

Relative Reinforcing Effects of Cocaine, Remifentanyl, and Their Combination in Rhesus Monkeys

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ABSTRACT

Human polydrug abusers often take combinations of opioids and stimulants, but it is not clear why. Behavioral economics with demand curve analysis is uniquely able to separate two of the possibilities: that the drug combination increases the reinforcing potency of the component drugs or that the drug combination is a more effective reinforcer than either drug alone. Rhesus monkeys self-administered a range of doses of cocaine, remifentanyl, and combinations of the drugs through indwelling intravenous catheters; the number of responses required for each drug infusion increased across drug-availability

sessions. Combining small doses of cocaine and remifentanyl that by themselves resulted in very low rates of responding yielded rates of responding that were higher than the maximum maintained by any dose of the constituent drugs. Nevertheless, demand curve analysis demonstrated that the drug combination was equally elastic as the component drugs, indicating that it was not more effective as a reinforcer than either cocaine or remifentanyl alone. This suggests that enhanced self-administration of this particular drug combination is due primarily to the drug enhancement of the potency of the other drug.

The abuse of two or more drugs in temporal proximity is thought to be a prevalent form of psychoactive drug use (Ball and Ross, 1991; Higgins et al., 1994; Schutz et al., 1994). One possible mechanism for this use is that combinations of small doses of the two drugs produce a reinforcing effect that is similar to, but no greater than, larger doses of either drug. A second possibility is that combinations of drugs produce a qualitatively different and quantitatively greater reinforcing effect than would be possible with any dose of either drug by itself.

Different procedures have been used in monkeys to evaluate the reinforcing effects of drug combinations. Mello et al. (1995), using a second-order schedule, found that adding heroin to cocaine did not result in an increased number of infusions obtained, suggesting no increase in the reinforcing effectiveness of the drug combination. A similar conclusion was reached by Rowlett and Woolverton (1997) and Rowlett et al. (1998) using progressive ratio schedules. In progressive ratio schedules, the response requirement for drug delivery is systematically increased until responding stops (breakpoint). Cocaine increased the potency of heroin as a reinforcer, and heroin similarly increased the potency of cocaine as a rein-

forcer, but the breakpoints produced by the combination were no greater than that produced by either drug alone.

Progressive ratio schedules have also been used in rats to assess the reinforcing functions of drug combinations. Duvauchelle et al. (1998) reported enhancements in potency with no change in breakpoints of combinations of cocaine and heroin. Ranaldi and Munn (1998) found that adding heroin to cocaine did not alter the potency of cocaine but that it did produce higher breakpoints than that of cocaine alone, suggesting an enhancement of the reinforcing effectiveness of the drug combination. Ward et al. (2005) evaluated the reinforcing effects of cocaine, heroin, and their combination using both progressive ratio and choice paradigms. They found the combination did not produce higher breakpoints than cocaine alone. In the choice studies, however, Ward et al. (2005) found that rats given the opportunity to choose between infusions of a standard dose of cocaine, and a cocaine-heroin combination, consistently chose the drug combination. Although the authors interpreted this as evidence that combinations of cocaine and heroin are more reinforcing than cocaine alone, these results would also occur if heroin was only increasing the potency of cocaine as a reinforcer.

Negus (2005) approached this issue in a more quantitative manner. He conducted an isobolographic analysis of monkeys' behavior when they were choosing between 1) food and various doses of cocaine, 2) food and various doses of heroin, or 3) food and three specific ratios of doses of cocaine and

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ABBREVIATIONS: None.

heroin in combination. The isobolographic analysis demonstrated that two of the drug combinations produced less reinforcing effect than would be expected by a simple addition of drug effects. One combination ratio (3.2 cocaine:1.0 heroin) produced the same reinforcing effect as would be anticipated by simple addition of effects. This combination also produced a leftward shift in the heroin dose-response function of percentage of drug choice over food, rate of responding, and total reinforcers.

The majority of these studies indicate that combining a stimulant and an opioid does not result in a stimulus with an enhanced reinforcing effectiveness. The following study was designed to ask this question using a behavioral economic procedure that separates conceptually the effects of changes in potency from changes in effectiveness of reinforcers. This analysis produces demand functions, which relate reinforcer consumption (micrograms per kilogram per session) and its price (response requirement/dose per infusion). With small response requirements and/or large doses, consumption is defended against increasing price by increased responding—the inelastic portion of the demand function. Eventually, price becomes sufficiently high to result in steeply declining consumption. This is the elastic portion of the function. The fundamental principle of demand curve analysis is that more effective reinforcers will yield demand functions with less elasticity, so comparing the elasticity of the various demand functions provides a way to evaluate the relative reinforcing effectiveness of various stimuli: differences in elasticity can be interpreted as differences in reinforcing effectiveness (Bickel et al., 1993; Hursh, 1993). Reinforcers with similar effectiveness, but with differences in potency, should have similar elasticity because demand functions do not reflect, and are not sensitive to, simple differences in potency (Hursh and Winger, 1995). This makes demand function analysis useful for distinguishing between changes in reinforcing potency and changes in reinforcing effectiveness of drug combinations.

