Pharmacology Biochemistry and Behavior, Vol. 43, pp. 61-70, 1992
Printed in the U.S.A.

0091-3057/92 $5.00 + .00

Δ^9-Tetrahydrocannabinol Interactions With Phencyclidine and Ethanol: Effects on Accuracy and Rate of Responding

PAMELA DOTY,*[1] LINDA A. DYKSTRA*† AND MITCHELL J. PICKER*

*Departments of *Psychology and †Pharmacology,*
University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-3270

Received 8 August 1991

DOTY, P., L. A. DYKSTRA AND M. J. PICKER. *Δ^9-Tetrahydrocannabinol interactions with phencyclidine and ethanol: Effects on accuracy and rate of responding.* PHARMACOL BIOCHEM BEHAV 43(1) 61-70, 1992.—The effects of Δ^9-tetrahydrocannabinol (Δ^9-THC) in combination with phencyclidine (PCP) or ethanol were examined in rats responding under a fixed-consecutive-number schedule of food presentation. Under this schedule, a minimum of 13 consecutive responses on one lever followed by one response on another lever produced food. When administered alone, PCP (0.1-10.0 mg/kg) and Δ^9-THC (0.1-5.6 mg/kg), but not ethanol (0.3-1.7 g/kg), decreased accuracy. PCP, Δ^9-THC, and ethanol alone all produced dose-dependent decreases in rate of responding. A dose-effect curve for PCP or ethanol was then redetermined in combination with selected doses of Δ^9-THC (0.125-1.75 mg/kg) and the data were analyzed according to the effect-addition and dose-addition models of additivity. When administered in combination, Δ^9-THC produced dose-dependent leftward shifts in the PCP dose-effect curves for both accuracy and rate of responding. The interactions for PCP + Δ^9-THC combinations were effect-additive for accuracy. In contrast, the type of interaction obtained for PCP + Δ^9-THC combinations on rate of responding depended upon the particular doses combined, as well as on the model used to analyze the interactions. According to the effect-addition model, these interactions were additive at low doses of Δ^9-THC and supraadditive at the highest dose. However, according to the dose-addition model the interactions at the higher doses of Δ^9-THC were infraadditive. Δ^9-THC also shifted the ethanol dose-effect curve for rate of responding to the left but did not alter the ethanol dose-effect curve for accuracy. The interactions for ethanol + Δ^9-THC combinations were effect-additive for accuracy and both effect- and dose-additive for rate of responding. The present investigation clearly illustrates the importance of examining an extensive range of dose combinations on different behavioral measures, as well as the use of appropriate analyses in studies designed to evaluate the interactions between drugs.

Phencyclidine Δ^9-Tetrahydrocannabinol Ethanol Drug interactions
Fixed-consecutive-number schedule Effect-addition Dose-addition Rats

THE widespread practice of polydrug abuse is well documented. For example, reports indicate that the most widely used illicit drug, marijuana, is rarely used alone (38). Rather, marijuana is most often used in combination with alcohol and somewhat less frequently with other abused drugs, including phencyclidine (PCP), amphetamine, and diazepam (2,8, 25,33). In many instances, the combination of marijuana and ethanol has produced greater effects on physiological measures and psychomotor performance than those produced by either drug alone (7,24). Despite evidence that polydrug abuse does occur and that many drug interactions have clinical significance, relatively few studies have examined the effects of combining different drugs of abuse.

Previous studies in laboratory animals indicate that when Δ^9-tetrahydrocannabinol (Δ^9-THC), the isomer believed to be responsible for marijuana's behavioral effects, is combined with PCP or ethanol, the resulting effects are greater than those produced by either drug alone. Both PCP and ethanol, for example, potentiate Δ^9-THC-induced hypothermia (30, 31). Using behavioral tasks, inactive doses of Δ^9-THC have been shown to potentiate PCP- and ethanol-induced decreases in conditioned avoidance and schedule-controlled responding (30,31).

Few studies have investigated the effects of Δ^9-THC administered in combination with PCP or ethanol on behavioral tasks requiring complex discriminations. Studies evaluating performance decrements on repeated acquisition, fixed-consecutive-number (FCN), and delayed matching-to-sample procedures indicate that PCP alone consistently decreases accuracy in several species (27,28,37). In contrast to the effects

[1] Requests for reprints should be addressed to Pamela Doty, Department of Psychiatry, The University of Chicago, Box 411, 5841 S. Maryland Avenue, Chicago, IL 60637.

produced by PCP on these discriminations tasks, the effects of Δ^9-THC are more variable. Some reports indicate that Δ^9-THC decreases accuracy in rhesus monkeys and chimpanzees responding under discrimination tasks such as temporal discrimination, delayed matching-to-sample, or delayed nonmatching-to-sample procedures (1,9,11). In contrast, others indicate that Δ^9-THC produces little or no effect on accuracy in rhesus monkeys, patas monkeys, or pigeons responding under discrimination tasks such as repeated acquisition, delayed matching-to-sample, or concurrent discrimination procedures (1,19,20,37). Thus, the extent to which Δ^9-THC disrupts accuracy appears to be related to the discrimination task or species used to examine its effects. Like Δ^9-THC, ethanol has been reported to produce variable effects on discrimination performance, with some studies reporting small decreases in accuracy (3,10,21,22) and others reporting little or no effect on accuracy (16).

In contrast to the number of studies that have evaluated the effects of PCP, Δ^9-THC, and ethanol alone on complex discriminations, only one study has evaluated the interactions between Δ^9-THC and PCP on these tasks. In that study, behaviorally inactive doses of Δ^9-THC potentiated the accuracy-decreasing effects of PCP in primates responding under a repeated acquisition procedure (37). To date, there are no studies evaluating the interactive effects of Δ^9-THC and ethanol on complex discrimination tasks in laboratory animals.

The purpose of the present investigation was to evaluate the effects produced by combinations of Δ^9-THC and PCP or ethanol in rats responding under an FCN schedule. To characterize these interactions, dose–effect curves for PCP or ethanol were determined alone and in combination with selected doses of Δ^9-THC. To assess whether the effects of PCP + Δ^9-THC or ethanol + Δ^9-THC combinations could be predicted based upon their individual effects, the data were quantified by comparing predicted outcomes based upon effect-addition and dose-addition models to obtained effects. The effect-addition and more recently the dose-addition model have been widely used to examine drug interactions using behavioral endpoints as the dependent measures. According to the effect-addition model, additivity is defined as a summation of the individual effects of two drugs. According to the dose-addition model, additivity is defined as the relative potency of the interacting drugs to produce a specified effect (39). Some advantages and disadvantages of these models are discussed in terms of their relevance to the present data.

METHOD

Subjects

Fourteen male Long-Evans hooded rats were maintained at 80–85% of their free-feeding weights (300–350 g). Six had been exposed previously to an FCN 8 schedule of food presentation and to acute doses of PCP or ethanol. Rats were individually housed with continuous access to water in a colony room maintained on a 12 L : 12 D cycle.

