saline, flupenthixol, and quadazocine alone and in combination were administered by slow infusion (0.10 ml/min) in a volume of 5 ml through one lumen of the double lumen catheter from 9:30 to 10:20 each morning. These procedures were identical to those used in our previous studies of buprenorphine's effects on cocaine and speedball self-administration (Mello and Negus 1998). For the remaining 23 hrs of each experimental day, 0.10 ml saline was delivered every 20 min to maintain catheter patency.

Sequence of Flupenthixol + Quadazocine Treatment Conditions

Flupenthixol and quadazocine were selected for study because flupenthixol antagonizes the reinforcing and discriminative stimulus effects of cocaine alone and quadazocine antagonizes the reinforcing and discriminative stimulus effects of *mu* opioid agonists alone (Bertalmio and Woods 1989; Negus et al. 1996; see Mello and Negus 1996 for review). The effects of daily treatment with saline or quadazocine and flupenthixol alone or in combination on speedball- and food-maintained responding were studied. Each treatment condition was studied chronically for 10 days to evaluate the stability of any effects observed (see Mello and Negus 1996 for discussion). At the end of each treatment condition, monkeys were returned to saline control treatment and maintenance dose of cocaine for at least four days and until responding for cocaine and food returned to baseline levels. Cocaine (0.032 mg/kg/inj) was used as the maintenance drug to ensure high baseline rates of drug-maintained responding before each speedball substitution and treatment condition. This saline treatment interval was designed to prevent any effects of one treatment condition from influencing the effects of a subsequent treatment condition. Speedball combinations were substituted for the maintenance dose of cocaine in an irregular order.

Experiment 1. In this experiment, the effects of ascending doses of flupenthixol + quadazocine on food- and speedball-maintained responding were examined in four monkeys. Flupenthixol + quadazocine were administered in combinations consisting of a 1:10 ratio of flupenthixol to quadazocine (0.0032 mg/kg/day flupenthixol + 0.032 mg/kg quadazocine to 0.018 mg/kg/day flupenthixol + 0.18 mg/kg quadazocine). These relative and absolute doses of flupenthixol + quadazocine were based on previous studies that examined the potency of flupenthixol in blocking the effects of cocaine self-administration (Negus et al. 1996) and the potency of quadazocine in antagonizing the effects of heroin and other *mu* agonists (Negus et al. 1993; Negus, unpublished observations).

Experiment 2. In this experiment, a complete speedball dose-effect curve was determined. The speedball dose-effect curve consisted of the following cocaine and heroin combinations: 0.001 mg/kg/inj cocaine + 0.00032 mg/kg/inj heroin; 0.0032 mg/kg/inj cocaine + 0.001 mg/kg/inj heroin; 0.01 mg/kg/inj cocaine + 0.0032 mg/kg/inj heroin; 0.032 mg/kg/inj cocaine + 0.01 mg/kg/inj heroin. Each speedball dose combination was studied for 10 days during saline treatment. The effects of treatment with one dose combination of flupenthixol (0.018 mg/kg/day) + quadazocine (0.18 mg/kg/day) on the speedball dose-effect curve were then studied in three monkeys. Each of four speedball dose combinations (0.0032 mg/kg/inj cocaine + 0.001 mg/kg/inj heroin; 0.01 mg/kg/inj cocaine + 0.0032 mg/kg/inj heroin; 0.032 mg/kg/inj cocaine + 0.01 mg/kg/inj heroin; 0.01 mg/kg/inj cocaine + 0.032 mg/kg/inj heroin) was available for ten days during flupenthixol + quadazocine treatment.

Drugs

Cocaine HCl and heroin (3,6-diacetylmorphine HCl) were obtained in crystalline form from the National Institute on Drug Abuse, NIH. The purity of cocaine and heroin was certified by Research Triangle Institute, Research Triangle Park, North Carolina, to be greater than 98%. Flupenthixol HCl was acquired from Research Biochemicals International, Natick, MA. Quadazocine methanesulfonate was provided by Sanofi Pharmaceuticals, Inc., Malvern, PA. All drugs were dissolved in sterile saline or sterile water, filter-sterilized using a 0.22 micron Millipore filter, and stored in sterile, pyrogen-free vials. All doses are expressed for the salt forms of the drugs described above.

Data Analysis

The dependent variables were the number of saline or speedball injections per day and the number of food pellets per day. Statistical analyses were based on the mean (±S.E.M.) number of injections and food pellets per day delivered over the entire 10 days of each treatment. Changes in drug- and food-maintained responding during treatment with flupenthixol + quadazocine administered alone or in combination were statistically compared with the saline treatment baseline with an ANOVA for repeated measures and Contrast tests or Fishers post-hoc tests. Huynh-Feldt Epsilon factors were used to adjust for degrees of freedom of within-group means (Super ANOVA Software Manual; Abacus Concepts, Inc., Berkeley, CA, 1989). In addition, the mean numbers of injections and food pellets delivered each day during a 10-day medication or saline treatment condition are shown graphically for each of three speedball combinations. Daily patterns of speedball- and food-maintained responding were compared with ANOVA for repeated measures during saline treatment and flupenthixol + quadazocine treatment.

