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SOBERING AGENT: EFFECTIVENESS MEASUREMENT AND DEVELOPMENT

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16. Abstract This study examined three drugs: Amantadine, Doxapram and Maalox, to determine if they could inhibit the rate of absorption of alcohol into the blood stream and/or antagonize the behavioral impairment induced by alcohol. Fifteen subjects received five experimental treatments (placebo alone, alcohol alone, and alcohol with each of the three drugs) on five occasions separated by one week intervals. Drug treatments, administered prior to alcohol, were Amantadine at 4.41 mg Kg B.W., Doxapram at 2 mg Kg/B.W., and Maalox at 44 mg Kg/B.W. The alcohol treatment was .99 gm alcohol Kg/B.W. After alcohol administration, blood alcohol concentrations (BAC) were obtained by breath sampling every 15 minutes, to determine the rate of alcohol absorption. Subjects performed a behavioral test battery when BAC's were .10% and .05% on the declining curve. The five-item battery consisted of a critical tracking task, a divided-attention task, a rate of information processing task, a body sway task and a hand steadiness task. The test battery was administered three times on each experimental day, the first battery prior to treatment, and the second and third testing when the BAC had dropped to .10% and .05% respectively. The absorption of alcohol was delayed by the drugs, but only Doxapram produced a delay of practical importance and statistical significance. All of the experimental tasks proved sensitive to the effect of alcohol. There was no evidence that the combination of the drugs with the alcohol produced a lesser degree of impairment on the experimental tasks than produced by alcohol alone. This study demonstrates that some drugs have the ability to delay alcohol absorption into the blood stream and thus produce lower blood alcohol concentrations. These lower BAC's would reduce the probabilities of accidents following alcohol consumption.

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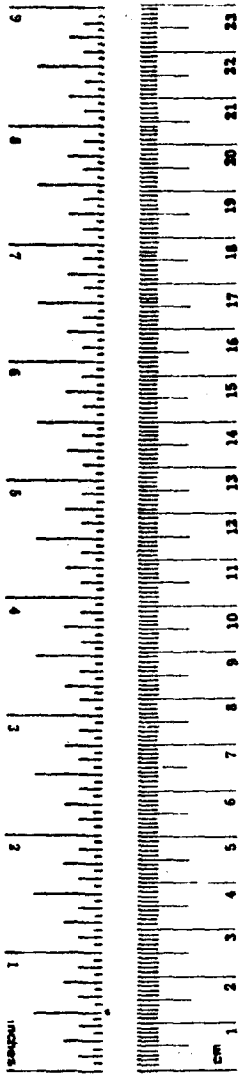
METRIC CONVERSION FACTORS

Approximate Conversions to Metric Measures

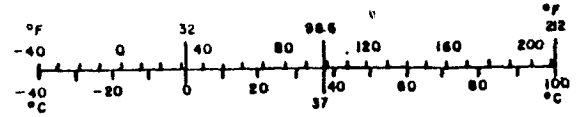
Symbol	When You Know	Multiply by	To Find	Symbol
		LENGTH		
in	inches	*2.5	centimeters	cm
ft	feet	30	centimeters	cm
yd	yards	0.9	meters	m
mi	miles	1.6	kilometers	km
		AREA		
in^2	square inches	6.5	square centimeters	cm^2
ft^2	square feet	0.09	square meters	m^2
yd^2	square yards	0.8	square meters	m^2
mi^2	square miles	2.6	square kilometers	km^2
	acres	0.4	hectares	ha
		MASS (weight)		
oz	ounces	28	grams	g
lb	pounds	0.45	kilograms	kg
	short tons (2000 lb)	0.9	tonnes	t
		VOLUME		
tsp	teaspoons	5	milliliters	ml
Tbsp	tablespoons	15	milliliters	ml
fl oz	fluid ounces	30	milliliters	ml
c	cups	0.24	liters	l
pt	pints	0.47	liters	l
qt	quarts	0.95	liters	l
gal	gallons	3.8	liters	l
ft^3	cubic feet	0.03	cubic meters	m^3
yd^3	cubic yards	0.76	cubic meters	m^3
		TEMPERATURE (exact)		
°F	Fahrenheit temperature	5/9 (after subtracting 32)	Celsius temperature	°C

*1 in = 2.54 (exactly). For other exact conversions and more detailed tables, see NBS Misc. Publ. 286, Units of Weights and Measures, Price $2.25, SD Catalog No. C13.10:286.



Approximate Conversions from Metric Measures

Symbol	When You Know	Multiply by	To Find	Symbol
		LENGTH		
mm	millimeters	0.04	inches	in
cm	centimeters	0.4	inches	in
m	meters	3.3	feet	ft
m	meters	1.1	yards	yd
km	kilometers	0.6	miles	mi
		AREA		
cm^2	square centimeters	0.16	square inches	in^2
m^2	square meters	1.2	square yards	yd^2
km^2	square kilometers	0.4	square miles	mi^2
ha	hectares (10,000 m^2)	2.5	acres	
		MASS (weight)		
g	grams	0.035	ounces	oz
kg	kilograms	2.2	pounds	lb
t	tonnes (1000 kg)	1.1	short tons	
		VOLUME		
ml	milliliters	0.03	fluid ounces	fl oz
l	liters	2.1	pints	pt
l	liters	1.06	quarts	qt
l	liters	0.26	gallons	gal
m^3	cubic meters	35	cubic feet	ft^3
m^3	cubic meters	1.3	cubic yards	yd^3
		TEMPERATURE (exact)		
°C	Celsius temperature	9/5 (then add 32)	Fahrenheit temperature	°F



ADDENDUM

The purpose of this study was to determine if selected drugs can either inhibit the rate of alcohol absorption into the blood stream (delay absorption and/or suppress peak BAC level), and/or reduce the impairing effects of alcohol on performance (behavioral tests associated with driving). Specifically, the study examined three drugs: Doxapram and Amandtadine (both central nervous system antagonists), and Maalox (anti-absorption agent).