Apparatus

Four plastic and aluminum operant-conditioning chambers measuring 23 cm long, 19 cm high, and 20 cm wide were used. On the front panel of each chamber were two centrally mounted response levers 5 cm long located 9 cm from the chamber floor and 1.3 cm from either wall. Two stimulus lights were located 2.5 cm above each lever. When illuminated, the lights above the right lever were red and the lights above the left lever were white. On the ceiling of each chamber were two centrally mounted white houselights 2.5 cm from the rear wall. When operated, a pellet dispenser could deliver a 45-mg Noyes food pellet (P. J. Noyes Co., Lancaster, NH) into a trough centrally located under the two levers 1 cm from the chamber floor. The minimum force required to operate the response levers was 0.3 N. Each chamber was equipped with an exhaust fan that supplied ventilation and white noise to mask extraneous sounds. Scheduling of experimental events and data collection were controlled by a TRS model III microcomputer.

Behavioral Procedure

The beginning of each experimental session was signalled by the illumination of the houselight and the stimulus lights located above the two response levers. After preliminary lever-press training, rats were trained to respond under an FCN schedule of food presentation. Initially, at least one response on one lever (designated the work lever) followed by a subsequent response on another lever (designated the reinforcement lever) produced a food reinforcer (FCN 1). Over the next few sessions, the minimum response requirement on the work lever was increased gradually to 13. Under this FCN 13 schedule, a minimum of 13 responses on the work lever, followed by a response on the reinforcement lever, produced food. Responding fewer than 13 times on the work lever before switching to the reinforcement lever reset the response requirement. The experimental sessions terminated when the rat had received 50 food reinforcers or after 30 min had elapsed, whichever came first. Sessions were conducted 5 days per week.

Pharmacological Procedure

When the number of response runs per reinforcer and rate of responding showed no increasing or decreasing trends, dose–effect curves for Δ^9-THC (0.1–5.6 mg/kg) and PCP (0.1–10.0 mg/kg) were determined in one group of seven rats and for Δ^9-THC (0.1–5.6 mg/kg) and ethanol (0.3–1.7 g/kg) in a second group of seven rats. At least five doses of each drug were administered at least once in an irregular order 30 min prior to the experimental session. Drugs were administered at most twice per week, typically on Tuesday and Friday. The vehicle for each drug was administered on Thursday, with data obtained during these sessions serving as the nondrug control. Injections were given IP in a volume of 1 ml/kg for PCP and Δ^9-THC and in a volume of 10 ml/kg for ethanol.

After examining the effects of PCP, ethanol, and Δ^9-THC alone, the PCP (0.1–10.0 mg/kg) or ethanol (0.1–1.7 g/kg) dose–effect curve was redetermined in the presence of selected doses of Δ^9-THC (0.125–1.75 mg/kg) using five doses below the Δ^9-THC ED_{50} for rate of responding and one dose above. The selection of these doses of Δ^9-THC allowed the evaluation of drug combinations that produced no effect on rate of responding to drug combinations that substantially decreased response rate. Since even the lowest dose combinations of ethanol and Δ^9-THC suppressed rate of responding, it was necessary to use a dose of ethanol that had not been tested alone (0.1 g/kg). Moreover, the doses of Δ^9-THC administered in combination with PCP or ethanol could not be determined prior to the initial testing of the dose combinations. Consequently, some of the Δ^9-THC doses were not administered alone prior to the testing of the drug combinations. Thus, for subsequent analyses (see the Data Analysis section) the predicted effects of Δ^9-THC doses given in combination with PCP or ethanol were estimated by log-linear interpola-

tion; the 0.1- and 0.3-mg/kg doses of Δ^9-THC were used as the anchor points of the linear regression line to estimate the values of 0.125, 0.5, and 0.75 mg/kg Δ^9-THC and the 1.0- and 3.0-mg/kg doses were used as the anchor points for the 1.25- and 1.75-mg/kg doses of Δ^9-THC.

During all dose combinations, the selected dose of Δ^9-THC was administered IP on one side of the peritoneal cavity, followed by PCP or ethanol on the other side. Nondrug control data for drug combinations were obtained by administering double vehicle injections, the PCP or ethanol vehicle on one side of the peritoneal cavity and the Δ^9-THC vehicle on the other. At the end of the second phase of testing (approximately 7–8 months after the start of drug testing), various doses of PCP, Δ^9-THC, and ethanol were administered alone to determine whether sensitivity or tolerance to their effects had developed during the course of the experiment. Since a number of rats were no longer available for testing at this point in the study, only selected doses of PCP, Δ^9-THC, and ethanol were examined.

Drugs

PCP hydrochloride was dissolved in saline, Δ^9-THC in a solution of ethanol, emulphor and saline in a ratio of 1 : 1 : 8 (both drugs supplied by the National Institute on Drug Abuse, Rockville, MD), and absolute ethanol (U.S.P.) was diluted in distilled water.

Data Analysis

The number of response runs per reinforcer and rate of responding were recorded during each experimental session. A response run that consisted of at least 13 consecutive responses on the work lever before switching to the reinforcement lever was recorded as a correct response run, whereas a response run that consisted of less than 13 consecutive responses on the work lever before switching to the reinforcement lever was recorded as an incorrect response run. Although recorded, consecutive responses on the reinforcement lever were not counted as incorrect response runs. The number of response runs per reinforcer expressed as a function of dose provided a measure of accuracy. Rate of responding on both levers across the 30-min session was computed as a percentage of vehicle control rates and expressed as a function of dose.

The dose of drug that decreased rate of responding to 50% of control (i.e., the ED_{50} value) and the 95% confidence limits for PCP, Δ^9-THC, and ethanol alone, and for PCP or ethanol in combination with Δ^9-THC were determined. ED_{50} values were derived mathematically by log-linear interpolation using at least three points on the descending limb of the dose–effect curve unless the descending limb consisted of one dose that produced little effect on rate (80–100% of control) and another dose that almost eliminated responding (20–0% of control). In these instances, only those two points were used to determine the ED_{50} value. The slope of the linear regression line fitted to the descending limb of each dose–effect curve was also determined.

The effect-addition model of additivity was used to evaluate the interactions between Δ^9-THC and PCP or ethanol on accuracy and rate of responding. According to this model, predicted outcomes were calculated by summing the effect obtained with Δ^9-THC alone to the effect obtained with either PCP or ethanol alone. The effects of the doses of Δ^9-THC given in combination with PCP or ethanol were interpolated from the dose–effect curve determined for Δ^9-THC administered alone. The effects predicted could then be compared with the actual data obtained for combinations of Δ^9-THC and PCP or ethanol. For example, response runs per reinforcer were increased from a control value of 1.59 to 2.05 (i.e., an increase of 0.46) when 1.0 mg/kg Δ^9-THC was administered alone and from a control value of 1.35 to 1.68 (i.e., an increase of 0.33) when 1.0 mg/kg PCP was administered alone. Therefore, if the interaction between 1.0 mg/kg Δ^9-THC and 1.0 mg/kg PCP were additive the predicted increase would be 0.79 (i.e., 0.46 + 0.33). If the obtained effect and 95% confidence limits were less than the predicted value, the drug interaction was termed infraadditive. If the obtained effect and 95% confidence limits were greater than the predicted value, the drug interaction was termed supraadditive. Predictions based upon the effect-addition model of additivity for interactions on rate of responding were calculated in a similar manner. However, for rate of responding, if the obtained ED_{50} and 95% confidence limits were less than the predicted ED_{50}, the interaction was termed supraadditive. If the obtained ED_{50} and 95% confidence limits were greater than the predicted ED_{50}, the interaction was termed infraadditive.