RESULTS

Experiment 1: Effects of Flupenthixol + Quadazocine on Speedball- and Food-Maintained Responding

Figure 1 shows the effects of 10 days of treatment with saline, flupenthixol + quadazocine combinations, as well as flupenthixol and quadazocine alone on speedball- (row 1) and food- maintained responding (row 2). During saline baseline treatment, monkeys self-administered an average of 65 ± 1.9 (mean ± SE) speedball injections and 60 ± 2.2 (mean ± SE) food pellets. Treatment with the first two flupenthixol + quadazocine combinations produced a non-significant increase in speedball self-administration and had minimal effects on food-maintained responding. When 0.018 mg/kg/day flupenthixol was given in combination with 0.18 mg/kg/day quadazocine, speedball self-administration decreased significantly in comparison to the saline treatment baseline ($p < .01$), and food-maintained responding remained at baseline levels. In contrast, when the same doses of flupenthixol alone (0.018 mg/kg/day) or quadazocine alone (0.18 mg/kg/day) were administered, speedball self-administration did not change significantly from saline treatment baseline levels. Moreover, speedball-maintained responding was significantly higher during treatment with quadazocine alone ($p < .01$) and flupenthixol alone ($p < .03$) than during combined quadazocine and flupenthixol treatment at the highest dose. Food-maintained responding decreased slightly after flupenthixol alone and increased slightly after quadazocine alone.

Figure 2 shows the average number of speedball injections and food pellets delivered during each day of

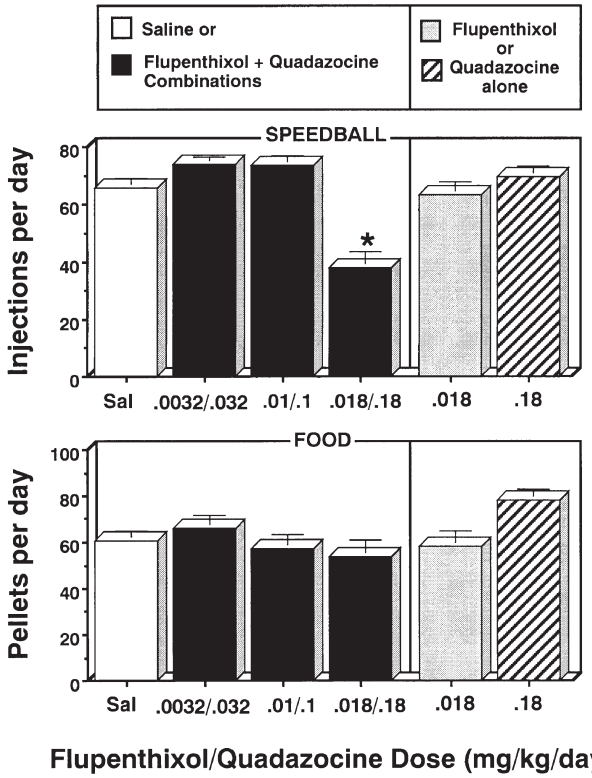

Figure 1. Effects of saline, ascending doses of flupenthixol + quadazocine combinations and flupenthixol + quadazocine alone on speedball- and food-maintained responding. Speedball- and food-maintained responding are shown as open rectangles during saline treatment, as closed rectangles during treatment with flupenthixol + quadazocine combinations, and as a grey rectangle during treatment with flupenthixol alone, and a striped rectangle during treatment with quadazocine alone. Saline and doses of flupenthixol + quadazocine (mg/kg/day) are shown on the abscissa. The average number of speedball injections per day (row 1) or food pellets per day (row 2) are shown on the left ordinate. Speedballs consisted of a unit dose of cocaine (0.01 mg/kg/inj) and heroin (0.0032 mg/kg/inj) in combination. Each data point represents the average number of injections or food pellets ($\bar{x} \pm$ S.E.) during 10 consecutive days of saline or drug treatment in a group of four monkeys. The asterisk indicates a significant change from the saline treatment baseline ($p < .01$).

the 10-day treatment with saline (row 1), flupenthixol alone (0.018 mg/kg/day) (row 2), quadazocine alone (0.18 mg/kg/day) (row 3), and with a combination of flupenthixol (0.018 mg/kg/day) + quadazocine (0.18 mg/kg/day) (row 4). Data are daily averages (mean ± SE) for a group of four monkeys. During treatment with flupenthixol alone, speedball-maintained responding did not differ from saline control treatment conditions on any day. Food-maintained responding tended to decrease during flupenthixol treatment but was not significantly below the saline treatment baseline on any day (Figure 2, row 2). Speedball-maintained responding was slightly higher during treatment with quadazocine alone than during saline treatment, but these differences were not statistically significant on any day (Figure 2, row 3). Food-maintained responding was also higher during quadazocine treatment than during saline control treatment, but these differences were not statistically significant (Figure 2, row 3).