Doxapram (central nervous system antagonist) delayed alcohol asborption (peak BAC) up to one-hour over an "alcohol-only" treatment condition. Doxapram also suppressed peak BAC level 10-15%. Amantadine and Maalox had no measurable effect on absorption rate or on peak BAC level. All performance tasks (behavioral tests associated with driving) proved sensitive to the effects of alcohol (degradation of performance). The performance degradation associated with the combination of alcohol and any of the drugs tested (Doxapram, Amantadine, Maalox) was not significantly less than that associated with alcohol alone.

It should be pointed out that while Doxapram did delay alcohol absorption rate and suppress peak BAC level 10-15% (statistically significant), performance decrements due to alcohol on behavioral tasks associated with driving were not ameliorated. Therefore, conclusions concerning reduced probability of highway accidents (i.e., lower BAC due to the presence of Doxapram), should be entered into with caution; since BAC was not reduced sufficiently by Doxapram to overcome the behavioral impairing effects of alcohol.

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INTRODUCTION

Despite considerable effort by both governmental and private agencies over the past decade, the use of alcohol remains the single most significant contributor to the production of fatalities and serious injuries on the highway. The massive investment in programs of deterrents and rehabilitation for the apprehended drinking driver has produced little evidence that morbidity rates related to accident usage have been significantly reduced. Barring a substantial change in the social attitudes regarding drinking and driving by the U.S. population, a successful countermeasure program against drinking and driving will require new and novel approaches.

This study is an early exploration of the feasibility of using drugs to reduce or counteract the impairing effects of alcohol. Its utility depends on our knowledge that except for a few individuals who drink to oblivion, the majority of individuals have the quantity of their drinking determined by social and economic constraints. Therefore, a reduced degree of intoxication for the majority of individuals would not lead them to increase their alcohol consumption. Given this assumption, any technique which either reduces the blood alcohol concentration for a given alcohol intake or otherwise reduces the effect on driving of that given alcohol intake, will result in a driver who is less likely to be involved in alcohol-related accidents.

A companion study (Burns and Moskowitz, 1980) has demonstrated that food intake can reduce the blood alcohol concentration of individuals by up to 50 percent, depending upon the time, quantity and type of food intake. This project examined three drugs to determine if they could either similarly inhibit the absorption of alcohol into the blood stream or alternately antagonize the behavioral impairment induced by alcohol. Two of the drugs were selected primarily as potential antagonists of alcohol by a group of pharmacological consultants. The underlying hypothesis assumes that even as Naloxone prevents the behavioral response to opiates by occupying that drug's receptor sites, similar possibilities existed for interference with some neuropharmacological stage of alcohol action on the central nervous system. The two drugs selected primarily as possible alcohol antagonists are Amantadine and Doxapram. The third drug, Maalox, was selected as a possible anti-absorbent agent on the suggestion of the NHTSA technical manager. The rationale for their inclusion follows below.

It should be noted that the selection process occurred some three years prior to the final study execution and represented the state-of-the-art opinion of the consultants at that time. However, work on the neuropharmacology of alcohol has proceeded at a brisk pace and it is likely that other suggestions or rationale for drugs might be offered today (cf. Mendelson, 1980).

The selection of Amantadine (a prescription drug) was based on the possibility that some of the behavioral effects of alcohol are due to the inhibition of catecholamine formation by alcohol, lowering dopamine levels with a reduction in brain norepinephrine and serotonin. This would reduce the availability of neurotransmitters. Amantadine increases catecholamine metabolism, increases the rate of dopamine synthesis and the release of both dopamine and norepinephrine in many brain areas. Thus, the selection of Amantadine was based on the suggestion that by increasing neurotransmitter availability, it might offset the impairment effects of alcohol if that were due to the reduction of those neurotransmitters. Animal work by Professor LeBlanc of the University of Toronto has supported the ability of Amantadine to offset alcohol-induced impairment.

Doxapram hydrochloride (Dopram, a prescription drug) is a centrally acting respiratory stimulant as well as an analgesic agent. It was selected for this study by the consultants because there is evidence that it can reverse, to some degree, the depressant effects of anesthetics and barbiturates on the central nervous system and respiration. The suggestion was that since alcohol is a depressant, as are the anesthetics and barbiturates, doxapram might similarly stimulate the subjects and counteract the effects of alcohol.

At the suggestion of the NHTSA technical manager, the revised design included a third drug, Maalox, to be examined for anti-absorption properties. Maalox is an antacid reputed to reduce stomach motility and coat the interior of the stomach, actions possibly leading to decreased rates of alcohol absorption.

The basic design of this study involved a comparison of five treatments. One treatment was a placebo, another was an alcohol-alone treatment, and the remaining three treatments involved the combination of alcohol with one of the drugs. In all cases the drug was administered prior to the alcohol. After the treatment, breath samples for blood alcohol concentration determinations and performance testing were obtained frequently from the subjects. The blood alcohol concentration samples permit the determination of the effects of the drugs on the absorption of the alcohol.

As will be discussed later, the mean peak BAC attained did vary as a function of the presence of the drug treatments, indicating changes in alcohol absorption. To examine the issue of whether the drugs also produced a change in the performance deficit induced by alcohol, it was necessary to design the experiment so that the effects of the drugs on absorption and on performance could be logically separated. Therefore, performance testing took place at fixed BAC level points rather than at some fixed time after completion of drinking. For each subject,

performance was delayed in time until his BAC level had reached .10% and .05%, the two BAC points selected for testing. Thus, the design permits the determination if the presence of the drug at a given BAC affects the magnitude of the impairment usually associated with alcohol at that level.