Materials and Methods

Subjects and Apparatus. Three adult rhesus monkeys (two males and one female, weighing 8–12.7 kg) served as subjects. They were individually housed in stainless steel cages that measured 83.3 by 76.2 by 91.4 cm in depth. The monkeys had ad libitum access to water and were fed 10 to 15 primate biscuits twice each day after each session of drug availability. Each monkey wore a Teflon mesh jacket (Lomir Biomedical, Malone, NY) that connected to a flexible hollow metal tether that fastened to the monkey's jacket on one end and to the rear of the cage on the other. The monkeys had been adapted to the jacket and tether and had intravenous catheters surgically implanted for previous studies on the effects of various opioid antagonists on serum levels of adrenocorticotrophic hormone and cortisol (Williams et al., 2004). The intravenous catheters, implanted in the jugular or femoral veins of the monkeys, passed subcutaneously to the animals' midscapular area and exited the monkey where the tether joined the jacket. The intravenous catheter passed through the tether, left the rear of the housing cage and attached to another catheter that was part of the infusion pump system. All studies were conducted in accordance with the Guide for the Care and Use of Laboratory Animals as adopted and promulgated by the National Institutes of Health.

Each cage had a stimulus panel attached to one side. This panel contained two response levers, and three stimulus lights arranged horizontally above the levers. The lights on either side, located over

the response levers, could be illuminated in red; the center light was illuminated in green whenever the infusion pump was operating. An IBM PS/2 computer, located in an adjoining room and programmed with Med-PC (MED Associates, Georgia, VT) software, controlled the experiments.

Procedure. The monkeys acquired lever pressing for 10 $\mu\text{g}/\text{kg}$ per infusion cocaine under a fixed ratio 1 schedule, in which every lever press made in the presence of the red stimulus light resulted in a drug infusion. There were two drug self-administration sessions available each day; each session was 130 min in duration. Following acquisition of lever pressing, the left lever and left stimulus light were inactivated. The light/dark cycle was adjusted to accommodate other experiments in the monkey laboratory; the lights were turned on in the housing room at 4:00 AM and turned off at 7:00 PM. The morning sessions began at 6:20 AM, and the afternoon sessions began at 2:30 PM. The onset of each session was indicated by the onset of the rightmost stimulus light on the panel. When this light was illuminated, the stipulated number of responses on the rightmost lever resulted in intravenous delivery of cocaine, remifentanyl, or saline. Each infusion consisted of 1 ml of solution, delivered over 5 s, followed by a 5-s infusion of saline by a second pump.

The response requirement was increased across sessions. During the first exposure to each dose of either drug, 10 responses were required for each drug infusion (fixed ratio 10). On the next session, the ratio requirement increased to 32, and on subsequent sessions, this requirement increased to fixed ratios 100, 320, 1000, and 1780. When the monkey failed to earn any drug infusions at a particular fixed ratio, the ratio requirement on the subsequent session was returned to 10, and saline replaced the drug solution for at least one session. When the number of saline infusions decreased to less than 30 in a single session, the drug solution was again made available on fixed ratio 10, and the ratio series was repeated. Each dose of both drugs was made available through three series of ratio increases.

All monkeys were exposed to this ratio series using each of three doses of cocaine: 10, 30, and 100 $\mu\text{g}/\text{kg}$ per infusion. The dose order was different for each monkey. Three doses of remifentanyl (0.03, 0.1, and 0.3 $\mu\text{g}/\text{kg}$ per infusion) were then assessed using the same procedure. Subsequently, cocaine and remifentanyl were combined in a single reservoir and made available for self-administration. Small doses of both drugs were used in the combinations: 10 $\mu\text{g}/\text{kg}$ per infusion cocaine + 0.03 $\mu\text{g}/\text{kg}$ per infusion remifentanyl, 10 $\mu\text{g}/\text{kg}$ per infusion cocaine + 0.1 $\mu\text{g}/\text{kg}$ per infusion remifentanyl, and 30 $\mu\text{g}/\text{kg}$ per infusion cocaine + 0.03 $\mu\text{g}/\text{kg}$ per infusion remifentanyl. The procedure was the same as that with the single drugs.

Data Analysis. Rates of responding were calculated as the number of responses made during the time the stimulus light was illuminated, signaling drug availability. Demand curves were described using a modification of the normalization procedure described by Hursh and Winger (1995). In brief, for each dose of both drugs and for the drug combination, a normalized dose, q , was calculated as 100 divided by the number of reinforcers taken at that dose or dose combination at the smallest fixed ratio value. Demand curves were calculated based on this normalized dose, with normalized price (P) = FR/q and normalized consumption (Q) as number of reinforcers at each fixed ratio $\times q$. The log of normalized consumption was plotted as a function of the log of the normalized price using Prism (GraphPad Software Inc., San Diego, CA). A nonlinear regression was plotted using the exponential function $\log Q = \log(L) e^{-aP}$, where L is the maximal consumption level at zero price, and a is the rate of decline in consumption with price.