When flupenthixol + quadazocine were administered in combination, both speedball- and food-maintained responding decreased significantly below baseline on day 3 of treatment ($p < .05$) (Figure 2, row 4). Speedball-maintained responding remained significantly below baseline on days 4–6 of treatment ($p < .05$), then gradually returned to baseline levels on treatment days 7–10. Food-maintained responding was not significantly different from saline treatment baseline levels during days 1 and 2 and 4–10 of treatment with flupenthixol + quadazocine.

Chronic administration of flupenthixol and the highest doses of flupenthixol + quadazocine was associated with mild sedation in all four monkeys. However, these sedative effects (decreased locomotor activity and responsiveness to presentation of preferred foods) were transient and minimal sedation was observed after two or three days of treatment. No sedation was observed during treatment with quadazocine alone or lower doses of flupenthixol + quadazocine combinations (0.0032 mg/kg/day flupenthixol + 0.032 mg/kg/day quadazocine to 0.01 mg/kg/day flupenthixol + 0.10 mg/kg/day quadazocine).

Experiment 2: Effects of a Flupenthixol + Quadazocine Combination on the Speedball Dose-Effect Curve

Saline Treatment. Figure 3 shows the effects of treatment with saline or with the combination of 0.018 mg/kg/day flupenthixol + 0.18 mg/kg/day quadazocine on the speedball dose-effect curve (left panel) and concurrent food-maintained responding (right panel). When saline was available for self-administration, monkeys took an average of 21 ± 4 (mean ± SE) injections per day and 86 ± 6 (mean ± SE) food pellets per day. When a 3:1 cocaine/heroin speedball combination was available during saline control treatment, the speedball dose-effect curve had an inverted-U shape. The lowest speedball dose did not maintain significantly more responding than saline. However, speedball doses of 0.0032 mg/kg/inj cocaine + 0.001 mg/kg/inj heroin to 0.032 mg/kg/inj cocaine + 0.01 mg/kg/inj heroin each maintained significantly more responding than saline ($p < .05$–.001). A unit dose of 0.0032 mg/kg/inj cocaine + 0.001 mg/kg/inj heroin was at the peak of the speedball dose-effect curve and maintained 67 ± 3 (mean ± SE) speedball injections per day. Food-maintained responding decreased significantly below levels mea-