Performance was examined through use of a five-item test battery. The tasks included a divided-attention task testing visual search and compensatory tracking skills, a rate of information processing task, a critical tracking task, a test of body sway and a test of hand steadiness.

Thus, the final design examined two issues: Whether these drugs when taken prior to alcohol ingestion inhibit the absorption of the alcohol into the blood stream from the intestinal system, and whether they offset the behavioral impairment induced by alcohol. The experimental design compared fifteen subjects seen on five occasions, each receiving the five treatments. Response measures were blood alcohol concentration curves over time and performance scores on the behavioral test battery.

METHOD

Participants

Participants were fifteen adult males ranging in weight from 141 to 183 lbs., with a mean of 164.5 lbs. Vision was a minimum of 20/30 with correction. They were moderate to low heavy users of alcohol, as defined by a quantity frequency index (Cahalan, Cissin and Crossley, 1969), taking no drugs currently and without histories of either chronic or heavy use of illicit drugs.

Treatments

There were five treatments; a placebo alcohol with placebo drug, active alcohol with placebo drug, and three active drugs with active alcohol conditions. In the placebo-placebo condition, a placebo capsule containing 5 mg of lactose was presented in combination with orange juice, covered by a teaspoon of vodka floated on top. In the active alcohol-placebo drug treatment, a placebo capsule was followed by the alcohol treatment. In the Amantadine treatment, Amantadine was presented via capsule with an active alcohol treatment. In the Doxapram treatment, a small amount of orange juice containing the Doxapram was followed by an active alcohol treatment. Finally, in the Maalox treatment, Maalox was presented as a liquid followed by active alcohol.

The active alcohol treatment was .99 gm alcohol/Kg B.W., consumed over a half-hour period. This produced a mean peak blood alcohol concentration (BAC) of .122% after the alcohol-alone treatment. Drug treatments were administered immediately prior to the consumption of the alcohol. They were: Doxapram in liquid form at a 2 mg/Kg B.W. dosage; Maalox in liquid form at 44 mg/Kg B.W., and Amantadine in capsule form at 4.41 mg/Kg B.W. The Amantadine capsules had to be reconstituted to adjust for individual bodyweights, and it is estimated that a potential error no greater than 5% in dosage might have occurred. Dose equivalents for a 150 pound subject would be 2.85 ounces ethanol, 135 mg Doxapram, 300 mg Amantadine and 3 gm Maalox.

Behavioral Testing Battery

The behavioral testing battery consisted of five tasks which are described below. These are: 1) a divided-attention task requiring simultaneous performance

of a compensatory tracking task and a peripheral visual search-and-recognition task, 2) a rate of information processing task using a backward masking technique, 3) a critical tracking task, 4) a Romberg body sway task and 5) a hand steadiness task.

Divided-Attention Task

To provide a divided-attention task, the participant was required to simultaneously perform a compensatory tracking task and a visual search-and-recognition task. The visual search task consisted of the recognition of the appearance of the numeral "2" in a constantly changing display of 24 numerals selected randomly from 0 to 9.

The participant sat at the center of a horizontal arc of 76.2 cm radius and 33.7 cm height; the total extent of the arc subtends a horizontal angle of 120^{o} and a vertical angle of 24.5^{o}. The subject's eyes were at the vertical midpoint of the arc, the center of which is the tracking display described below. The 24 numerals were presented by red LED displays of 0.9 cm height. They were located at 10^{o}, 15^{o} and 20^{o} to the right and left of the arc midpoint, and at 5^{o} and 10^{o} above and below the midline. When a trial was initiated, all displays were lit, and then random display changes occurred every one to eight seconds. A target number "2" appeared on the average every 25 s, and the participant responded to it as rapidly as possible using a four-way lever in his left hand to indicate the quadrant in which the target appeared.

The display elements for the compensatory tracking task were two parallel illuminated bars, oriented vertically. The right bar was maintained at a constant height of 5.00 cm while the height of the left bar varied as the sum of the forcing function was generated by a digital random number generator and converted to an analog signal. A uniform noise spectrum with a 40 db/octave cut-off at 0.2 Hertz was used. The subject's task was to maintain the variable bar at the same height as the fixed bar.

The bars were 0.3 cm in width and the variable bar had a total maximum excursion of 10.0 cm. The participants were seated facing the display at a distance of 76.2 cm with their position fixed by a chin rest. At that distance the total maximum bar excursion subtended

a visual angle of 7.46 degrees. A white-noise masking signal presented distraction from extraneous sounds.

Participants tracked by use of a single axis fingertip force/displacement stick manipulated by the right hand (a forearm support was provided). Stick movements were spatially compatible with the display bar so that "up" pressure on the stick resulted in an "up" movement of the bar. The controlled system was a pure gain, i.e., a fixed stick force resulted in a fixed bar displacement. The response measure was mean absolute error in centimeters (error being the instantaneous discrepancy in the heights of the two bars).

Divided-attention test trials were of 12-minute duration. Response measures on the visual search portion of the task included number of failures to respond to the signals, number of incorrect responses, and response time for correct responses to the signals. The tracking task response measure was the mean error score, as previously defined. In addition, the two divided-attention measures (reaction time and error score) were converted to z scores (mean = 50; σ = 10) and a combined z score per participant per trial was calculated as a measure for the divided-attention task as a whole.

A divided-attention task is included in the test battery because it is an experimental analog of the attention-sharing demand of driving, where attention must be shared between tracking control of the vehicle upon the highway and monitoring the environment for other information including potential sources of danger.

Information Processing Rate Task

Participants looked into a three field tachistoscope, fixating on a small cross at a distance of 91.44 cm. When the individual was ready, a test card containing four letters, each 1.6 cm in height and spanning 10.8 cm, was presented for 15 ms. Following the test stimulus there was a dark interstimulus interval of either 50, 75 or 100 ms, followed by a masking stimulus of random bits of letters presented for 500 ms. Participants were required to record four letters by writing after each trial. Sets of 12 stimuli at each interstimulus interval were presented in both ascending and descending orders of interstimulus intervals for a total of 72 trials.