The dose-addition model of additivity was used to evaluate the interactions between Δ^9-THC and PCP or ethanol on rate of responding. Predicted values based on the dose-addition model were determined according to isobolographic analysis (18). For this model, the ED_{50} values for rate of responding for PCP, Δ^9-THC, or ethanol were plotted on the proper coordinates according to the isobolographic method. The diagonal line that connects the two points represents the dose combinations that would be predicted to decrease rate of responding by 50% if the two drugs interacted in a dose-additive manner. Predicted values of the ED_{50} for Δ^9-THC in combination with PCP or ethanol were interpolated from the theoretical dose-additive line. The drug interaction was termed additive if the dose of PCP or ethanol necessary to produce a given effect (e.g., an ED_{50}) in combination with Δ^9-THC fell along the predicted diagonal on the isobologram. The drug interaction was termed supraadditive if the data and 95% confidence limits fell below the predicted diagonal (i.e., if it takes less PCP or ethanol than predicted to produce the given effect) and infraadditive if they fell above the predicted diagonal (i.e., if it takes more PCP or ethanol than predicted to produce the given effect).

RESULTS

Control Performance

Under control conditions in the Δ^9-THC + PCP group, where single injections of the PCP vehicle and Δ^9-THC vehicle were administered prior to the session, mean number of response runs per reinforcer was 1.46 (range across rats 1.16–1.98) and rate of responding was 1.44 responses/s (range across rats 1.0–2.31). Similar values were obtained in the Δ^9-THC + ethanol group following single control injections of the ethanol and Δ^9-THC vehicles, where the mean number of response runs was 1.33 (range across rats 1.10–1.63) and rate of responding was 1.57 responses/s (range across rats 1.05–2.16). For both groups, these values did not differ from noninjected control days or from double vehicle control injections.

Effects of PCP, Δ^9-THC, and Ethanol Administered Alone

Figure 1 shows the effects of PCP, Δ^9-THC, and ethanol on both response runs per reinforcer (top panels) and rate of responding (bottom panels). At doses that decreased rate of responding, PCP and Δ^9-THC increased the number of re-

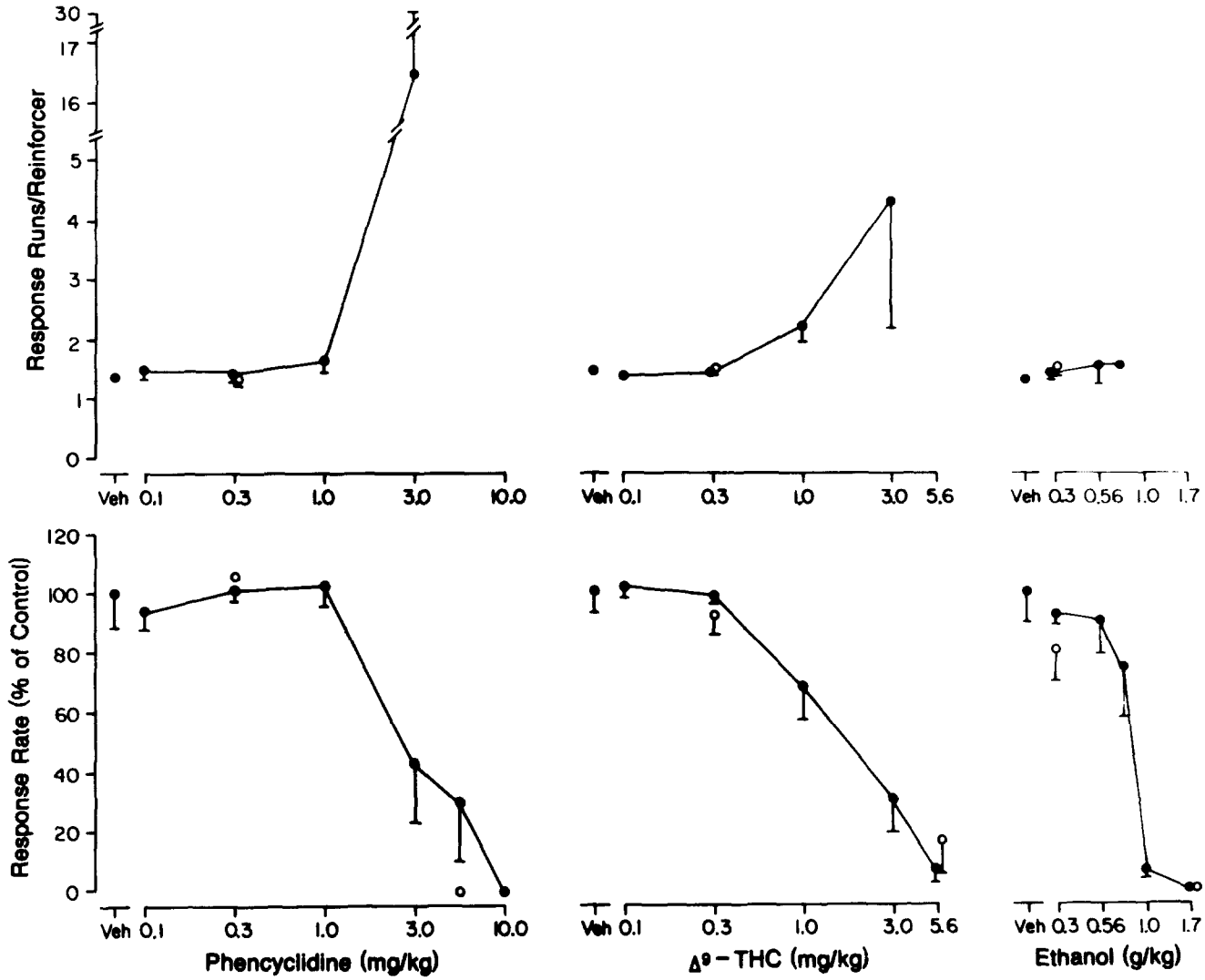

FIG. 1. Mean response runs per reinforcer (top panels) and mean rate of responding (bottom panels) plotted as a function of PCP (n = 7), Δ^9-THC (n = 14), or ethanol (n = 7) dose in rats responding under an FCN 13 schedule of food presentation. Rate of responding is expressed as a mean percent of individual vehicle control values. Data were excluded when an individual rat failed to obtain at least one reinforcer or when two thirds of animals tested failed to respond. The data above "veh" indicate mean number of response runs per reinforcer or mean rate of responding during single vehicle control sessions in which the appropriate drug vehicle was administered. The vertical lines represent 1 SE below the mean; when not indicated, the SE fell within the data point. (●), initial determination of the dose-effect curve; (○), redetermination of the dose-effect curve for PCP (n = 4), Δ^9-THC (n = 8–11), and ethanol (n = 5) following completion of the combination tests.

sponse runs per reinforcer. The maximum mean increase in response runs per reinforcer for PCP was 16.41, which occurred at 3.0 mg/kg, a dose that decreased rate of responding to 43% of the vehicle control value. The maximum mean increase in response runs per reinforcer produced by Δ^9-THC was 4.34, which occurred at 3.0 mg/kg, a dose that decreased rate of responding to 31% of the vehicle control value. In contrast to PCP and Δ^9-THC, ethanol had no effect on the mean response runs per reinforcer, even at doses that substantially decreased rate of responding. PCP, Δ^9-THC, and ethanol all produced dose-dependent decreases in rate of responding. After combinations of Δ^9-THC and PCP or ethanol were tested, the effects of selected doses of these drugs administered alone were redetermined. The effects of these drugs on response runs per reinforcer and rate of responding were similar to those obtained during the initial dose-effect determination with the exception that the rate-decreasing effects of 5.6 mg/kg PCP were slightly increased.

