**UNIT-PRICE ANALYSIS OF OPIOID CONSUMPTION BY MONKEYS
RESPONDING UNDER A PROGRESSIVE-RATIO SCHEDULE OF
DRUG INJECTION**

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Several reports have indicated that drug consumption in self-administration procedures is a function of the ratio of the instrumental requirement to the dose of drug, a quantity termed unit price. We evaluated three predictions from this unit-price model in a reanalysis of data on opioid self-administration in rhesus monkeys responding under a progressive-ratio schedule (Hoffmeister, 1979). We evaluated whether consumption was inversely related to unit price, and compared the goodness of fit of an equation devised by Hursh, Raslear, Shurtleff, Bauman, and Simmons (1988) to that of a linear model predicting consumption as a function of dose. We also tested whether consumption was constant when the same unit price was comprised of different combinations of dose and instrumental requirement. Consumption declined overall as unit price increased. The equation devised by Hursh et al. and the linear model based on dose fit the data equally well. Drug consumption was not uniform at a given unit price. The analyses suggest limits on the unit-price model as a characterization of drug consumption.

Key words: codeine, dextropropoxyphene, heroin, opioid, pentazocine, progressive-ratio schedules, unit price, drug self-administration, lever press, rhesus monkey

Drug self-administration procedures in non-human animals are used to study the reinforcing effects of drugs and to predict abuse liability (Schuster, 1976; Woolverton & Nader, 1990). All drug self-administration procedures are similar to those described in the early 1960s (Davis & Nichols, 1963; Weeks, 1962), in which emitted responses result in drug delivery according to a specified contingency. Two variables, the instrumental requirement (IR) and the amount of drug delivered (dose), are fundamental in the control of drug self-administration. These two variables can be combined into a ratio of the instrumental requirement to dose. This ratio is termed unit price. Thus, unit price = IR/dose; any combination of IR and dose defines a given unit price, and an infinite number of different combinations of IR and dose can be used to generate the same unit price.

Bickel, DeGrandpre, Higgins, and Hughes (1990) reanalyzed several drug self-administration studies and concluded that drug intake was a negatively accelerated function of unit price. Bickel et al. (1990) also proposed that an increase in IR was functionally equiv-

alent to a decrease in dose. This hypothesis implies that drug intake will be constant at a particular unit price, regardless of the dose and IR. Bickel, DeGrandpre, Hughes, and Higgins (1991), DeGrandpre, Bickel, Hughes, and Higgins (1992), and Bickel, Hughes, DeGrandpre, Higgins, and Rizzuto (1992) reported that unit price predicted consumption of coffee or cigarettes by human subjects. Some investigators have fitted to their data an equation originally presented by Hursh, Raslear, Shurtleff, Bauman, and Simmons (1988):

$$\ln(Q) = \ln(L) + b[\ln(P)] - a(P). \quad (1)$$

In this equation, Q is the predicted quantity consumed at some unit price P , L is the quantity consumed at the lowest unit price measured, b is the initial slope of the curve at the lowest unit price measured, and a is the acceleration in slope of the curve with increases in unit price.

Where goodness-of-fit correlations for predicted and obtained drug consumption using Equation 1 are reported, the values range from .74 in an experiment in which rhesus monkeys self-administered cocaine (Nader, Hedeker, & Woolverton, 1993) to 1.00 in an experiment in which human subjects self-administered (smoked) cigarettes (Russell, Wilson, Patel, Cole, & Feyerabend, 1973, cited in DeGrandpre et al., 1992). For comparison, Nader et al. (1993) reported that a linear

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model that included dose and instrumental requirement as separate regressors gave a goodness-of-fit correlation of .91, reliably better than they obtained with Equation 1.

Clearly, the conditions under which unit price may or may not predict drug consumption need to be delineated. In this context, we applied the unit-price model to data reported by Hoffmeister (1979) on the self-administration of opioids by rhesus monkeys in a progressive-ratio (PR) procedure. Our analysis was intended to test the prediction that consumption would generally decline as unit price increased, and to compare the fit of Equation 1 to a simpler model, in which consumption was analyzed as a linear function of dose:

$$C = m(d) + k, \quad (2)$$

where C is drug consumption in an experimental session, d is the dose per injection, and m and k represent the slope and intercept of the line. In addition, the prediction of constant consumption at a given unit price was tested by comparing consumption when a unit price consisted of a relatively higher IR-dose combination to that when the same unit price consisted of a lower IR-dose combination.