The response measure was the mean number of correctly identified letters in correct order averaged across the three interstimulus intervals. A more extensive description of the apparatus and procedure can be found in Moskowitz and Murray (1976).

The task is a measure of information processing rate. The set of four letters placed in the initial sensory storage system of the nervous system must be transferred to the short-term memory storage, if it is to be reported. Experiments have demonstrated this transfer occurs at a rather linear rate. However, the masking stimulus interferes with the sensory storage image and prevents transferring the information. Thus, the task measures the amount of information which can be transferred in periods of 50, 75 and 100 ms, the intervals between test and masking stimuli (ignoring the 15 ms fixed duration of the test stimulus). By comparing the amount of information reported under placebo and active treatments, it can be determined if a drug affects the amount and, thus, the rate of information processing. Alcohol previously has been demonstrated to impede the rate of information processing (cf. Moskowitz and Murray, 1976).

Critical Tracking Task

The Critical Tracking Task (CTT) is a compensatory tracking task which gradually increases in difficulty during a trial. The operator is required to close the loop in a compensatory control system which contains an unstable controlled element. As the level of instability becomes greater during the trial, the task becomes more and more difficult, and eventually the operator is unable to compensate for the unstable system and loses control. The operator's task can be likened to the problem of balancing a stick on one's fingertip, with the stick's length decreasing with time. The degree of stability is controlled by linearly increasing the value of the parameter λ with time, where λ is an inverse time constant in the following equation:

$$Y_{c(s)} = \frac{\lambda}{s-\lambda}$$

where $Y_{c(s)}$ = transfer function of the unstable controlled element in Laplace notation. λ = inverse time constant controlling the degree of instability.

A theoretical analysis of this task indicates that the unstable dynamics force the operator to adopt a pure-gain mode of behavior (introducing either lead or lag will decrease performance). The just-controllable levels of instability λ_c is then limited by λ_e the sum of the effective time delays in the display and operator portions of the loop. The advantage of this task is that it forces the operator to his or her maximum level of performance and, therefore, is more sensitive to the effects of stressors than would be a less demanding task.

A System Technology, Inc. Mark IV CTT device was used. The display was a horizontal line displayed on a CRT. The operator's control was a fingertip force stick which also provided a small amount of displacement. Before the start of the trial the line was centered on the display; when the trial started it would gradually move off-center and the operator's task was to keep it centered on the display with the control stick. As the instability level increased, the line eventually went off the display and the trial ended. The score (λ_c) was immediately displayed to the subject as a displacement of the line from the bottom of the screen; this distance was also recorded by the experimenter. Typically, a trial would last 10 to 15 s, with 30 s being an extremely long trial.

The initial value of λ was 2.1 radians/s^2 and the initial rate of increase of λ was 0.41 radians/s^2. When an error of 0.5 cm was exceeded on the scope face, the rate of increase of λ was decreased to 0.10 radians/s^2 to provide a slower approach to the loss-of-control point. (Effectively, the slower λ rate was usually actuated a second or two after the trial started.) Typical values of λ obtained by a practiced subject would be in the range of 5 to 7; an extremely good score would be on the order of 8 to 9.

Subjects performed 30 trials at each session in three blocks of 10 trials each, with a short rest between blocks. The first set of five trials was considered practice and was not included in the analysis. The final subject score was the mean of the last 25 trials.

Body Sway (Romberg Test)

Body sway was measured by a device consisting of a circular plastic disc approximately 7" in diameter with a series of small bar magnets mounted around its

circumference. A dual pulley assembly was attached to the center of the disc and a string attached to each pulley. A small lead weight was attached to the end of one string wound on its pulley so as to exert a force tending to rotate the disc in a clockwise direction. The string connected to the other pulley was wound in the opposite direction and was secured at its other end to a leather harness attached around the upper torso of the subject. As the subject swayed back and forth, the disc would rotate back and forth either because of the direct force applied by the subject as he swayed away from the device or by the force exerted by its counterbalancing weight as he swayed toward the device. The diameter of the disc, the location of the magnets, and the ratio of the pulley to the disc caused a magnet to pass a magnetic reed relay causing its contacts to close and increment a magnetic digital counter approximately each quarter of an inch of subject sway. Two such devices mounted at 90° to each other were attached to the subject so as to measure separately lateral and anterior/posterior sway.

Before each test round, a check was made to ensure that the lateral and anterior/posterior counters and the stop watch were set to zero and that the power operating the counters was turned off. The subject took his position on a square outlined on the floor. The harness was attached, in all cases, high on the chest with the strap passing immediately below the armpits. After the strings coming from the pulleys were properly secured, the subject was asked to put his head back and to close his eyes. Once the proper position was assumed, the power and stop watch were turned on simultaneously; after 60 seconds, the power was turned off. The response measures were the number of quarter inch movements in the anterior-posterior plane and the number of movements in the lateral plane. The number of movements in each plane was added together for each subject and served as his score.

Standing Hand Steadiness

During this test, the subject stood holding a stylus inserted into a hole in a 4" x 6" brass plate. The tip of the stylus was a cylindrical steel rod 1 mm in diameter and 5.17 cm long. The hole in which the stylus was inserted was 6.4 mm in diameter. Any contact between the stylus and the plate activated an electric stop clock which recorded the duration of contact, an electronic

counter which counted the number of contacts, and an audio oscillator which generated a tone to indicate to the subject that contact was being made.