Effects of PCP in Combination with Δ^9-THC

Figure 2 shows the effects of PCP determined in combination with increasing doses of Δ^9-THC. When combined with PCP, low doses of Δ^9-THC produced little effect on response runs per reinforcer, whereas higher doses (1.25 and 1.75 mg/kg) shifted the PCP dose-effect curve to the left. In no in-

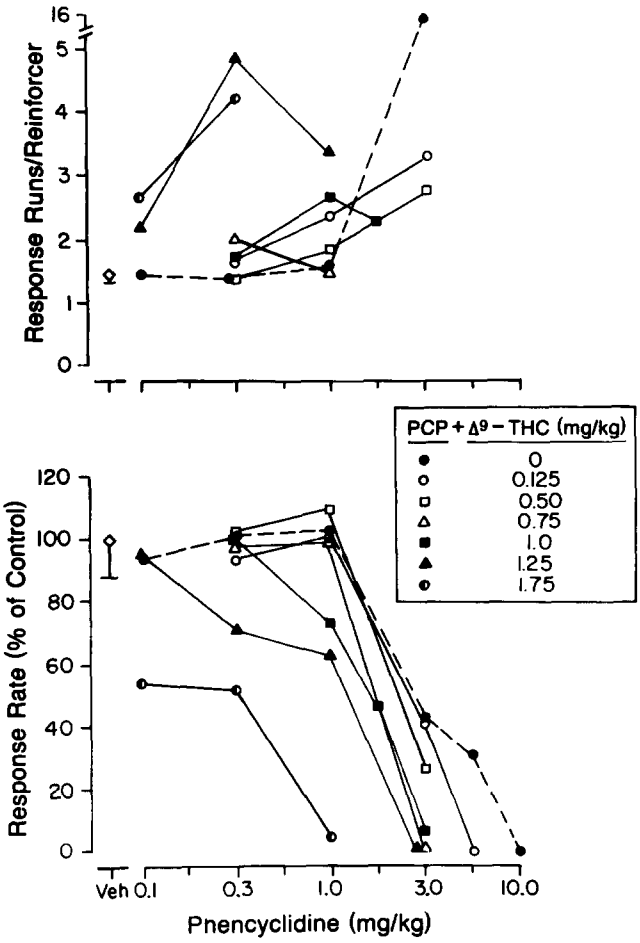

FIG. 2. Effects of selected doses of Δ^9-THC when administered in combination with PCP (n = 5-6) on mean response runs per reinforcer (top panels) and mean rate of responding (bottom panels) in rats responding under an FCN 13 schedule. The data above "veh" indicate mean number of response runs per reinforcer or mean rate of responding during double vehicle control sessions in which the appropriate drug vehicles were administered. Details are as described in Fig. 1.

stance did the effects produced by PCP + Δ^9-THC combinations exceed the maximum effect on response runs per reinforcer produced by a dose of PCP 3.0 mg/kg alone.

The PCP dose-effect curve for rate of responding was not shifted when combined with the lowest doses of Δ^9-THC. In contrast, higher doses of Δ^9-THC (0.75-1.75 mg/kg) produced dose-dependent leftward shifts of the PCP dose-effect curve, with the highest dose of Δ^9-THC (1.75 mg/kg) shifting the PCP ED_{50} approximately one log unit to the left of that obtained when PCP was administered alone. When this dose of Δ^9-THC was administered in combination with PCP, even the 0.1-mg/kg dose of PCP substantially decreased rate of responding. This dose of PCP had no effect when administered alone. In addition to shifting the PCP dose-effect curve to the left, high doses of Δ^9-THC altered the slope of the PCP dose-effect curve. For example, following the administration of 1.25 and 1.75 mg/kg Δ^9-THC, the slope of the PCP dose-effect curve was decreased to −58.3 and −22.5, respectively. This contrasts with the relatively steep slope of the PCP dose-effect curve alone, −99.4.

Effects of Ethanol in Combination with Δ^9 -THC

Figure 3 shows the effects of ethanol determined in combination with selected doses of Δ^9-THC. Ethanol did not increase response runs per reinforcer above the control value of 1.46. The administration of selected doses of Δ^9-THC in combination with ethanol generally did not change ethanol's effects on response runs per reinforcer; however, it did alter ethanol's rate-decreasing effects. Doses of Δ^9-THC (0.75-1.25 mg/kg) shifted the ethanol dose-effect curve for rate of responding to the left. The highest dose of Δ^9-THC, 1.25 mg/kg, shifted the ethanol ED_{50} approximately 1/2 log unit to the left of that obtained when ethanol was administered alone. Moreover, Δ^9-THC decreased the slope of the ethanol dose-effect curve. For example, when administered alone the slope of the ethanol curve was −243.8, whereas when administered in combination with 1.25 mg/kg Δ^9-THC the slope was −121.2.

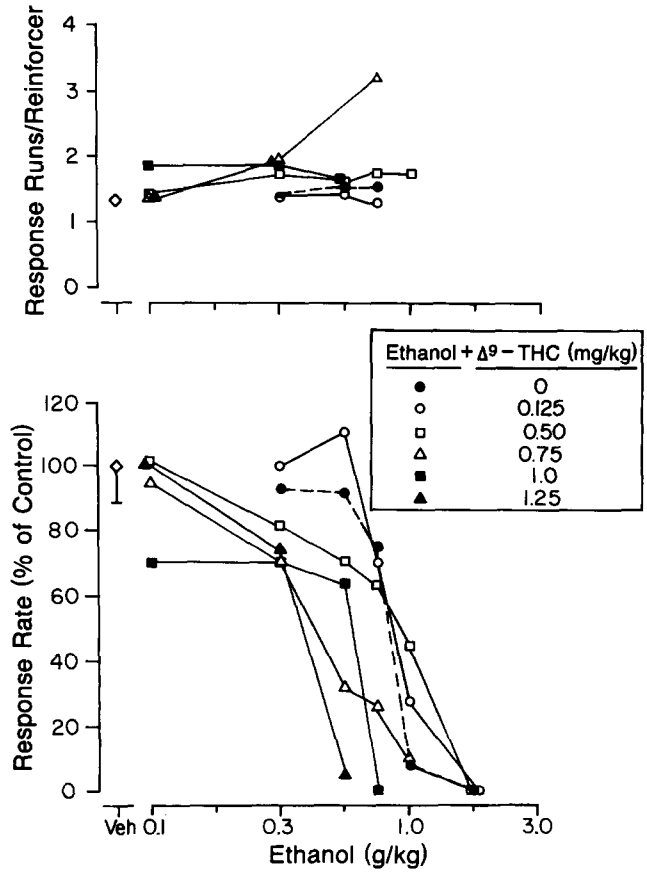

FIG. 3. Effects of selected doses of Δ^9-THC when administered in combination with ethanol (n = 4-6) on mean response runs per reinforcer (top panels) and mean rate of responding (bottom panels) in rats responding under an FCN 13 schedule. The data above "veh" indicate mean number of response runs per reinforcer or mean rate of responding during double vehicle control sessions in which the appropriate drug vehicles were administered. Details are as described in Fig. 1.