METHOD

In Hoffmeister's (1979) experiment, monkeys were trained to self-administer injections of codeine. Under baseline conditions, injections of 1.0 mg/kg were delivered upon completion of a fixed-ratio (FR) 100 IR. Trials were separated by 3 hr so that an animal could receive a maximum of eight injections in a 24-hr session. After performance stabilized under baseline conditions, doses of heroin (0.001 to 0.5 mg/kg), codeine (0.01 to 16 mg/kg), dextropropoxyphene (0.05 to 10 mg/kg), and pentazocine (0.05 to 10 mg/kg) were substituted for the baseline dose of codeine, and the IR was increased in daily sessions. Only one IR was in effect during a session. The IR was increased daily by doubling it until the number of injections decreased to two or fewer per day. At this point, baseline conditions were reinstated for a minimum of 3 days before testing the next dose of drug. During the experiment, there were 2-week periods in which trials were discontinued to minimize the development of physical dependence.

For the present paper, data were analyzed separately for each animal. These analyses include data (Hoffmeister, 1979, p. 184) only for conditions in which the number of injections was greater than zero and less than eight, the minimum and maximum numbers of injections permitted by the procedure. This excluded some data from the analyses, but also ensured that behavior was not unduly constrained by procedural limitations of the experiment. Data therefore represent the animals' responses to changing doses and instrumental requirements, rather than responses to dose-dependent minimum or maximum consumption.

Unit prices were calculated for each dose and IR combination. After unit prices were calculated, Equation 1 was fitted to the data. This required two steps. First, nonlinear regression was used to estimate a , b , and L . These were then entered into Equation 1 to derive predicted values for consumption at each unit price. Equation 2 was fitted to the data in a like manner, first fitting m and k and then using the fitted values to derive predicted values as a function of unit price.¹

Pearson r correlations between obtained and predicted values were calculated to measure goodness of fit for Equations 1 and 2. We used a Wilcoxon signed rank test to compare the goodness-of-fit r values obtained with Equations 1 and 2. For this analysis, each r obtained with Equation 1 for a given animal and drug was assigned to one group and the corresponding r obtained with Equation 2 was assigned to the other group.

To test the prediction that consumption would be constant at a given unit price, we examined consumption at all points at which a given unit price was represented by more than one IR-dose combination in any subject. There were 44 unit prices that met this criterion; 39 occurred twice in a subject and five occurred three times. In the cases in which there were two values, consumption in the condition in which the unit price was composed of a lower IR/lower dose combination was assigned to a "low" group, and consumption in the condition with the higher IR/

¹ An analysis of the linear relationship between consumption and IR showed that there was a statistically significant correlation between these two variables in only one case. The mean r was .191 (range, .044 to .696). Accordingly, we did not include IR in our linear model.

Fig. 1. Dextropropoxyphene consumption as a function of unit price (left panels) and dose (right panels). Open circles represent consumption in both panels. Lines in the left panels represent values predicted with Equation 1. Lines in the right panels represent values predicted with Equation 2. Each panel contains 1 subject's data. Note that the nonlinear appearance of the righthand functions results from the logarithmic scaling.

Fig. 2. Pentazocine consumption as a function of unit price and dose. Other details as in Figure 1.

Fig. 3. Codeine consumption as a function of unit price and dose. Other details as in Figure 1.

Fig. 4. Heroin consumption as a function of unit price and dose. Other details as in Figure 1.

higher dose combination was assigned to a “high” group. Where there were three values, the intermediate IR-dose combination was discarded and consumption from the re-

maining conditions was assigned to the “low” and “high” groups as above. We then used a Wilcoxon signed rank test to compare the low and high groups to evaluate the prediction of

Table 1

Coefficients and goodness-of-fit statistics for Equation 2. Values in parentheses are *p* values for each coefficient and overall goodness of fit.