Plate height adjustment was made for each subject prior to the first test round. The plate was secured in a metal vise and the vise was placed on a height-adjustable stand. Then, while facing the plate, the subject was asked to extend his arm at a right angle to his trunk. The height of the plate was adjusted by raising or lowering the stand to a level that brought the hole in the plate even with the subject's extended arm; the plate was maintained at this level for the remainder of the test sessions.

Before each test round, a check was made to ensure that the timer, counter and stop watch were set to zero. Then the subject, while holding the stylus, took his stance. This involved standing on a marked line, one foot in front of the other, while facing the stand. Adjustment for distance was made by having the subject move along the marked line. The final position was attained when the probe, with the subject's arm fully extended, was inserted into the hole approximately half its length.

Once the required position was assumed, the subject was given several seconds to steady himself. Next, a single switch operating the counter, timer and audio-oscillator was turned on and the stop watch was started. After 40 seconds, the switch was turned off, and test scores for duration of contact and number of contacts were entered in the test log. Finally, the timer, counter and stop watch were reset to zero. Three trials of 40 seconds each were administered.

Sitting Hand Steadiness

This task was essentially the same as standing hand steadiness except that (1) the subject was seated, (2) the diameter of the hole in the metal plate was smaller than that used in the preceding task, and (3) the vise holding the metal plate was situated on a table in front of the subject.

Before each test round, a check was made to ensure that the counter, timer and stop watch were set to zero. Next, a plate containing a hole with a diameter of 3.9 mm was secured in the vise and placed close to the edge of

the table. Following the preliminaries, the subject was seated in a chair facing the plate. The subject's distance to the plate was adjusted by moving the chair closer to or farther from the table, as required. The proper distance was attained when the probe was inserted to approximately one-half its length through the plate's hole while the subject's arm was fully extended. Once the desired position was assumed, the subject was given several seconds to steady himself. Then, the switch operating the counter, timer and the oscillator was turned on and simultaneously the stop watch was started. After a 40-second time period, the test scores were recorded and the timer, counter and stop watch were reset to zero. Three trials of 40 seconds each were administered.

The final subject scores for the hand steadiness task were the average of the scores on all six trials, that is, for both sitting and standing hand steadiness. Two final scores were generated; average duration and number of contacts for a 40-minute trial.

Design

The design was a 5x5 Latin square with five treatments administered to five subjects in a counterbalanced order. There were fifteen subjects examined in three replications of the 5x5 Latin square.

Procedure

Subjects received two days of training on the behavioral test battery at least one week prior to the beginning of the experimental sessions. They then returned for five experimental treatment days spaced one week apart. Subjects were required to agree to consume no food or beverages except water for ten hours prior to a test session. They also agreed not to consume alcohol for 24 hours preceding a session or marihuana for 4 days prior to a session. No other drugs, prescription or illicit, could be taken during the entire study. On experimental test days subjects were required to submit a urine sample for drug screening purposes, and a breath sample was taken to insure that no alcohol was present.

On each test day subjects performed three experimental test batteries. The first test battery occurred prior to receiving any treatment. At the conclusion of the first behavioral test battery, either an active drug or drug

placebo was administered, followed immediately by an active alcohol or alcohol-placebo treatment. BAC measurements via a breath sampling gas chromatograph were taken at roughly 15-minute intervals following the ingestion of the alcohol. However, these breath samples had to be taken before or after portions of the behavioral battery, resulting in some variation in time of BAC sampling.

The second behavioral testing period, which was the first post-treatment testing period, occurred when the subject's BAC had dropped to .10% BAC. The third behavioral testing period occurred when the subject's BAC had dropped to .05%.

RESULTS AND DISCUSSION

Figure 1 presents the blood alcohol concentration over time for the four active treatments. The figure indicates a drug effect on the rate of absorption of the alcohol in the blood stream. The BAC curves for two hours following alcohol and drug ingestion exhibit lower BAC's, and peak BAC's occurring later in time than under the alcohol-only treatment. There were no differences in the blood alcohol concentration level by two hours after completion of drinking. The only drug treatment which produced a statistically significant lower BAC curve was Doxapram. An analysis of variance for drug treatment effect for both the time to reach peak BAC and the peak BAC was significant beyond the .01% level. Peak BAC was reached in 30 minutes for the alcohol treatment alone and delayed to 105 minutes in the presence of Doxapram. At these times peak BAC's were .116% and .104% respectively.

Thus, it is clear that a drug, in this case Doxapram, can reduce the rate of alcohol absorption, resulting in lower BAC's and consequently producing the socially desirable result of reducing the impairment associated with a given level of alcohol intake.

Table 1 presents the standard deviation of the BAC among subjects on the four active treatments at 15-minute intervals. As might be expected, the variance for the first few time sampling points was greater than later since this was the absorption period, but there appeared no significant differences in variability of BAC levels between the alcohol-drug treatments and the alcohol-alone treatments. This suggests that the effect of the drug treatments in reducing absorption rate is not accompanied by any increased variability in the absorption rate among the subjects.

Examination was made of the elimination rate of alcohol (metabolism rate) obtained by dividing the difference between the lowest and highest BAC recording by the time over which the BAC changed. As Figure 1 suggests, the drug-alcohol treatments had the same rate of elimination of alcohol as the alcohol-alone treatment, demonstrating that the drugs had not affected the metabolism rate. The average change of BAC per hour was .017% in all four active treatments, a figure close to the national average.

As noted above, subjects were examined on five performance tasks at three time periods on each of five test days, under each of the five drug-alcohol experimental treatments. Figures and tables 2 through 9 summarize the mean performance scores for the fifteen testing samples (3 tests on 5 days).