Analysis of Drug Interactions

Response runs per reinforcer. Dose-addition analysis was not used to evaluate the interactions between Δ^9-THC and PCP or ethanol on response runs per reinforcer because the dose-addition model requires the determination of dose combinations necessary to produce a specified effect. In the present study, the maximal increase in response runs per reinforcer produced by PCP, Δ^9-THC, and ethanol was 16.41, 4.34, and 1.58, respectively. Therefore, it was not possible to determine a dose of each of these drugs that produced a common effect on accuracy. However, these interactions could be evaluated using effect-addition analysis. Recall that according to the effect-addition model, predicted values are determined by summing the effects obtained with a given dose of PCP or ethanol alone to those obtained with a given dose of Δ^9-THC alone. Then, the predicted values are compared to those obtained when Δ^9-THC is given in combination with PCP or ethanol. The obtained data were considered effect-additive if the 95% confidence limits of the obtained data overlapped the predicted values.

Table 1 shows the obtained and predicted values for the PCP + Δ^9-THC combinations on response runs per reinforcer. The effect-addition model predicted increases in response runs per reinforcer when PCP was combined with increasing doses of Δ^9-THC. In 12 of 13 instances, the combinations of PCP and Δ^9-THC resulted in interactions that did not differ from the predicted values.

Table 2 shows the obtained and predicted values for the ethanol + Δ^9-THC combinations on response runs per reinforcer. The effect-addition model predicted only small increases in response runs per reinforcer when ethanol was combined with doses of Δ^9-THC because ethanol alone had little effect on this measure. As seen with combinations of PCP and Δ^9-THC, in 11 of 12 instances the combinations of ethanol and Δ^9-THC resulted in interactions that did not differ from the predicted values.

Rate of responding. The interactions between Δ^9-THC and PCP or ethanol on rate of responding were evaluated using both effect-addition and dose-addition analysis. Again, according to the effect-addition model, predicted values are determined by summing the effects obtained with a given dose of PCP or ethanol alone to those obtained with a given dose of Δ^9-THC alone. Using the dose-addition model, predicted values were interpolated from the theoretical dose-additive line on the isobologram that connects the Δ^9-THC ED_{50} with either the PCP or ethanol ED_{50}. Then, the predicted ED_{50} values were compared to those obtained when Δ^9-THC was given in combination with PCP or ethanol. The obtained data were considered additive if the 95% confidence limits of the obtained data overlapped the predicted values.

Figure 4 shows the ED_{50} values predicted from the effect-addition and dose-addition models, as well as data obtained for PCP + Δ^9-THC combinations (top) or for ethanol + Δ^9-THC combinations (bottom). The effect-addition model predicted little change for the ED_{50} values for PCP or ethanol even when combined with a dose of Δ^9-THC as high as 1.0 mg/kg. In contrast, the dose-addition model predicted that the ED_{50} values for PCP or ethanol when combined with Δ^9-THC would decrease as the dose of Δ^9-THC increased.

In fact, the ED_{50} value obtained for PCP decreased when combined with increasing doses of Δ^9-THC. Whether PCP + Δ^9-THC combinations produced additive, supraadditive, or infraadditive effects depended upon the model employed for the analysis. According to the effect-addition model, when PCP was combined with 1.0 mg/kg Δ^9-THC the effects were supraadditive, whereas the interactions were additive (note overlapping 95% confidence limits) when PCP was combined with lower doses of Δ^9-THC (0.125–0.75 mg/kg). According to the dose-addition model, when PCP was combined with Δ^9-THC (0.5, 0.75, and 1.0 mg/kg) the effects were infra-additive.

As seen with combinations of PCP and Δ^9-THC, the ED_{50} value for ethanol decreased when combined with increasing doses of Δ^9-THC. The interactions obtained with ethanol + Δ^9-THC combinations were generally effect- and dose-additive with the exception of one dose combination. According to the effect-addition model, the effects of ethanol in combination with the highest dose of Δ^9-THC (1.25 mg/kg) were supraadditive, whereas according to the dose-addition model the effects were additive.

DISCUSSION

The present study showed that PCP and Δ^9-THC decreased accuracy (response runs per reinforcer) in rats responding under an FCN 13 schedule. In contrast, ethanol had no effect on accuracy even at doses that substantially decreased rate

TABLE 1

NUMBER OF RESPONSE RUNS PER REINFORCER OBTAINED AND PREDICTED WITH PCP/Δ^9-THC COMBINATIONS

Δ^9-THC (mg/kg)	PCP (mg/kg)					
	0.1		0.3		0.1	
	Obtained	Predicted	Obtained	Predicted	Obtained	Predicted
0	1.48		1.41		1.63	
0.125	–	1.50	1.67	1.42	2.39	1.63
0.50	–	1.83	1.41	1.75	1.88	1.96
0.75	–	2.19	2.00	2.11	1.51*	2.32
1.00	–	1.84	1.69	1.91	2.70	2.19
1.25	2.21	2.79	4.88	2.71	3.41	2.92
1.75	2.67	2.64	4.22	2.83	–	3.09

–, dose combination not obtained.
*Nonoverlap of 95% confidence limits.

TABLE 2

NUMBER OF RESPONSE RUNS PER REINFORCER OBTAINED AND PREDICTED WITH ETHANOL/Δ^9-THC COMBINATIONS

Δ^9-THC (mg/kg)	ETHANOL (g/kg)					
	0.3		0.56		0.75	
	Obtained	Predicted	Obtained	Predicted	Obtained	Predicted
0	1.41		1.55		1.55	
0.125	1.39	1.55	1.42	1.69	1.33*	1.70
0.50	1.76	1.71	1.88	1.85	1.76	1.86
0.75	1.97	1.70	1.62	1.92	3.20	1.91
1.00	1.90	1.99	1.68	2.17	–	2.18
1.25	1.95	2.34	–	2.64	–	2.47

–, dose combination not obtained.
*Nonoverlap of 95% confidence limits.

of responding. When administered in combination, Δ^9-THC produced dose-dependent leftward shifts in the PCP dose-effect curves for accuracy and rate of responding and in the ethanol dose-effect curve for rate of responding.