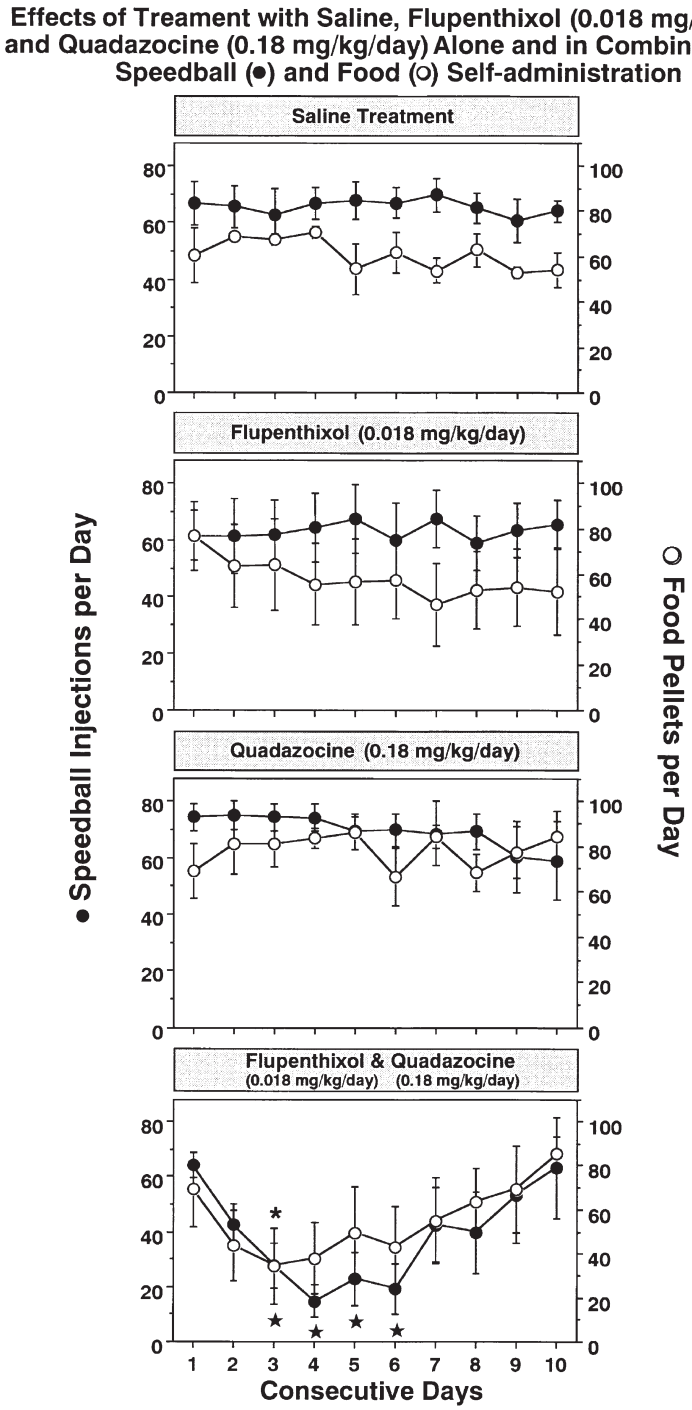

Figure 2. Effects of saline, flupenthixol alone, quadazocine alone or a flupenthixol + quadazocine combination on daily speedball- and food-maintained responding over 10 days of treatment. Consecutive days of treatment are shown on the abscissae. Speedball injections per day are shown on the left ordinate (closed circles) and food pellets per day are shown on the right ordinate (open circles). Speedballs consisted of a unit dose of cocaine (0.01 mg/kg/inj) and heroin (0.0032 mg/kg/inj) in combination. Food and speedball self-administration data ($\bar{x} \pm$ S.E.) are shown during 10 days of saline treatment (row 1), during flupenthixol treatment alone (row 2), during quadazocine treatment alone (row 3), and during combined flupenthixol + quadazocine treatment (row 4). Each data point is based on four monkeys. Stars indicate statistically significant changes in speedball self-administration from the saline treatment baseline (★ = $p < .05$). Asterisks indicate statistically significant changes in food self-administration from the saline treatment baseline (* = $p < .5$).

sured during saline self-administration at speedball doses of 0.01 mg/kg/inj cocaine + 0.0032 mg/kg/inj heroin and above ($p < .05$).

Flupenthixol + Quadazocine Treatment. Treatment with the flupenthixol + quadazocine combination produced an approximately 10-fold rightward shift in the peak of the speedball self-administration dose-effect curve and a 3-fold shift in the descending limb of the dose-effect curve. The two speedball unit doses that were at the peak of the dose-effect curve during saline treatment did not maintain significantly greater levels of self-administration than saline during flupenthixol + quadazocine treatment. Moreover, responding for these two speedball doses was significantly lower during flupenthixol + quadazocine treatment than during saline treatment ($p < .02$). A speedball dose of 0.032 mg/kg/inj cocaine and 0.01 mg/kg/inj heroin was at the peak