As noted in the introduction and the procedure, behavioral testing was delayed until the subject's BAC level had dropped to .10% and .05% for the two testing periods. Thus, regardless of the effects of the

FIGURE 1

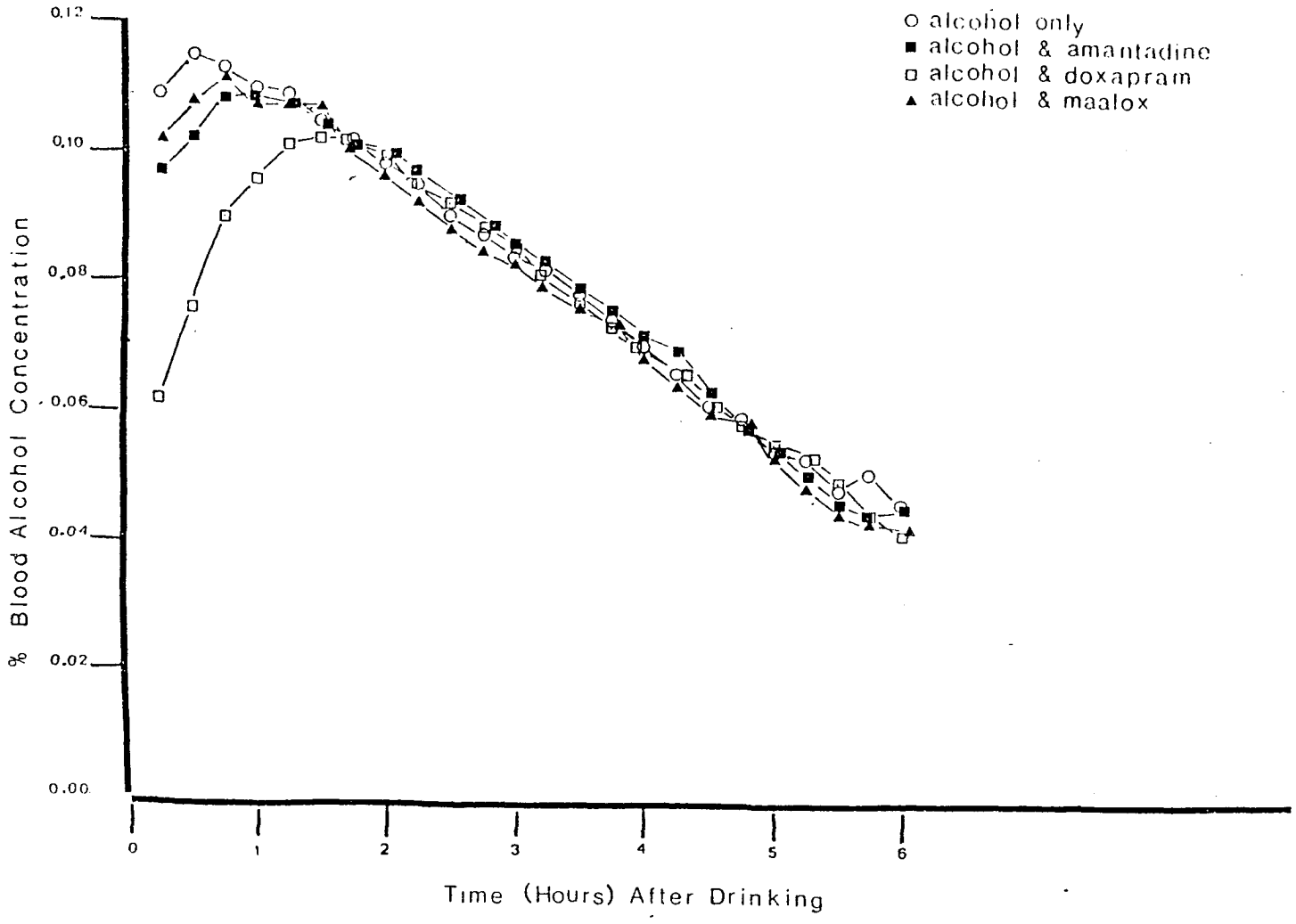
alcohol only
alcohol & amantadine
alcohol & doxapram
alcohol & maalox
% Blood Alcohol Concentration
0.12
0.10
0.08
0.06
0.04
0.02
0.00
0
1
2
3
4
5
6
Time (Hours) After Drinking

TABLE 1

STANDARD DEVIATIONS OF BLOOD ALCOHOL CONCENTRATIONS
(Between subject variability in BAC)

Time (Minutes)	15	30	45	60	75	90	105	120	135	150	165	180	195	210	225	240	255	270	285	300	315	330	345
ALCOHOL ONLY	.023	.019	.015	.015	.012	.013	.013	.013	.014	.014	.014	.014	.014	.015	.016	.016	.018	.019	.017	.017	.017	.017	.012
ALCOHOL & AMANTADINE	.027	.022	.017	.013	.013	.013	.015	.011	.010	.010	.010	.010	.010	.010	.010	.011	.011	.012	.012	.012	.014	.015	.016
ALCOHOL & DOXAPRAM	.015	.012	.011	.009	.012	.013	.012	.013	.014	.013	.013	.013	.012	.012	.012	.012	.013	.013	.014	.012	.010	.008	.008
ALCOHOL & MAALOX	.023	.022	.018	.014	.014	.011	.011	.011	.009	.011	.013	.013	.013	.012	.013	.012	.013	.014	.013	.014	.014	.014	.012