Differences between demand functions was determined using the Prism software function for comparing two curves. This function assessed the question of whether the best fit value for all parameters was different between the data sets that made up the demand functions. The program used an F ratio, $F = [(\text{SS}_{\text{null}} - \text{SS}_{\text{alt}})/(\text{DF}_{\text{null}} - \text{DF}_{\text{alt}})]/[\text{SS}_{\text{alt}} - \text{DF}_{\text{alt}}]$, to calculate the differences between the functions. The null hypothesis was that the data sets described a single function. When the null hypothesis was accepted at $p > 0.05$,

the program plotted a single curve. When the null hypothesis was rejected, separate curves were applied to each data set. The values noted in the results provide the F ratios, the degrees of freedom, and the probability that the two or three plotted functions in each graph are different from each other.

Results

Rates of responding maintained by the individual monkeys are shown for the three doses of cocaine (Fig. 1, left) and for the three doses of remifentanyl (Fig. 1, right) across the range of fixed ratio response requirements. The smallest dose of both drugs yielded consistent decreases in rates of responding as fixed ratio increased. The intermediate dose was more likely to produce a bell-shaped function: rates of responding increased as ratio increased across low values; further increases in response requirement resulted in decreased rate of responding. This was true for the largest of the three doses as well, except for monkey 3593 (Fig. 1, bottom left) who showed monotonic increases in response rates as the response requirement increased with the largest dose. The fixed ratio at which rates of responding peaked was higher for the largest dose of cocaine. Cocaine also maintained a higher peak rate of responding than did remifentanyl in two of the three monkeys and similar or slightly lower rates of responding than remifentanyl in the third monkey (3511).

Rates of responding maintained by the smallest dose of cocaine alone, and when combined with each of the two small

doses of remifentanyl, are shown in Fig. 2 (left). The low rates of responding maintained by this dose of cocaine were greatly enhanced by the addition of remifentanyl. Responding was slightly better maintained at large fixed ratio values (100, 320, 1000, or 1780, depending on the monkey) when 0.1 $\mu\text{g}/\text{kg}$ per infusion remifentanyl compared with 0.03 $\mu\text{g}/\text{kg}$ per infusion remifentanyl was combined with cocaine, but this was a small effect in all monkeys. It is perhaps of interest that adding remifentanyl to a small dose of cocaine increased rates of responding at small fixed ratio values of 32 or 100. This is different from the effect of increasing the cocaine dose, which tended to increase response rates at larger fixed ratio values (Fig. 1). In addition, for two of the monkeys, the maximal rate maintained by adding remifentanyl to cocaine was higher than that maintained by the dose of cocaine that produced the maximal response rates (100 $\mu\text{g}/\text{kg}$ per infusion). For the third monkey, 3593, the maximal response rate produced by the addition of remifentanyl to cocaine was about the same as that maintained by 100 $\mu\text{g}/\text{kg}$ per infusion cocaine alone.

Rates of responding maintained by the smallest dose of remifentanyl alone and when combined with the two smallest doses of cocaine are shown in Fig. 2 (right). Again, the combination of cocaine and remifentanyl produced substantial