Drug	Animal	<i>L</i>	<i>b</i>	<i>a</i>	<i>r</i>
Codeine	1010	10.90	-1.447	0.00001869	.625
		(.0001)	(.0001)	(.8012)	(.0220)
	1210	7.785	-0.860	-0.00005050	.817
		(.0007)	(.0291)	(.9540)	(.0021)
	1605	9.071	-1.156	-0.0002230	.548
		(.0001)	(.0005)	(.8313)	(.0345)
Dextropropoxyphene	1010	7.404	-0.921	-0.0001204	.911
		(.0023)	(.0096)	(.4245)	(.0001)
	1210	6.175	-0.701	-0.0003066	.875
		(.0002)	(.0052)	(.0678)	(.0001)
	1605	6.640	-0.781	-0.0001115	.840
		(.0001)	(.0005)	(.1622)	(.0001)
Heroin	1010	10.096	-1.171	-0.000001454	.810
		(.0001)	(.0001)	(.3080)	(.0001)
	1210	9.455	-1.078	-0.0000005693	.846
		(.0001)	(.0001)	(.4255)	(.0001)
	1605	8.920	-1.048	-0.0000007158	.842
		(.0001)	(.0001)	(.6391)	(.0001)
Pentazocine	1010	4.808	-0.385	-0.001	.835
		(.0001)	(.0620)	(.0129)	(.0001)
	1210	6.773	-0.803	-0.00006302	.610
		(.0001)	(.0001)	(.1230)	(.0094)
	1605	5.783	-0.649	-0.0003460	.645
		(.0001)	(.0007)	(.0175)	(.0016)

equal consumption when unit prices were equal.

RESULTS

For all drugs, consumption generally declined as unit price increased (Figures 1 through 4, left panels). Table 1 shows the coefficients obtained when the data were fitted with Equation 1, the *p* values for each coefficient, and the goodness of fit for each curve and its associated *p* value. All values of *L* (consumption at the lowest price) and all but one value of *b* (initial slope of the function) were statistically significantly different from zero, as were all values of *r* (goodness of fit). None of the values of *a* (acceleration in slope of the fitted curve) were statistically different from zero when either codeine or heroin consumption was analyzed; however, two of the values of *a* were significantly different from zero when dextropropoxyphene and pentazocine consumption were analyzed, and two others approached statistical significance. These analyses show that heroin and codeine consumption decreased as linear functions of

unit price. Pentazocine and dextropropoxyphene consumption also showed linear decreases as unit price increased, although in some cases there was a reliable acceleration in slope as unit price increased. The mean *r* for Equation 1 was .767.

Analysis of consumption as a function of dose showed that for all drugs, consumption increased as dose increased (Figures 1 through 4, right panels). Fitted values obtained when data were analyzed with Equation 2 are shown in Table 2, along with associated *p* values. All values of *m* (slope) were statistically significantly different from zero. None of the values of *k* (intercept) were statistically different from zero. All goodness-of-fit *r* values obtained with Equation 2 were statistically significant. The mean *r* for Equation 2 was .837.

The Wilcoxon signed rank test used to compare the goodness-of-fit values of Equations 1 and 2 showed no statistically significant difference between them ($Z = -1.647$, $p = .09$), indicating that neither accounted for more variance in the data.

The Wilcoxon test on the low and high IR-dose groups showed that consumption was

higher in the high conditions (i.e., when a unit price consisted of higher values of IR and dose) ($Z = -3.22, p = .001$). Consumption was higher with higher IR-dose combinations in 31 cases, equal in two cases, and lower in 11 cases. Thus, even though the IRs were higher in these conditions, any consumption-decreasing effect that IR might have had was offset by the increase in dose. Figure 5 shows dextropropoxyphene and pentazocine consumption as a function of unit price and dose. Figure 6 presents the codeine and heroin data in the same way. Although there are some points at which consumption appears to converge on a single function, it is usually higher at higher doses when unit prices are the same or comparable. Also, although all panels show declines in consumption as unit price increases, the data also show numerous cases in which consumption increases as unit price increases, as long as the higher unit price represents greater values of dose and IR.