FIGURE 2

CRITICAL TRACKING TASK

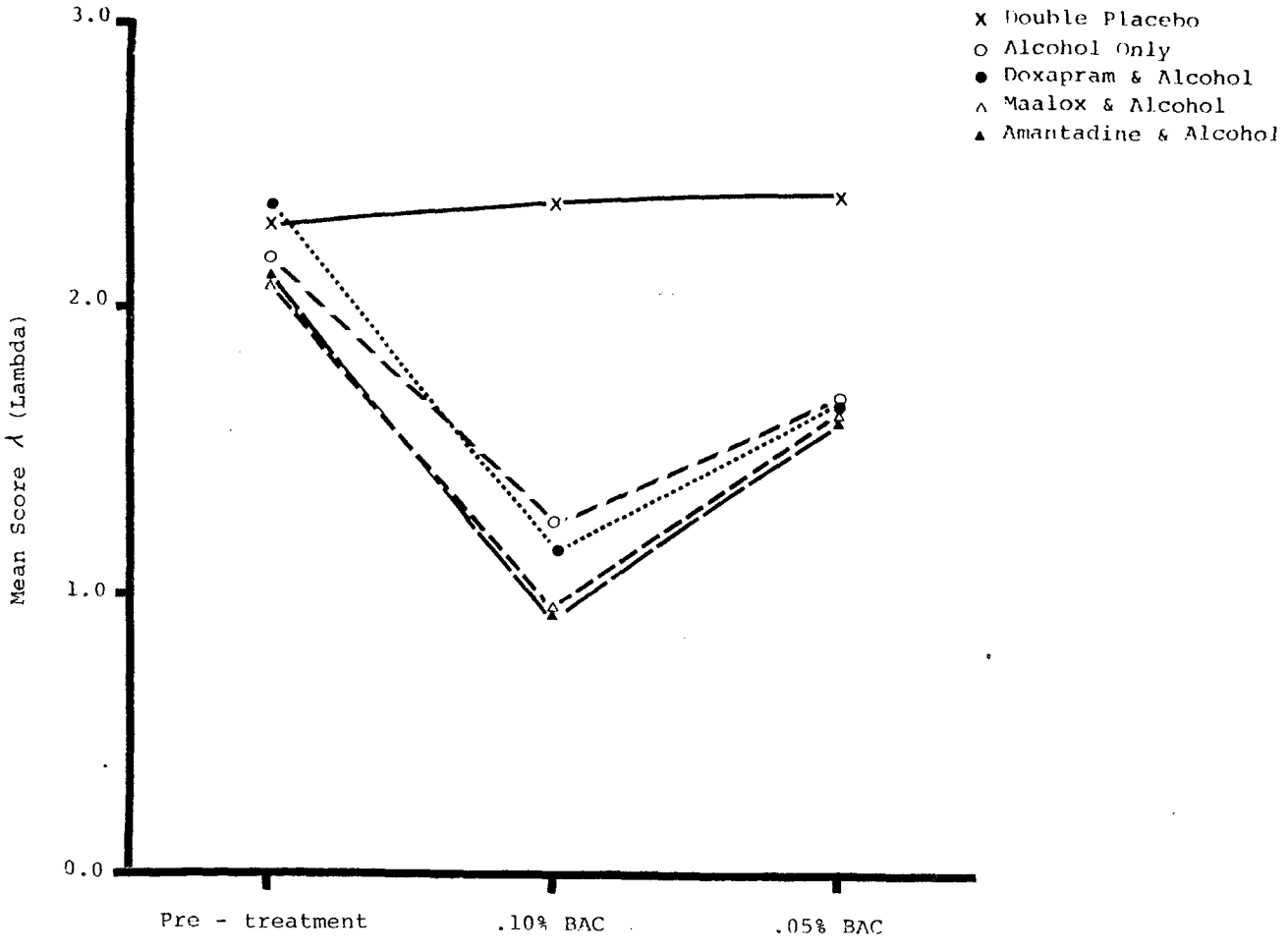

FIGURE 3

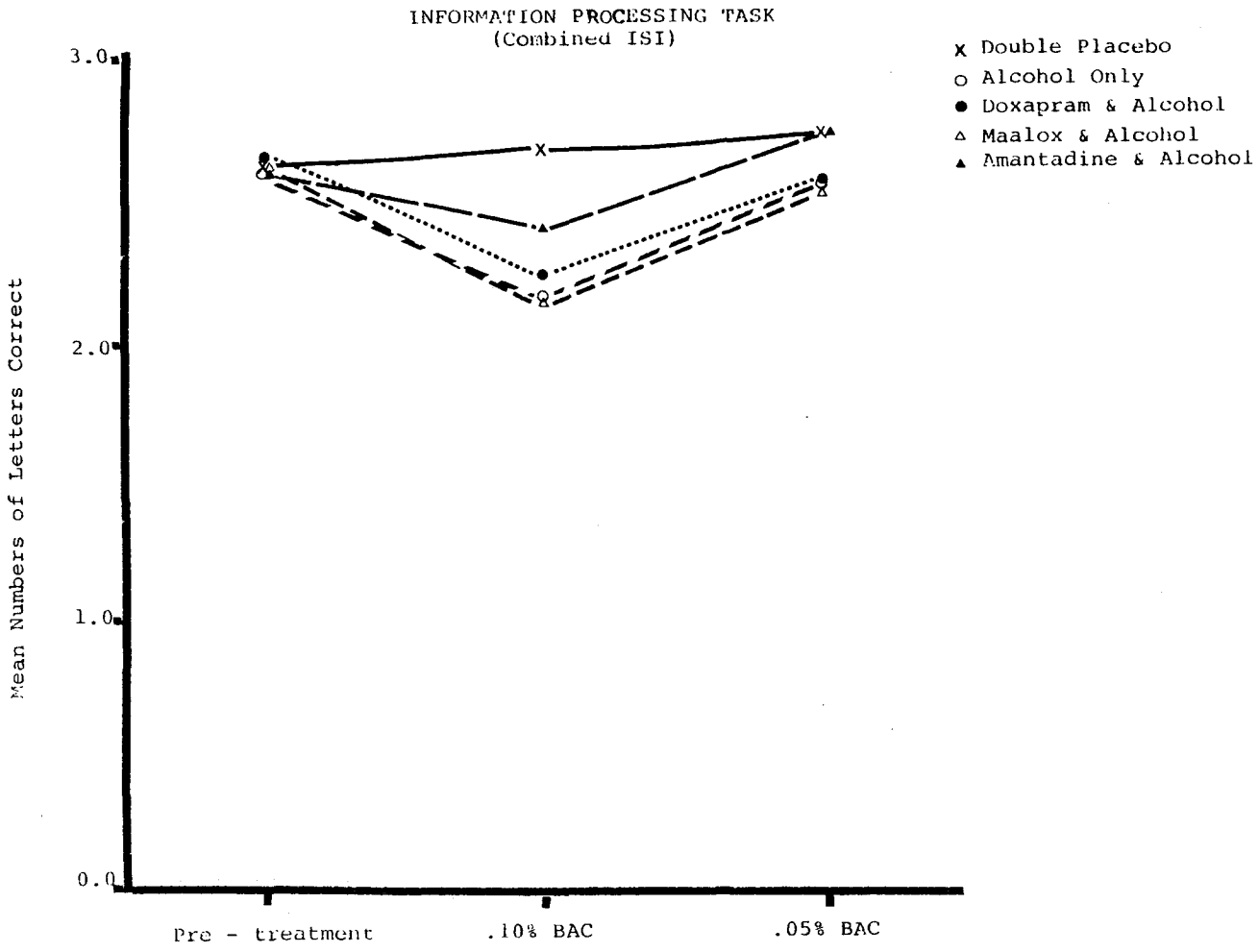
INFORMATION PROCESSING TASK
(Combined ISI)
Mean Numbers of Letters Correct
3.0
2.0
1.0
0.0
Pre - treatment
.10% BAC
.05% BAC
Double Placebo
Alcohol Only
Doxapram & Alcohol
Maalox & Alcohol
Amantadine & Alcohol