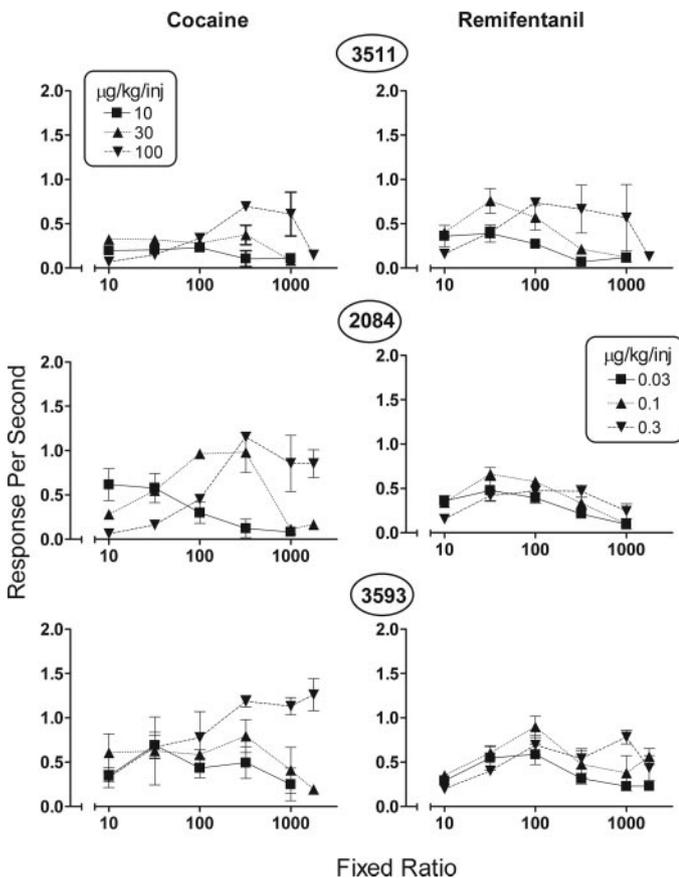


Fig. 1. Rates of responding (responses per second) maintained by intravenous cocaine (left) or intravenous remifentanyl (right) by each of three rhesus monkeys across increasing fixed ratio values. The different symbols and connecting line types designate different doses of each drug in micrograms per kilogram per infusion.

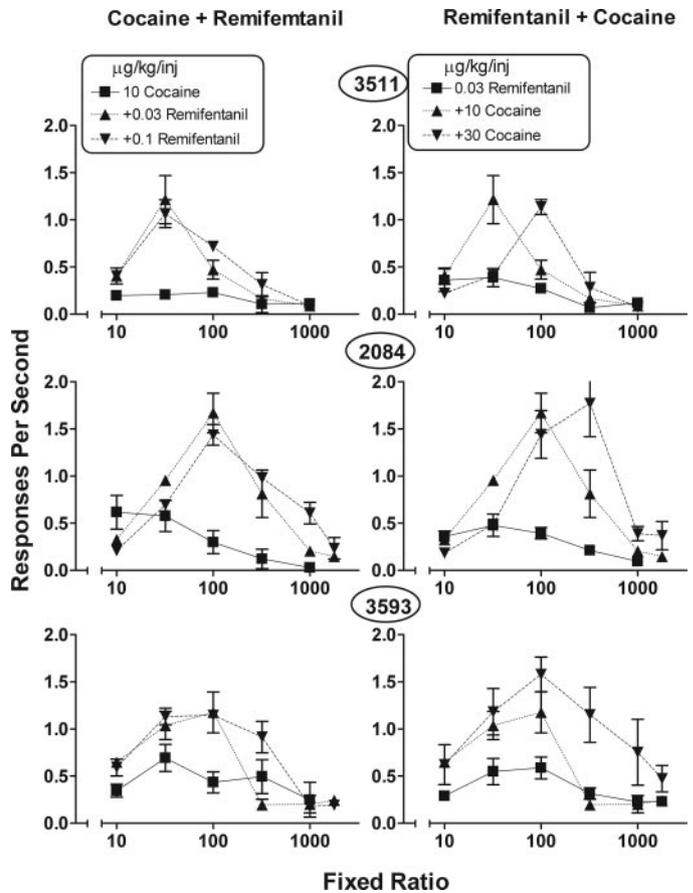


Fig. 2. Rates of responding maintained across increasing fixed ratio values by the addition of two small doses per infusion of remifentanyl to a standard, small dose per infusion of cocaine (left) and by the addition of two small doses per infusion of remifentanyl to a standard, small dose per infusion of remifentanyl (right). The solid squares show rates maintained by the smallest dose per infusion of remifentanyl and cocaine when these doses were available by themselves. The solid triangles and inverted triangles indicate the effect on response rates of adding the other drug to this standard.

increases in rates of responding compared with behavior maintained by the small dose of remifentanyl alone. As the added dose of cocaine increased, there was a greater tendency for responding to be maintained at higher rates with increasing fixed ratio requirements than was shown when two doses of remifentanyl were added to a small dose of cocaine. A tendency for responding to be elevated at the small fixed ratio (10) requirements was not observed. However, the maximum rate of responding maintained by the combination was higher than that maintained by the dose of remifentanyl that produced the highest response rates (Fig. 2).

Table 1 shows the number of injections of cocaine, remifentanyl, and the combinations taken by each monkey at each dose or dose combination. These are the values that, when multiplied by the drug dose and then normalized, constitute the consumption ordinates of the demand functions. Demand curve analyses of self-administration of cocaine (left) and remifentanyl (right) are shown in Fig. 3. With cocaine, the two larger doses constituted a single function for two monkeys (monkey 3593: $F_{2,7} = 2.45$, $p > 0.05$; monkey 3511: $F_{2,5} = 1.98$, $p > 0.05$). For the third monkey, 2084, the small amount of variability in the data resulted in the two larger doses fitting two functions, but this was barely statistically reliable ($F_{2,6} = 5.16$; $p = 0.05$) and does not detract from the general finding here and previously (Hursh and Winger, 1995) that larger doses of cocaine fall on a single demand curve. The smallest dose of cocaine did not fit on the function described by the two larger doses for any of the monkeys (monkey 3511: $F_{2,9} = 10.57$, $p < 0.05$; monkey 2084: $F_{2,10} = 143$, $p < 0.05$; monkey 3593: $F_{2,12} = 5.69$, $p < 0.05$). For remifentanyl, all three doses described a single demand function for each monkey (monkey 3511: $F_{4,8} = 1.99$, $p > 0.05$; monkey 2084: $F_{4,8} = 0.10$, $p > 0.05$; monkey 3593: $F_{4,12} = 2.20$, $p > 0.05$).