DISCUSSION

These data allow investigation of unit price and the demand law as descriptors of self-administration of opioids in a progressive-ratio procedure. The data were consistent with the prediction that consumption would decline as unit price increased. In all but one case the coefficient in Equation 1 representing slope (b) was statistically significantly different from zero, indicating that consumption declined as a function of unit price. The appearance of the demand curves was somewhat different than that in other reports. In some cases the pentazocine and dextropropoxyphene demand curves increased in slope as unit price increased, as shown by the statistically significant values of the acceleration coefficient, a . However, none of the heroin or codeine demand curves produced statistically significant values of a , indicating a linear decline in consumption as unit price increased. The a coefficient can be considered to be a measure of changes in elasticity of demand (Allison, 1983, p. 102), with nonzero values of a indicating increasing price elasticity.

None of the curves showed the region of zero slope at lower prices that is often reported. Exclusion of data where consumption

Table 2
Coefficients and goodness-of-fit statistics for Equation 3. Values in parentheses are p values for each coefficient and overall goodness of fit.

Drug	Animal	m	k	r
Codeine	1010	3.990 (.0048)	0.791 (.9281)	.728 (.0048)
	1210	5.77 (.0012)	-7.694 (.5718)	.840 (.0012)
	1605	3.879 (.0008)	3.732 (.6281)	.767 (.0008)
Dextropropoxyphene	1010	5.628 (.0001)	-0.059 (.9834)	.953 (.0001)
	1210	6.227 (.0001)	-2.378 (.4304)	.937 (.0001)
	1605	3.421 (.0028)	0.847 (.8618)	.695 (.0028)
Heroin	1010	5.130 (.0001)	-0.086 (.3723)	.938 (.0001)
	1210	4.743 (.0001)	0.008 (.4255)	.935 (.0001)
	1605	5.156 (.0001)	-0.055 (.5852)	.929 (.0001)
Pentazocine	1010	3.282 (.0015)	3.187 (.5187)	.708 (.0015)
	1210	4.777 (.0001)	-0.376 (.8711)	.887 (.0001)
	1605	3.110 (.0002)	3.339 (.3444)	.730 (.0002)

was at the procedural maximum is probably partially responsible for the strong linearity of the consumption functions. However, inclusion of those points would raise the question of whether procedural limitations or unit price was the most important determinant of consumption.

Comparison of the goodness-of-fit statistics for Equations 1 and 2 revealed that they accounted for similar amounts of variance in the data. The failure to account for more variance with the more complex Equation 1 is somewhat surprising; Equation 1 has three free parameters, whereas Equation 2 has only two. Given equally valid predictors, addition of free parameters should improve the fit of a function. The result of the goodness-of-fit comparisons is reminiscent of that of Nader et al. (1993). They reported that unit price analysis using Equation 1 decreased the proportion of variance accounted for when compared to a linear model that included dose and instrumental requirement as separate regressors. Nader et al. also reported that when considered separately in the regression equa-

Fig. 5. Dextropropoxyphene and pentazocine consumption as functions of unit price and dose. Lines connect points representing consumption at a particular dose. Each panel contains 1 animal's data.

Fig. 6. Codeine and heroin consumption as functions of unit price and dose. Other details as in Figure 5.

tion, the variance in consumption due to dose was greater than that due to instrumental requirement.

The unit-price model predicts constant consumption at a given unit price. The data reported in this paper were not consistent with that prediction. Our analysis is a direct test of the unit-price model because it compares points representing consumption when the same unit price is made up of more than one IR-dose combination. Thus, it is a more rigorous test of the unit-price model than are previous analyses in which the evaluation was based upon the fit of an equation or equations incorporating unit price (Bickel et al., 1991, 1992; DeGrandpre et al., 1991). Differences in consumption as large as sixfold, clearly biologically significant, were seen at some unit prices.