The finding that PCP decreased accuracy under an FCN 13 schedule is consistent with previous studies that showed PCP consistently decreases accuracy in several species responding under an FCN 8 schedule (26,27), as well as with other tasks requiring complex discriminations (19,36,37). Previous reports indicate that Δ^9-THC's accuracy-decreasing effects depend upon the task and species examined (1,6, 11,20,32,37), and in the present investigation Δ^9-THC produced only small decreases in accuracy. The lack of accuracy-decreasing effects obtained with ethanol are consistent with reports indicating little or no decreases in accuracy in several species (3,16,21,22). The effects of PCP, Δ^9-THC, and ethanol when administered alone on rate of responding were consistent with previous reports in several species responding under both simple schedules of food presentation (13,15,17) and complex discriminations (3,27,37).

When Δ^9-THC was combined with PCP, the PCP dose-effect curve for both accuracy and rate of responding shifted leftward. In fact, many of the doses of Δ^9-THC that shifted the PCP dose-effect curve to the left produced little or no effect when administered alone. Since the interaction phase of this study required approximately 8 months to complete, the leftward shifts in the PCP dose-effect curves could have been due to an increased sensitivity to PCP rather than to the interaction between PCP and Δ^9-THC; however, when PCP's effects were redetermined following the interaction phase of the study they were similar to those determined initially. Thus, alterations in the PCP dose-effect curve were not due to changes in the effects of PCP alone. Moreover, the leftward shifts in the PCP dose-effect curve for accuracy and rate of responding produced by Δ^9-THC are consistent with previous reports that behaviorally inactive doses of Δ^9-THC alter PCP's effects on hypothermia, conditioned avoidance responding, and schedule-controlled behavior in rats (30), as well as on repeated acquisition performance in monkeys (37).

When Δ^9-THC was combined with ethanol, the ethanol dose-effect curve for rate of responding, but not for accuracy, shifted leftward. As previously noted, many of the doses of Δ^9-THC that shifted the ethanol dose-effect curve to the left produced little or no effect when administered alone. Moreover, redetermination of ethanol's effects at the end of the study indicated that the effects of ethanol did not change during the course of the study. Previous studies have also demonstrated that behaviorally inactive doses of Δ^9-THC alter ethanol's effects on a variety of other measures including sleep, hypothermia, motor performance, schedule-controlled behavior, and conditioned avoidance responding (13,31,34).

Since the present study examined a range of doses of Δ^9-THC in combination with a range of doses of PCP and ethanol, these interactions could be further quantified using the effect-addition and dose-addition models of additivity. Recall that the effect-addition model defines additivity in terms of the summation of the individual effects of the drugs, whereas the dose-addition model defines additivity in terms of the relative potency of the interacting drugs to produce a specified effect (39). Although the effect-addition model benefits from its simplicity, it does have major theoretical limitations [e.g., see (39)]. For example, this model predicts that doses of a drug that have no effect on a given dependent measure should not alter the effects produced by other drugs. Furthermore, there is data to suggest that this model does not provide an adequate prediction of the simplest type of drug interaction, the administration of a drug with itself (41). The dose-addition model has the advantage of taking both dose and effect into account. As such, this model has been shown to predict accurately the interactions when a drug is administered with itself, as well as when two drugs with common pharmacological actions are administered in combination (40,41). Although offering a number of advantages from a theoretical perspective, there are disadvantages to the use of the dose-addition model, including the large number of dose combinations required for such an analysis, as well as the requirement that the two drugs of interest produce a common endpoint.

Given that these two models have different theoretical foundations, it is not surprising that in the present study these models showed clear differences in their predicted outcomes. For example, the effect-addition model predicted little change in the PCP or ethanol ED_{50} when combined with doses of Δ^9-THC that produced little effect when administered alone. This model assumes that since the doses of Δ^9-THC given in combination with PCP or ethanol were below the threshold for producing a behavioral effect, Δ^9-THC should not alter the effects of PCP. In contrast, the dose-addition model predicted the PCP or ethanol dose-effect curve would shift progressively to the left as the dose of Δ^9-THC was increased. This discrepancy between the two models highlights the rele-

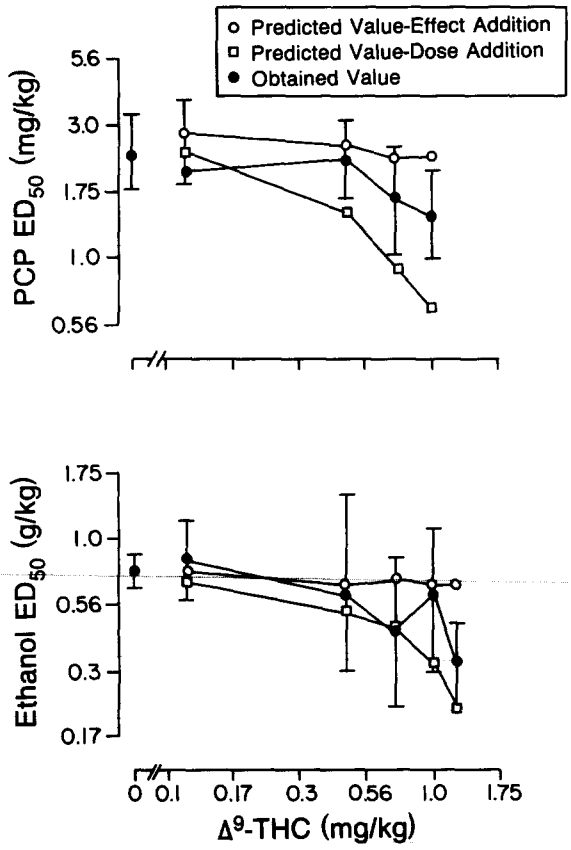

FIG. 4. Obtained and predicted ED_{50} values for rate of responding for PCP + Δ^9-THC (top) or ethanol + Δ^9-THC (bottom) combinations. Vertical lines represent the 95% confidence limits. In the instances where the dose of Δ^9-THC administered alone produced greater than a 50% decrease in rate of responding, obtained and predicted ED_{50} values for drug combinations could not be determined (e.g., 1.25 mg/kg Δ^9-THC in the PCP group).

vance of the particular model used to analyze drug interactions to the interpretation of the results.

The results of PCP + Δ^9-THC interactions in the present investigation contrast with an earlier study (37) in which effect-addition analysis showed that Δ^9-THC potentiates the accuracy-decreasing effects of PCP on a repeated acquisition task in patas monkeys. The conflicting results between the two studies may be related to the fact that this study evaluated the effects of only two doses of Δ^9-THC in combination with PCP. Given that the interactions observed between drugs have been shown to depend upon the particular dose combinations examined (12,42), such discrepancies are not surprising. Further differences between the two studies may be related to the tasks used to examine the drug interactions. While the repeated acquisition task requires learning a different response chain each session, the FCN schedule requires performance of the same response sequence each session. Studies have shown that the performance of a complex discrimination is generally less sensitive to the disruptive effects of drugs on accuracy than the acquisition of a complex discrimination (35).