A comparison of the demand functions for cocaine, remifentanyl, and the drug combination is shown in Fig. 4. For monkey 3511, all three functions fell on a single curve, indicating that there was no difference among the reinforcing effectiveness of cocaine compared with remifentanyl, or compared with the drug combinations ($F_{4,30} = 0.83$; $p > 0.05$).

For monkey 2084, cocaine and the drug combination have demand functions with equivalent slopes, whereas remifentanyl was less reinforcing (more elastic) than cocaine or the drug combination ($F_{4,35} = 9.15$; $p < 0.05$). For monkey 3593, the demand function for cocaine was slightly but significantly less elastic than were the functions for the combination and remifentanyl ($F_{4,37} = 2.75$; $p < 0.05$). The demand functions for the combination and remifentanyl were not different from each other ($F_{2,28} = 1.14$; $p > 0.05$).

These results indicate, despite that a combination of remifentanyl and cocaine could maintain higher rates of responding than either drug by itself, the combination did not differ in elasticity from either drug available singly; this suggests that it was not a more effective reinforcer than either drug alone.

Discussion

Both cocaine and remifentanyl, delivered intravenously, functioned as reinforcers in a situation in which response requirements increased across sessions. For both drugs, small doses maintained low response rates that decreased further as the response requirement increased; larger doses maintained rates that initially increased with increasing response requirement, and decreased with further increases in response requirement. Both of these drugs have been found previously to produce this bell-shaped pattern of responding in situations where response requirement increased across sessions (Winger, 1993; Ko et al., 2002). The maximum rate of responding maintained by each drug was nearly the same for one monkey, but cocaine maintained higher maximum rates of responding than remifentanyl for the other two monkeys.

Rates of responding maintained by combinations of cocaine and remifentanyl showed similar bell-shaped patterns of responding across increasing response requirements. For each of the three monkeys, a combination of small doses of both drugs yielded higher rates of responding than the maximum rate maintained by any dose of the component drugs at any response requirement.

TABLE 1
Average number of injections

Monkey	FR	Cocaine			Remifentanyl ($\mu\text{g}/\text{kg}/\text{inj}$)			Combination (Coc + Rem)		
		10	30	100	0.03	0.1	0.3	10 + 0.03	30 + 0.03	10 + 0.1
3511	10	107	152	48	155	172	94	170	117	174
	32	44	64	33	74	123	77	164	80	154
	100	17	20	24	20	39	50	33	72	49
	320	2	8	16	1	5	15	4	7	7
	1000	0	0	4	0	0	4	0	0	0
	1780			0			0			
2084	10	230	145	45	156	159	94	148	108	115
	32	123	96	41	86	105	90	140	86	115
	100	30	63	37	25	41	33	91	77	87
	320	3	26	23	5	6	10	24	45	21
	1000	0	1	10	0	0	0	1	3	5
	1780		0	4				0	0	0
3593	10	164	207	145	142	160	113	219	200	208
	32	121	106	113	97	106	82	152	162	161
	100	30	39	50	41	59	53	73	93	72
	320	11	21	27	7	11	16	4	26	21
	1000	1	3	8	2	2	7	1	6	1
	1780		0	5	0	2	1		2	0

Coc, cocaine; FR, fixed ratio; inj, injection; Rem, remifentanyl.