The reasons for the apparent differences between studies in terms of the predictive utility of unit price need to be established. One possibility is that the differences result from some characteristic of the drugs used. This idea is concordant with Winger's (1993) results, in which methohexital consumption by rhesus monkeys was better explained by unit price analysis than was cocaine consumption. Alternatively, some as-yet-unspecified procedural variable may be important. Further, studies of unit price and drug consumption should exclude points representing procedural maxima and minima, because these can account for the region of zero slope at low prices and that of rapid decline in consumption at high prices. It should also be considered that the unit-price model has not yet been adequately tested. No prior test of the model has examined the range of unit prices that were possible in the present analysis. Moreover, in no prior report has the hypothesis of constant consumption at a given unit price been tested via a direct comparison (and statistical test) of equality of consumption at a given unit price when the unit price is comprised of more than one IR-dose combination.

The unit-price model remains intriguing as an account of drug consumption because drug consumption is widely reported to be positively correlated with dose and negatively correlated with IR. Both of these relationships are incorporated into a unit price. However, the present analysis suggests limits on the generality of the model. A more complete state-

ment of the relationship to consumption of dose, IR, and other as-yet-unspecified variables might enhance the model's predictive utility.

REFERENCES

- Allison, J. (1983). *Behavioral economics*. New York: Praeger.
- Bickel, W. K., DeGrandpre, R. J., Higgins, S. T., & Hughes, J. R. (1990). Behavioral economics of drug self-administration. I. Functional equivalence of response requirement and drug dose. *Life Sciences*, 47, 1501-1510.
- Bickel, W. K., DeGrandpre, R. J., Hughes, J. R., & Higgins, S. T. (1991). Behavioral economics of drug self-administration. II. A unit-price analysis of cigarette smoking. *Journal of the Experimental Analysis of Behavior*, 55, 145-154.
- Bickel, W. K., Hughes, J. R., DeGrandpre, R. J., Higgins, S. T., & Rizzuto, P. (1992). Behavioral economics of drug self-administration. IV. The effects of response requirement on the consumption of and interaction between concurrently available coffee and cigarettes. *Psychopharmacology*, 107, 211-216.
- Davis, W. M., & Nichols, J. R. (1963). A technique for the self-injection of drugs in the study of reinforcement. *Journal of the Experimental Analysis of Behavior*, 6, 233-235.
- DeGrandpre, R. J., Bickel, W. K., Hughes, J. R., & Higgins, S. T. (1992). Behavioral economics of drug self-administration. III. A reanalysis of the nicotine-regulation hypothesis. *Psychopharmacology*, 108, 1-10.
- Hoffmeister, F. (1979). Progressive-ratio performance in the rhesus monkey maintained by opiate infusions. *Psychopharmacology*, 62, 181-186.
- Hursh, S. R., Raslear, T. G., Shurtleff, D., Bauman, R., & Simmons, L. (1988). A cost-benefit analysis of the demand for food. *Journal of the Experimental Analysis of Behavior*, 50, 419-440.
- Nader, M. A., Hedeker, D., & Woolverton, W. L. (1993). Behavioral economics and drug choice: Effects of unit price on cocaine self-administration by monkeys. *Drug and Alcohol Dependence*, 33, 193-199.
- Russell, M. A., Wilson, C., Patel, U. A., Cole, P. V., & Feyerabend, C. (1973). Comparison of effect on tobacco consumption and carbon monoxide absorption of changing to high and low nicotine cigarettes. *British Medical Journal*, 4, 512-516.
- Schuster, C. R. (1976). Drugs as reinforcers in monkeys and man. *Pharmacological Reviews*, 27, 511-521.
- Weeks, J. R. (1962). Experimental morphine addiction: Method for automatic intravenous injections in unrestricted rats. *Science*, 138, 143-144.
- Winger, G. (1993). Fixed-ratio and time-out changes on behavior maintained by cocaine or methohexital in rhesus monkeys: 2. Behavioral economic analysis. *Experimental and Clinical Psychopharmacology*, 1, 154-161.
- Woolverton, W. L., & Nader, M. A. (1990). Experimental evaluation of the reinforcing effects of drugs. In M. W. Adler & A. Cowan (Eds.), *Modern methods in pharmacology: Vol. 6. Testing and evaluation of drugs of abuse* (pp. 165-192). New York: Wiley-Liss.

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