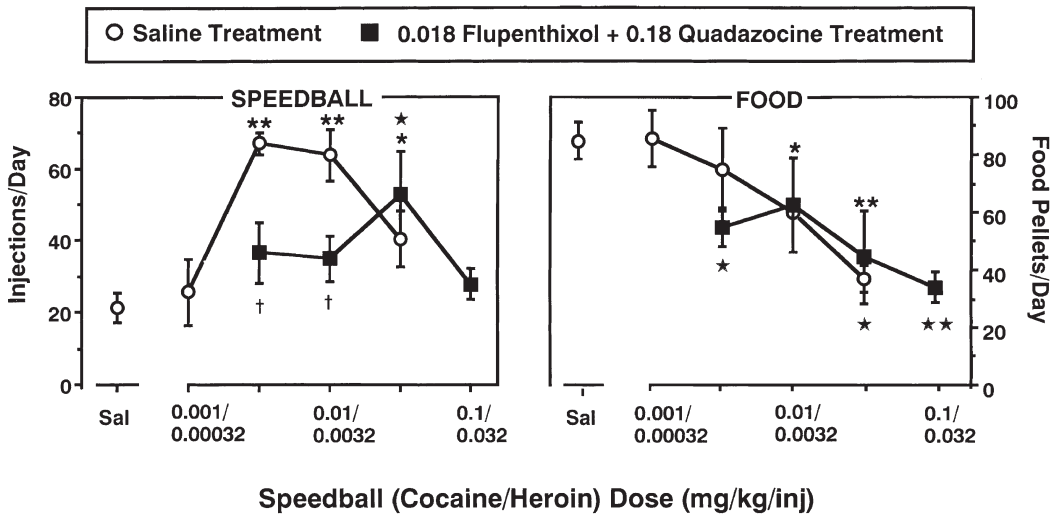

Figure 3. Effects of a quadazocine and flupenthixol combination on a speedball dose-effect curve. Dose-effect curves for cocaine (0.001–0.10 mg/kg/inj) in combination with heroin (0.00032–0.032 mg/kg/inj) are shown for a group of three monkeys (left panel). The unit doses of each cocaine and heroin combination are shown on the abscissa. Points above "Sal" show data from saline treatment sessions when saline was the solution available for self-administration. Self-administration of each cocaine-heroin combination during saline treatment (open circles) and during treatment with a flupenthixol (0.018 mg/kg/day) + quadazocine (0.18 mg/kg/day) combination (black squares) are shown on the left ordinate as injections per day. Each data point is the average of 10 days of speedball self-administration ($\bar{x} \pm$ S.E.M.). Food-maintained responding during saline self-administration (open circle), self-administration of cocaine and heroin combinations during saline treatment (open circles) and during quadazocine and flupenthixol treatment (black squares) is shown in the right panel. The number of banana pellets per day earned during each condition is shown on the right ordinate. The asterisks indicate a significant difference from "Sal" during saline treatment (* = $p < .05$; ** = $p < .01$). The stars indicate a significant difference from "Sal" during flupenthixol + quadazocine treatment (★ = $p < 0.05$; ★★ = $p < .01$). Daggers indicate that the number of speedball injections self-administered at the same speedball dose combinations were significantly different during saline treatment and flupenthixol + quadazocine treatment († = $p < .05$).

of the speedball dose-effect curve during flupenthixol + quadazocine treatment, and responding for this speedball dose was significantly higher than responding for saline. However, in contrast to saline control treatment, this speedball dose did not maintain higher levels of responding during flupenthixol + quadazocine reatment.

Levels of food-maintained responding during treatment with flupenthixol + quadazocine did not differ significantly from levels of food-maintained responding during saline treatment. Food-maintained responding during flupenthixol + quadazocine treatment was significantly below levels measured during the saline self-administration baseline ($p < .05$–.001) with one exception: food-maintained responding did not differ significantly from the saline self-administration baseline at a speedball dose of 0.01 mg/kg/inj cocaine and 0.0032 mg/kg/inj heroin.

Figure 4 shows daily patterns of speedball- and food-maintained responding during 10 days of treatment with saline (left column) and flupenthixol + quadazocine (right column). Responding maintained by the speedball dose that was at the peak of the dose-effect curve during saline treatment decreased significantly after one day of flupenthixol + quadazocine treatment ($p < .05$) (Figure 4, row 1). Speedball-maintained responding remained significantly below saline treatment levels during days 2–7 and day 10 of flupenthixol + quadazocine treatment. Food-maintained responding also decreased significantly for four days at the beginning of flupenthixol + quadazocine treatment ($p < .05$), then gradually returned towards baseline levels on days 5–10.

Daily levels of self-administration of the highest speedball dose (0.032 mg/kg/inj cocaine + 0.01 mg/kg/inj heroin) studied during both saline treatment and flupenthixol + quadazocine treatment are shown in Figure 4, row 2. During saline treatment, responding maintained by this high speedball dose was significantly lower than responding maintained by 0.0032 mg/kg/inj cocaine and 0.001 mg/kg/inj heroin ($p < .03$) (cf. rows 1 and 2, Figure 4). Food-maintained responding was also significantly lower during self-administration of the high speedball dose (0.032 mg/kg/inj cocaine + 0.01 mg/kg/inj heroin) than at the lower speedball dose (0.0032 mg/kg/inj cocaine + 0.001 mg/kg/inj heroin ($p < .05$). There was a tendency for food-