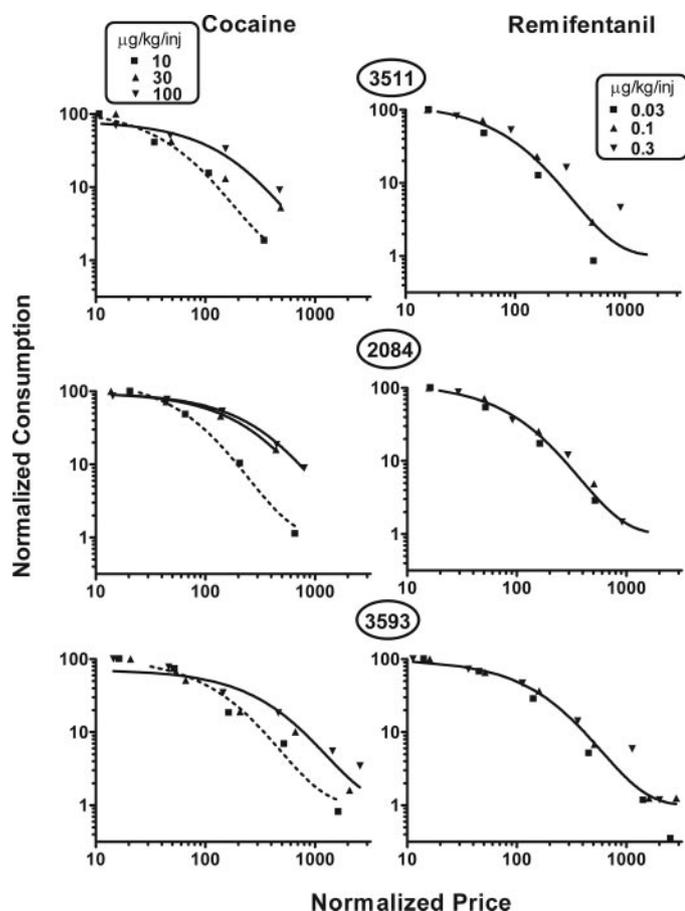


Fig. 3. Demand functions established by cocaine (left) and remifentanyl (right) when these drugs were available by themselves. When a single function is drawn (all graphs, right), there is no significant difference among the slope of the three curves (three doses) making up that curve. Normalized price is the fixed ratio divided by q , the normalized dose. Normalized consumption is the number of infusions taken in a session multiplied by q .

Normalized consumption of each drug and the drug combination was graphed on a log-log plot as a function of normalized price to yield demand functions for these three conditions. It is important to note that, theoretically, a single function should describe drug demand, regardless of dose, as long as reinforcing doses are used. This single function per drug is based on the assumption that doubling the dose per injection of drug results in the same behavior as dividing the response requirement for each injection in half (Bickel et al., 1993). When there is a single function, the price of the drug [fixed ratio/(dose/infusion)] determines the behavioral output, regardless of the particular response requirement or dose that comprises the price. Thus, fixed ratio 100 for 10 $\mu\text{g}/\text{kg}$ per infusion should maintain the same consumption as fixed ratio 1000 for 100 $\mu\text{g}/\text{kg}$ per infusion. From this single function, an elasticity measure can be obtained that reflects the reinforcing effectiveness of that drug, and single functions for two or more drugs can be compared. Because a single curve is obtained regardless of the dose of drug or the response requirement used, demand functions and elasticity measures are independent of the dose of the drugs used, which is not the case when rates of responding, breakpoints, or choice measures are used. When a measure is insensitive to dose, it is also insensitive to procedures that change po-

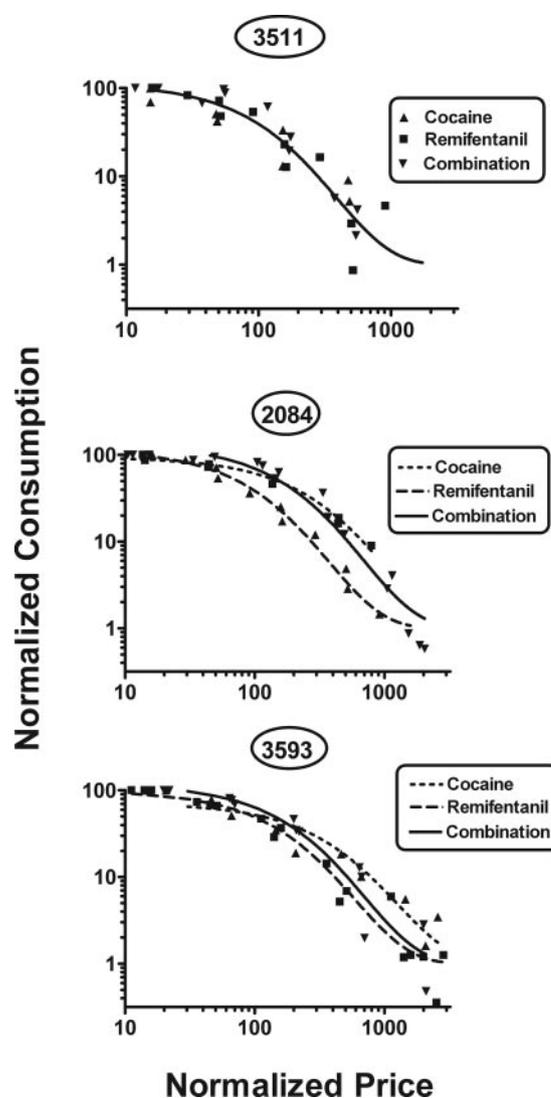


Fig. 4. Demand functions established by combinations of cocaine and remifentanyl for each of three monkeys. When a single function is drawn (monkey 3511), there is no significant difference among the slope of the three curves (cocaine, remifentanyl, and the combination) making up that curve. For monkey 2084, there is no difference between the demand functions obtained for cocaine and the drug combination, but both of these functions are significantly less elastic than the curve drawn for remifentanyl. For monkey 3593, the cocaine demand function is significantly less elastic than that obtained for the drug combination, which is no different from that obtained for remifentanyl.