Evaluation of the effects of Δ^9-THC + ethanol combinations on accuracy according to the effect-addition model are consistent with some clinical reports that combinations of Δ^9-THC and ethanol on cognitive tasks are effect-additive (4,5), although "enhanced" effects have been reported (24). However, a comparison of these studies is limited by many factors, including differences in species, tasks, and the failure to administer more than one dose of Δ^9-THC.

According to effect-addition analysis, combinations of PCP with low doses of Δ^9-THC produced additive interactions on rate of responding, whereas the interactions between PCP and the highest dose of Δ^9-THC were supraadditive. Previous studies that used the effect-addition model to evaluate interactions between PCP and Δ^9-THC on operant responding have reported additive as well as supraadditive effects (23,30,37). In contrast, according to the dose-addition model, the interactions between PCP and Δ^9-THC were infraadditive, with the exception of the lowest dose of Δ^9-THC, which produced additive interactions. The present investigation differs from previous reports that examined a limited number of dose combinations and have not used the dose-addition model to assess interactions between PCP and Δ^9-THC. It is not possible to derive predictions according to the dose-addition model from the data given in these earlier reports and, thus, a comparison cannot be made of the results in the present study with those from other studies. Interestingly, the interaction for one dose combination (PCP + 1.0 mg/kg Δ^9-THC) was supraadditive when evaluated by effect-addition analysis yet was infraadditive when evaluated by dose-addition analysis. This finding provides additional evidence that conclusions from the effect-addition model will often be in disagreement with those obtained by the dose-addition model (29,40). Thus, in the present investigation the interactions between PCP and Δ^9-THC on rate of responding were dependent upon the dose combination examined, as well as on the model of additivity used to evaluate the data.

When evaluated according to either the effect-addition or dose-addition model, the interactions between ethanol and Δ^9-THC on rate of responding were generally additive. It should be noted, however, that according to the effect-addition model supraadditivity was obtained at the 1.25-mg/kg dose of Δ^9-THC; according to the dose-addition model, the interaction at this dose combination was additive. Previous reports indicate that interactions between ethanol and Δ^9-THC on motor activity and conditioned avoidance response performance are often greater than those produced by either drug alone (14,31). In these investigations, the effect-addition model was used to analyze the data. Thus, the present results extend these findings to include rate of responding under an FCN schedule. Furthermore, the present findings suggest that supraadditive interactions between ethanol and Δ^9-THC may be limited to certain dependent measures and selected dose combination, and depend upon the model used to quantify the data.

An additional assumption of the effect-addition and dose-addition models is that the shifts in the dose-effect curves for the drug combinations are parallel. In the present investigation, the higher doses of Δ^9-THC produced a dose-related decrease or flattening in the slope of both the PCP and ethanol dose-effect curves. Without parallel slopes, it is possible that the obtained interactions between Δ^9-THC and PCP or ethanol could also depend upon the behavioral endpoint selected. Thus, dose-addition and effect-addition analyses were also calculated for the ED_{25} and ED_{75} values. Interestingly, unlike the differences found for the PCP ED_{50} values, none of the interactions between Δ^9-THC and PCP deviated from additivity when the ED_{25} and ED_{75} values were compared to predicted values based upon either model (data not shown).

In contrast, the interactions between Δ^9-THC and ethanol did not deviate from additivity at any behavioral endpoint evaluated (ED_{25}, ED_{50}, or ED_{75}) (data not shown). Although this type of analysis was not performed in earlier experiments examining the interaction between PCP and Δ^9-THC, such an effect does suggest that using a single behavioral endpoint (ED_{50}) may not adequately reflect the obtained interaction between two drugs.

Although the present investigation cannot resolve the issue as to whether the effect-addition or dose-addition model is more appropriate when analyzing drug interactions, these data clearly demonstrate the complexity of analyzing drug interactions. Furthermore, the present study demonstrates that conclusions made about the interactive effects of combinations of Δ^9-THC, PCP, and ethanol depend upon a number of variables, including the dose combination examined, behavior measured, model used to assess the interaction, and behavioral endpoint evaluated. Although interpretation of the clinical significance of the present findings would be difficult given the complexity of these results, these data provide a foundation for future investigations of the behavioral interactions between drugs of abuse.

ACKNOWLEDGEMENTS

This work was supported by NIDA Contract RFP271-87-8126. L.A.D. was a recipient of Research Scientist Award KO5/DA-00033 from the National Institute on Drug Abuse. These data were submitted by P.D. in partial fulfillment of the requirements for the Degree of Doctor of Philosophy at the University of North Carolina at Chapel Hill.