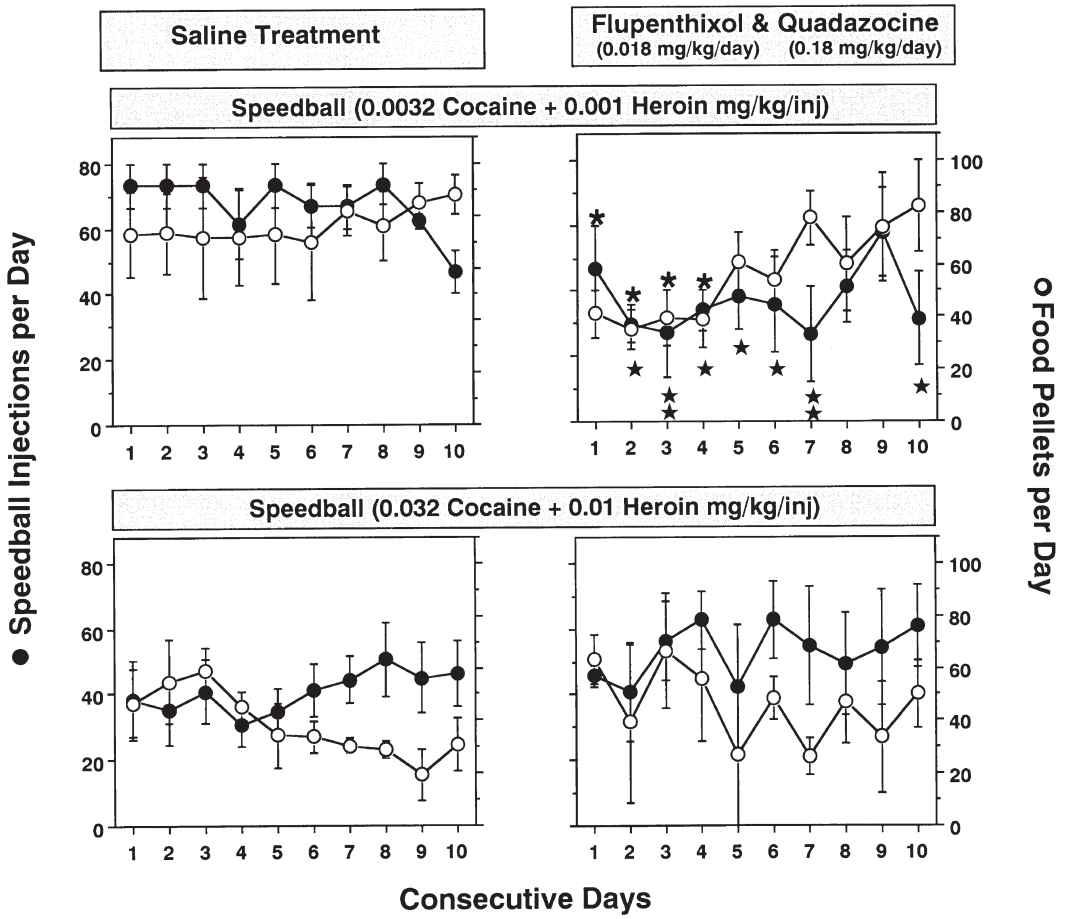

Figure 4. Effects of saline and a flupenthixol + quadazocine combination on daily speedball- and food-maintained responding over 10 days of treatment. Speedball- and food-maintained responding during 10 days of saline treatment is shown in the left column. Speedball- and food-maintained responding during flupenthixol (0.018 mg/kg/day) + quadazocine (0.18 mg/kg/day) treatment is shown in the right column. Consecutive days of treatment are shown on the abscissae. Speedball injections per day are shown on the left ordinate (closed circles) and food pellets per day are shown on the right ordinate (open circles). The unit doses of cocaine and heroin are shown in the grey box above each row. Each data point is based on three monkeys. Stars indicate statistically significant changes in speedball self-administration from the saline treatment baseline (★ = $p < .05$; ★★ = $p < .01$). Asterisks indicate statistically significant changes in food self-administration from the saline treatment baseline (* = $p < .05$; ** = $p < .01$).

maintained responding to decrease over 10 days of saline treatment and high dose speedball self-administration (Figure 4, row 2).

During flupenthixol + quadazocine treatment, this high speedball dose was at the peak of the speedball dose-effect curve (cf. Figure 3). Treatment with flupenthixol + quadazocine had no significant effects on the self-administration of 0.032 mg/kg/inj cocaine + 0.01 mg/kg/inj heroin at any time during the 10-day treatment (Figure 4, row 2). Food-maintained responding was more variable than during saline treatment; however, the average number of food pellets per day during this period were not significantly different during saline treatment + quadazocine and flupenthixol treatment.

DISCUSSION

Effects of Flupenthixol + Quadazocine Combinations on Speedball Self-Administration

The combined abuse of cocaine and opioids presents a difficult challenge for medication-based treatment. We postulated that a combination of medications targeted at both the stimulant and opioid components of the speedball might be necessary to effectively antagonize the reinforcing effects of this type of multiple drug self-administration. This is the first evaluation of the combined effects of a dopamine antagonist (flupenthixol) and an opioid antagonist (quadazocine) on speedball (cocaine + heroin) self-administration by rhesus monkeys. Our major finding was that chronic administra-

tion of flupenthixol + quadazocine combinations produced a significant reduction in the self-administration of a cocaine and heroin combination at the peak of the speedball dose-effect curve. Moreover, the highest dose combination of flupenthixol + quadazocine produced a rightward shift in the speedball self-administration dose-effect curve and surmountably antagonized the reinforcing effects of speedballs. In contrast, 10 days of treatment with the same doses of flupenthixol alone and quadazocine alone did not reduce speedball self-administration.

These findings are consistent with our earlier report that pretreatment with combinations of flupenthixol + quadazocine dose-dependently antagonized the discriminative stimulus effects of a speedball that consisted of a 10:1 ratio of cocaine to heroin, whereas, administration of flupenthixol alone or quadazocine alone was less effective (Negus et al. 1998a). Specifically, the speedball discriminative stimulus dose-effect curve was not altered by doses of flupenthixol (0.01 mg/kg) or quadazocine (0.1–0.32 mg/kg) that are sufficient to antagonize the discriminative stimulus effects of cocaine alone (Negus et al. 1996) or *mu* agonists alone (Bertalmio and Woods 1987). However, acute administration of both flupenthixol (0.01 mg/kg/day) + quadazocine (0.1 mg/kg) in combination shifted the speedball discriminative stimulus dose-effect curve approximately three-fold to the right (Negus et al. 1998a). Taken together, these findings suggest that receptor blockade of *both* the dopaminergic and opioid systems is necessary to antagonize the reinforcing and discriminative stimulus effects of speedball combinations that include active doses of both cocaine and heroin (Mello et al. 1995; Negus et al. 1998a). Some implications of these data for understanding the interactions between cocaine and opiates and their modulation by pharmacological antagonists are discussed below.