tency. Therefore, demand curves should remain in the same position and have the same elasticity if a drug is combined with its competitive antagonist, or if it is evaluated before and after the development of tolerance to its effects. Demand curves that have different elasticities reflect differences or changes in reinforcing effectiveness; demand curves using nalbuphine, for example, are more elastic than curves using alfentanil, and demand curves using cocaine are less elastic than curves using methohexital. This indicates that nalbuphine is fundamentally a less effective reinforcer than alfentanil and that cocaine is a more effective reinforcer than methohexital. These differences between drugs are not simply potency differences (Hursh and Winger, 1995).

The demand curves constructed using a normalized, exponential equation, described a single function for the two larger doses of cocaine and a single function for all three

doses of remifentanyl. The finding that the smallest dose of cocaine did not fall on the demand function established by the two larger doses replicates an earlier finding with this dose (Hursh and Winger, 1995) and suggests that this dose of cocaine is not an effective reinforcer at higher prices. The small dose of cocaine alone was not used to make further comparisons with remifentanyl or remifentanyl + cocaine.

Demand curves that resulted from combining cocaine and remifentanyl were never less elastic than demand functions obtained using one or both of these component drugs. In one monkey, there was an overlap among demands for cocaine, remifentanyl, and the combination. In two other monkeys, cocaine was less elastic (a better reinforcer) than remifentanyl; in one of these monkeys, the drug combination produced demand that was as elastic as cocaine, and in the other, the drug combination yielded demand that was equally elastic as remifentanyl. This indicates that combinations of cocaine and remifentanyl are not more effective reinforcers than either drug alone.

Observable relationships between rates of responding and the demand functions were not obvious. Monkeys 2084 and 3593 showed higher maximum response rates for cocaine than for remifentanyl, and the demand function for cocaine for these two monkeys was less elastic than was the demand function for remifentanyl. Cocaine and remifentanyl maintained similar maximum rates of responding in monkey 3511 and the corresponding demand function indicated that remifentanyl and cocaine had the same elasticity. Although this suggests that relative maximal rates of responding might be indicative of demand elasticity, this was not supported by the data with the drug combinations. Maximum rates of responding maintained by mixtures of remifentanyl and cocaine were consistently higher than those maintained by either component drug, but the combination was equally elastic as cocaine in two of the monkeys (3511 and 2084) and more elastic than cocaine in the third monkey (3593). Therefore, it was clear that maximum rates of responding on fixed ratio schedules did not adequately reflect the reinforcing effectiveness, as indicated by elasticity of demand, of the response-contingent stimuli. Elasticity of demand was able, however, to reflect the relative reinforcing effects of drugs.

When small doses of cocaine and remifentanyl were combined, rates of responding were dramatically increased: combinations of doses of each drug that by themselves produced rates of responding that were less than 0.5 responses per second, yielded maximum responses rates that ranged from 1.2 to 1.75 responses per second in the three monkeys. This apparently potentiated reinforcing effect of combinations of small drug doses has been reported by others. Rowlett et al. (2005) noted that adding small doses of the opioids alfentanil or nalbuphine to cocaine produced marked increases in responding maintained by small doses of cocaine, but it did not enhance rates of responding maintained by large doses of cocaine. The increased potency of cocaine and heroin combinations (Rowlett and Woolverton, 1997; Duvauchelle et al., 1998; Rowlett et al., 1998) also demonstrated the ability of combinations of small doses of cocaine and an opioid to produce a greater rate-maintaining effect than their constituents. That small-dose drug combinations increased response rates but did not affect demand elasticity, suggested that providing the small doses in combination was equivalent to increasing drug dose and did not reflect a qualitative or

quantitative difference in the effectiveness of the combination as a reinforcer.

Our results support findings of other investigators who have compared dose-based measures of behavior (Mello et al., 1995; Rowlett and Woolverton, 1997; Duvauchelle et al., 1998; Rowlett et al., 1998) as well as the isobolographic analysis of Negus (2005). In all of these studies, no enhancement of the reinforcing effect of cocaine or an opioid was conferred by combining the two drugs. In three studies using rats and identical progressive ratio schedules, two of the studies found that combinations of cocaine and heroin did not maintain higher breakpoints than did cocaine alone (Duvauchelle et al., 1998; Ward et al., 2005), and the remaining study reported that the combination of cocaine and heroin maintained higher breakpoints than cocaine alone (Ranaldi and Munn, 1998). It is difficult to identify differences among these studies that might explain the discrepant results, although each group used a different strain of rat and there were some apparent differences in sensitivity to the drugs.