REFERENCES

1. Aigner, T. G. Delta-9-tetrahydrocannabinol impairs visual recognition memory but not discrimination learning in rhesus monkeys. Psychopharmacology (Berl.) 95:507–511; 1988.
2. Balster, R. L.; Chait, L. D. The behavioral effects of phencyclidine in animals. In: Peterson, R. C.; Stillman, R. C., eds. Phencyclidine (PCP) abuse: An appraisal. Research Monograph No. 10. Rockville, MD: National Institute on Drug Abuse; 1978:78–728.
3. Barthalamus, G. T.; Leander, J. D.; McMillan, D. E. Combined effects of ethanol and diazepam on performance and acquisition of serial position sequences in pigeons. Psychopharmacology (Berl.) 59:101–102; 1978.
4. Belgrave, B. E.; Bird, K. D.; Chesher, G. B.; Jackson, D. M.; Libbe, K. E.; Starmer, G. A.; Teo, R. K. C. The effect of (−) trans-Δ^9-tetrahydrocannabinol, alone and in combination with ethanol, on human performance. Psychopharmacology (Berl.) 62:53–60; 1979.
5. Bird, K. D.; Boyleyn, T.; Chesher, G. B.; Jackson, D. M.; Starmer, G. A.; Teo, R. K. C. Intercannabinoid and cannabinoid–ethanol interactions and their effects on human performance. Psychopharmacology (Berl.) 71:181–188; 1980.
6. Branch, M. N.; Dearing, M. E.; Lee, D. M. Acute and chronic effects of Δ^9-tetrahydrocannabinol on complex behavior of squirrel monkeys. Psychopharmacology (Berl.) 71:247–256; 1980.
7. Chesher, G. B.; Franks, H. M.; Hensley, V. R.; Hensley, W. J.; Jackson, D. M.; Starmer, G. A.; Teo, R. K. C. The interaction of ethanol and Δ^9-tetrahydrocannabinol in man. Effects on perceptual, cognitive and motor functions. Med. J. Aust. 2:159–163; 1976.
8. Drug Abuse Warning Network, National Institute on Drug Abuse. Annual Data 1987. Series I, Number 7. Washington, DC: U.S. Department of Health and Human Services; 1989:iii–vi.
9. Elsmore, T. F. Effects of delta-9-tetrahydrocannabinol on temporal and auditory discrimination performance of monkeys. Psychopharmacology (Berl.) 26:62–72; 1972.
10. Elsner, J.; Adler, S.; Zbinden, G. Interaction between ethanol and caffeine in operant behavior of rats. Psychopharmacology (Berl.) 96:194–205; 1988.
11. Ferraro, D. P.; Grilly, D. M. Effects of chronic exposure to Δ^9-tetrahydrocannabinol on delayed matching-to-sample in chimpanzees. Psychopharmacologia 37:127–138; 1974.
12. Foltin, R. W.; Woolverton, W. L.; Schuster, C. R. Effects of psychomotor stimulants, alone and in pairs, on milk drinking in the rat after intraperitoneal and intragastric administration. J. Pharmacol. Exp. Ther. 226:411–418; 1983.
13. Frankenheim, J. M.; McMillan, D. E.; Harris, L. S. Effects of *l*-Δ^9- and *l*Δ^9-*trans*-tetrahydrocannabinol and cannabinol on schedule-controlled behavior in pigeons and rats. J. Pharmacol. Exp. Ther. 178:241–252; 1971.
14. Kalant, H.; LeBlanc, A. E. Effect of acute and chronic treatment of delta-9-tetrahydrocannabinol on motor impairment by ethanol in the rat. Can. J. Pharmacol. 52:291–297; 1974.
15. Katz, J. L.; Spealman, R. D.; Clark, R. D. Stereoselective behavioral effects of *N*-allylnormetazocine in pigeons and squirrel monkeys. J. Pharmacol. Exp. Ther. 232:452–461; 1985.
16. Laties, V. G.; Evans, H. L. Methylmercury-induced changes in operant discrimination by the pigeon. J. Pharmacol. Exp. Ther. 214:620–628; 1980.
17. Leander, J. D.; McMillan, D. E.; Ellis, F. W. Ethanol and isopropanol effects on schedule-controlled responding. Psychopharmacology (Berl.) 47:157–164; 1976.
18. Loewe, S. The problem of synergism and antagonism of combined drugs. Arzneimittelforsch 3:285–290; 1953.
19. McMillan, D. E. Effects of chemicals on delayed matching behavior in pigeons I: Acute effects of drugs. Neurotoxicology 2:485–498; 1981.
20. McMillan, D. E. Failure of acute and chronic administration of Δ^9-tetrahydrocannabinol to affect the repeated acquisition of serial position responses in pigeons. Pavl. J. Bio. Science 23:57–66; 1988.
21. Melia, K. F.; Ehlers, C. L. Signal detection analysis of ethanol on a complex conditional discrimination. Pharmacol. Biochem. Behav. 33:581–584; 1989.
22. Mello, N. K. Alcohol effects on delayed matching to sample performance by rhesus monkey. Physiol. Behav. 7:77–101; 1971.
23. Murray, T. F.; Craigmill, A. L. Interactions between Δ^9-tetrahydrocannabinol and phencyclidine in rats and mice. Proc. West Pharmacol. Soc. 19:362–368; 1976.
24. Perez-Reyes, M.; Hicks, R. E.; Bumberry, J.; Jeffcoat, R.; Cook, C. E. Interaction between marihuana and ethanol: Effects on psychomotor performance. Alcohol. Clin. Exp. Res. 12:268–276; 1988.
25. Peterson, R. C.; Stillman, R. C. Phencyclidine: An overview. In: Peterson, R. C.; Stillman, R. C., eds. Phencyclidine (PCP) abuse: An appraisal. Research Monograph No. 21. Rockville, MD: National Institute on Drug Abuse; 1978:1–17.
26. Picker, M.; Dykstra, L. A. Differential effects of opioid and nonopioid analgesics on conditional discriminations in pigeons. Psychopharmacology (Berl.) 94:405–411; 1988.
27. Picker, M.; Heise, J. W.; Dykstra, L. A. Evaluation of the effects of opioid agonists and antagonists under a fixed-consecutive-number schedule in rats. Pharmacol. Biochem. Behav. 27: 73–80; 1987.
28. Picker, M.; Massie, C. A.; Dykstra, L. A. Evaluation of the effects of opioid agonists and antagonists under a delayed matching-to-sample procedure in pigeons. Psychopharmacology (Berl.) 93:230–236; 1987.
29. Poch, G. The confusion about additive combinations. Trends Pharmacol. Sci. 2:256–257; 1981.
30. Pryor, G. T.; Husain, S.; Larsen, F. F.; McKenzie, C. E.; Carr, J. D.; Braude, M. C. Interactions of delta-9-tetrahydrocannabi-

nol and phencyclidine hydrochloride in rats. Pharmacol. Biochem. Behav. 7:331–345; 1977.
31. Pryor, G. T.; Larsen, F. F.; Carr, J. D.; Braude, M. C. Interactions of delta-9-tetrahydrocannabinol with phenobarbital, ethanol and chlordiazepoxide. Pharmacol. Biochem. Behav. 6:123–135; 1977.
32. Schulze, G. E.; McMillan, D. E.; Bailey, J. R.; Scallet, A.; Ali, S. F.; Slikker, W.; Paule, M. G. Acute effects of Δ^9-tetrahydrocannabinol in rhesus monkeys as measured by performance in a battery of complex operant tests. J. Pharmacol. Exp. Ther. 245: 178–186; 1988.
33. Siemens, A. J. Effects of cannabis in combination with ethanol and other drugs. In: Peterson, R. C., ed. Marijuana research findings: 1980. Research Monograph No. 31. Rockville, MD: National Institute on Drug Abuse; 1980:167–198.
34. Siemens, A. J.; Khanna, J. H. Acute metabolic interactions between ethanol and cannabis. Alcohol. Clin. Exp. Res. 1:343–348; 1977.
35. Thompson, D. M.; Moerschbaecher, J. M. Drug effects on repeated acquisition. In: Thompson, T.; Dews, P. B., eds. Advances in behavioral pharmacology. vol. 2. New York: Academic Press; 1979:229–259.
36. Thompson, D. M.; Moerschbaecher, J. M. Phencyclidine in combination with pentobarbital: Supra-additive effects on complex operant behavior in pigeons. Pharmacol. Biochem. Behav. 17: 353–357; 1982.
37. Thompson, D. M.; Winsauer, P. J. Delta-9-tetrahydrocannabinol potentiates the disruptive effects of phencyclidine on repeated acquisition in monkeys. Pharmacol. Biochem. Behav. 23:1051–1057; 1985.
38. Voss, H. L. Data from the 1985 National Household Survey. In: Gust, S. W.; Walsh, J. M., eds. Drugs in the workplace: Research and evaluation data. Research Monograph No. 91. Rockville, MD: National Institute on Drug Abuse; 1989:33–46.
39. Wessinger, W. D. Approaches to the study of drug interactions in behavioral pharmacology. Neurosci. Biobehav. Rev. 10:103–113; 1986.
40. Wessinger, W. D.; Evans, E. B. Modeling multiple agent interactions in behavioral pharmacology. J. Am. Coll. Toxicol. 7:953–962; 1988.
41. Woolverton, W. L. Analysis of drug interactions in behavioral pharmacology. In: Thompson, T.; Dews, P. B.; Barrett, J. E., eds. Neurobehavioral pharmacology. vol. 6. Hillsdale, NJ: Lawrence Erlbaum Associates; 1987:275–302.
42. Woolverton, W. L.; Balster, R. L. Effects of combinations of phencyclidine and pentobarbital on fixed-interval performance in rhesus monkeys. J. Pharmacol. Exp. Ther. 217:611–618; 1981.