Effects of Flupenthixol + Quadazocine Combinations on Food-Maintained Responding

During saline treatment, there was a speedball dose-dependent decrease in food-maintained responding. These results are consistent with our previous reports that self-administration of various speedball combinations, as well as cocaine and heroin alone, produces dose-dependent decreases in food-maintained responding under conditions identical to those reported here (Mello and Negus 1998; Mello et al. 1995; Negus et al. 1995). Food-maintained responding during speedball self-administration did not differ significantly during saline treatment and flupenthixol + quadazocine treatment. Thus, although flupenthixol + quadazocine treatment appeared to antagonize the reinforcing effects of speedballs, it did not antagonize the effects of speedballs on food-maintained responding.

The inability of the flupenthixol + quadazocine combination to attenuate speedball-induced decreases in food-maintained responding may reflect both a relative inability of flupenthixol to antagonize the rate-decreasing effects of cocaine and the non-selective rate-decreasing effects of flupenthixol itself. For example, flupenthixol surmountably antagonized the discriminative stimulus effects of cocaine in a food-maintained drug discrimination procedure (Negus et al. 1996). However, doses of flupenthixol that blocked the discriminative stimulus effects of cocaine produced rate-decreasing effects and did not reliably block the rate-decreasing effects of high doses of cocaine (Negus et al. 1996). Similarly, doses of flupenthixol that decreased cocaine self-administration also usually decreased rates of food-maintained responding (Negus et al. 1996). In contrast, opioid antagonists produced little effect on operant response rates at doses that consistently antagonize the rate-decreasing effects of opioid agonists (c.f., Negus et al. 1993).

In Experiment 1, the highest rates of food-maintained responding were observed during treatment with quadazocine alone. These data suggest that quadazocine antagonized the rate-decreasing effects of the heroin component of the speedball. Similarly, chronic treatment with buprenorphine often attenuated the rate-decreasing effects of heroin and speedball self-administration on food-maintained responding (Mello and Negus 1998). Taken together, these findings suggest that opioid antagonists readily block the rate-decreasing effects of opioid agonists, whereas dopamine antagonists are less effective in blocking the rate-decreasing effects of cocaine and also produce rate-decreasing effects of their own (see Mello and Negus 1996 for review).

Effects of Dopamine and Opioid Antagonists Alone on Speedball Self-Administration

The relative ineffectiveness of either flupenthixol or quadazocine alone in decreasing speedball self-administration may reflect the inability of either antagonist to block the reinforcing effects of *both* the cocaine and heroin components of the speedball mixture. There is considerable agreement in the preclinical literature that the reinforcing effects of opioids can be antagonized by opioid antagonists (see Mello and Negus 1996 for review), but opioid antagonists usually have little or no effect on cocaine-maintained responding (Corrigall and Coen 1991; Ettenberg et al. 1982; Mello et al. 1993b, 1990; Rowlett et al. 1998) or on cocaine discrimination (Dykstra et al. 1992; Spealman and Bergman 1992). Yet, there are exceptions to these general findings. For example, naltrexone treatment was more effective than methadone in reducing the number of cocaine-positive urines in opioid-dependent patients (Kosten et al.

1989a). Moreover, the opioid-mixed agonist-antagonist buprenorphine decreased cocaine self-administration in both clinical and pre-clinical studies (see Mello and Mendelson 1995 for review). Thus, opioids may modify the abuse-related effects of cocaine under some conditions.

Dopamine antagonists alter cocaine self-administration in a manner consistent with the conclusion that they antagonize cocaine's reinforcing effects. For example, dopamine antagonists increased rates of cocaine self-administration maintained by high unit doses on the descending limb of the cocaine dose-effect curve, and these effects were similar to the effect of decreasing the unit dose of cocaine (e.g., Caine and Koob 1994; Ettenberg et al. 1982; see Mello and Negus 1996 for review). Moreover, dopamine antagonist pretreatments produced rightward shifts in cocaine self-administration dose-effect curves (Negus et al. 1996; see Mello and Negus 1996 for review). However, dopamine antagonists also produce non-selective behavioral effects such as sedation and catalepsy, which may decrease operant responding maintained by both drug and non-drug reinforcers. These non-selective rate-decreasing effects probably contribute to dopamine antagonist-induced alterations in cocaine self-administration, although cocaine may attenuate some of the non-selective effects of dopamine antagonists under some conditions (e.g., Negus et al. 1996; Winger 1994). Relatively few studies have investigated the effects of dopamine antagonists on opioid self-administration, but dose-dependent decreases in opioid self-administration are usually reported (Ettenberg et al. 1982; Winger 1994). Whether dopamine antagonists antagonize the reinforcing effects of opioids or decrease opioid self-administration by producing non-selective decreases in rates of operant responding continues to be controversial (see Mello and Negus 1996 for review).