The question then becomes why use of stimulants and opioids seems to be so popular in drug abusers. Negus (2005) suggested three possibilities: 1) the drug combination may be less toxic than larger doses of the constituents; 2) the drug combinations may be taken when availability of one or both of the drugs is limited; and 3) drug abusers may use the drugs sequentially rather than simultaneously, and the reinforcing effects of sequential use may differ from those measured in these studies.

The second of these suggestions is particularly appealing and is supported by the findings in this and other studies. If small amounts of two drugs are available, the drug combination may have a reinforcing effect similar to a larger dose of either drug alone, and this likely is sufficient to result in abuse of drug combinations. The ability of one drug effectively to increase the potency of another drug may result in abuse of drug combinations. Certainly, drugs such as naltrexone that have as their only effect an ability to decrease the potency of another drug such as heroin can be extremely effective in reducing the use of the opioid agonist (Comer et al., 2006). Thus, in determining the abuse of drug combinations, enhancement by one drug of the reinforcing effectiveness of another drug may not be as important or occur as frequently as the enhancement by one drug of the reinforcing potency of the other drug.

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References

- Ball JC and Ross A (1991) *The Effectiveness of Methadone Maintenance Treatment*, Springer-Verlag, New York.
- Bickel WK, DeGrandpre RJ, and Higgins ST (1993) Behavioral economics: a novel experimental approach to the study of drug dependence. *Drug Alcohol Depend* 33:173–192.
- Comer SD, Sullivan MA, Yu E, Rothenberg J, Kleber HD, Kampman K, Dackis C, O'Brien CP, Chiang CN, and Hawks RL (2006) A randomized, placebo-controlled clinical trial of injectable, sustained-release naltrexone for the treatment of opioid dependence. *Arch Gen Psychiatry* 63:210–218.
- Duvauchelle CL, Sapoznik T, and Kornetsky C (1998) The synergistic effects of combining cocaine and heroin ("speedball") using a progressive-ratio schedule of drug reinforcement. *Pharmacol Biochem Behav* 61:297–302.
- Higgins ST, Budney AJ, Bickel WK, and Foerg FE (1994) Alcohol dependence and simultaneous cocaine and alcohol use in cocaine-dependent patients. *J Addict Dis* 13:177–189.

- Hursh SR (1993) Behavioral economics of drug self-administration: an introduction. *Drug Alcohol Depend* **33**:165–172.
- Hursh SR and Winger G (1995) Normalized demand for drugs and other reinforcers. *J Exp Anal Behav* **64**:373–384.
- Ko MC, Terner J, Hursh S, Woods JH, and Winger G (2002) Relative reinforcing effects of three opioids with different durations of action. *J Pharmacol Exp Ther* **301**:698–704.
- Mello NK, Negus SS, Lukas SE, Mendelson JH, Sholar JW, and Drieze J (1995) A primate model of polydrug abuse: cocaine and heroin combinations. *J Pharmacol Exp Ther* **274**:1325–1337.
- Negus SS (2005) Interactions between the reinforcing effects of cocaine and heroin in a drug-vs-food choice procedure in rhesus monkeys: a dose-addition analysis. *Psychopharmacology* **180**:115–124.
- Ranaldi R and Munn E (1998) Polydrug self-administration in rats: cocaine-heroin is more rewarding than cocaine-alone. *Neuroreport* **9**:2463–2466.
- Rowlett JK, Rodefer JS, and Spealman RD (2005) Self-administration of cocaine-opioid combinations by rhesus monkeys: evaluation of the role of mu receptor efficacy using labor supply analysis. *J Pharmacol Exp Ther* **312**:1289–1297.
- Rowlett JK, Wilcox KM, and Woolverton WL (1998) Self-administration of cocaine-heroin combinations by rhesus monkeys: antagonism by naltrexone. *J Pharmacol Exp Ther* **286**:61–69.
- Rowlett JK and Woolverton WL (1997) Self-administration of cocaine and heroin combinations by rhesus monkeys responding under a progressive-ratio schedule. *Psychopharmacology* **133**:363–371.
- Schutz CG, Chilcoat HD, and Anthony JC (1994) The association between sniffing inhalants and injecting drugs. *Compr Psychiatry* **35**:99–105.
- Ward SJ, Morgan D, and Roberts DC (2005) Comparison of the reinforcing effects of cocaine and cocaine/heroin combinations under progressive ratio and choice schedules in rats. *Neuropsychopharmacology* **30**:286–295.
- Williams KL, Broadbear JH, and Wood JH (2004) Noncontingent and response-contingent intravenous ethanol attenuates the effect of naltrexone on hypothalamic-pituitary-adrenal activity in rhesus monkeys. *Alcohol Clin Exp Res* **28**:566–571.
- Winger G (1993) Effects of fixed ratio and time out changes on behavior maintained by cocaine or methohexital in rhesus monkeys. 1. Comparison of reinforcing strength. *Exp Clin Psychopharmacol* **1**:142–153.

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