Implications for Polydrug Abuse Treatment

The limited effectiveness of pharmacotherapies designed for opiate abuse treatment in reducing polydrug abuse, as well as the lack of consistently effective pharmacotherapies for cocaine abuse treatment, is generally acknowledged (see Mendelson and Mello 1996 for review). Our findings that antagonism of both the cocaine and the heroin components is necessary to effectively antagonize the reinforcing effects of speedballs in rhesus monkeys, suggest that medication combinations targeted at both opioid and stimulant abuse also might improve clinical treatment of polydrug abuse. These data encourage further exploration of medication combinations as a new strategy for polydrug abuse treatment.

In psychiatry, medication combinations are often used to treat complex psychiatric disorders and this approach is sometimes referred to as polypharmacy (Reus 1993; Schöpf et al. 1989; Thase and Rush 1995; Wolkowitz 1993). For example, in depressed patients who were resistant to the effects of tricyclic antidepressants alone, the addition of thyroid hormone, lithium, and a variety of other agents often improved the therapeutic outcome (Reus 1993; Schöpf et al. 1989; Thase and Rush 1995). Similarly, in the treatment of schizophrenia, a number of drugs have been used in an effort to increase the effectiveness of neuroleptics, albeit with variable results (see Wolkowitz 1993 for review). In substance abuse treatment, patients with co-morbid psychiatric disorders may require antidepressants and/or anxiolytics (Mendelson and Mello 1996). However, we recognize that there may be limitations to the use of dopamine antagonist + opioid antagonist combinations for the clinical treatment of speedball abuse.

Dopamine antagonists have not proven effective for the clinical treatment of cocaine dependence (Mendelson and Mello 1996). Although opioid antagonists effectively antagonize opioid effects, lack of patient compliance has limited the general applicability of antagonist-based medications such as the opioid antagonist naltrexone (see Mello and Mendelson 1995; Mendelson and Mello 1996 for review). Another potential limitation of treatment with a dopamine antagonist + opioid antagonist combination is that this may have transient effects. It is unlikely that the effectiveness of quadazocine in reducing heroin self-administration diminishes over time, but dopamine antagonists often have transient effects on cocaine self-administration during chronic treatment (Kleven and Woolverton 1990; Negus et al. 1996; Richardson et al. 1994). The flupenthixol-related reduction of cocaine's reinforcing effects was transient in the present study, and this suggests that speedball self-administration was maintained primarily by cocaine during the last few days of the 10 day treatment. It is unlikely that higher doses of flupenthixol in combination with quadazocine would significantly prolong the effectiveness of this antagonist combination because higher doses of flupenthixol (0.01–0.032 mg/kg/day) also resulted in transient decreases in cocaine self-administration (Negus et al. 1996). However, flupenthixol is a relatively non-selective dopamine antagonist, and it is possible that more selective dopamine antagonists might be effective over a longer period of time.

The interactions between cocaine and opioids are complex and poorly understood, and both similarities and differences in the behavioral and neurochemical effects of speedballs and the component drugs alone have been reported (Foltin and Fischman 1992; Hemby et al. 1996, 1999; Mello et al. 1995; Negus et al. 1998a; Rowlett and Woolverton 1997; Walsh et al. 1996). Microdialysis studies in rodents found that self-administration of cocaine alone increased extracellular dopamine levels at the nucleus accumbens, and this effect was enhanced by the addition of heroin in a speedball (Hemby et al.

1999). Yet, self-administration of heroin alone did not increase dopamine levels (Hemby et al. 1999). In both rats and rhesus monkeys, however, cocaine-heroin combinations usually produced reinforcing effects that were similar to either cocaine alone or heroin alone (Hemby et al. 1999; Mello et al. 1995). Speedball discrimination by rhesus monkeys also appears to include aspects of both the cocaine and the heroin components, because both drugs substituted completely for the speedball cocaine-heroin combination (Negus et al. 1998a). Moreover, speedball-appropriate responding was produced by cocaine and several other indirect dopamine agonists as well as by heroin and several other *mu* opioid agonists but not by a number of other behaviorally active drugs (Negus et al. 1998a). Clinical laboratory studies have suggested that speedballs produce a unique profile of opioid and stimulant effects that also included aspects of both component drugs (Foltin and Fischman 1992). Our finding that administration of flupenthixol + quadazocine in combination antagonized the reinforcing effects of speedballs, whereas, administration of either antagonist alone did not, is consistent with this interpretation. It now appears that both the reinforcing and the discriminative stimulus effects of speedballs reflect some aspects of both the opioid and stimulant component drugs. These preclinical speedball models should be useful for evaluating novel medications and medication combinations for polydrug abuse treatment as well as for clarifying the behavioral interactions between cocaine and opioid drugs.

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