FIGURE 4

REACTION TIME TO PERIPHERAL SIGNALS
IN VISUAL SEARCH UNDER DIVIDED ATTENTION

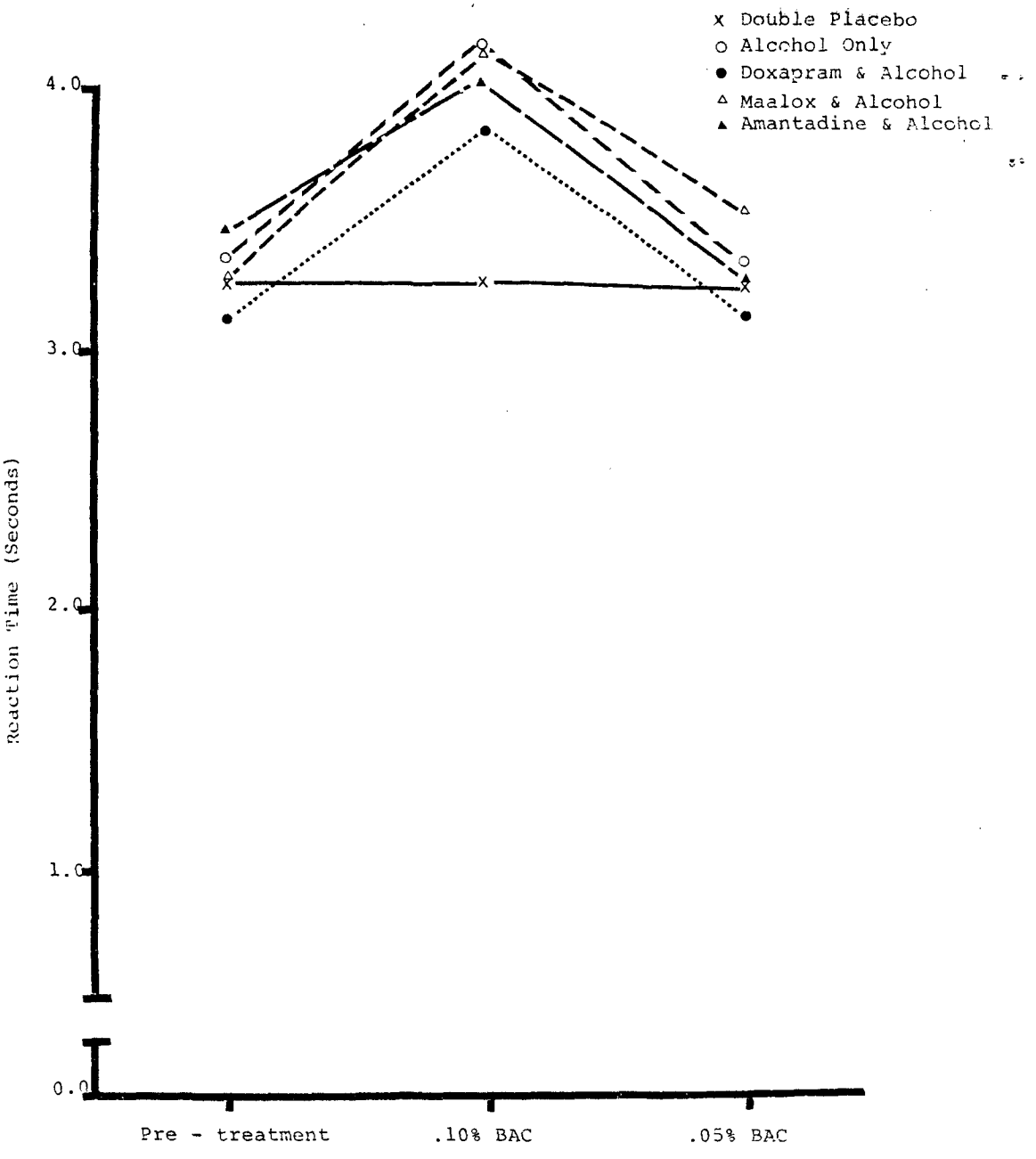

FIGURE 5

MEAN ERROR IN TRACKING UNDER DIVIDED ATTENTION

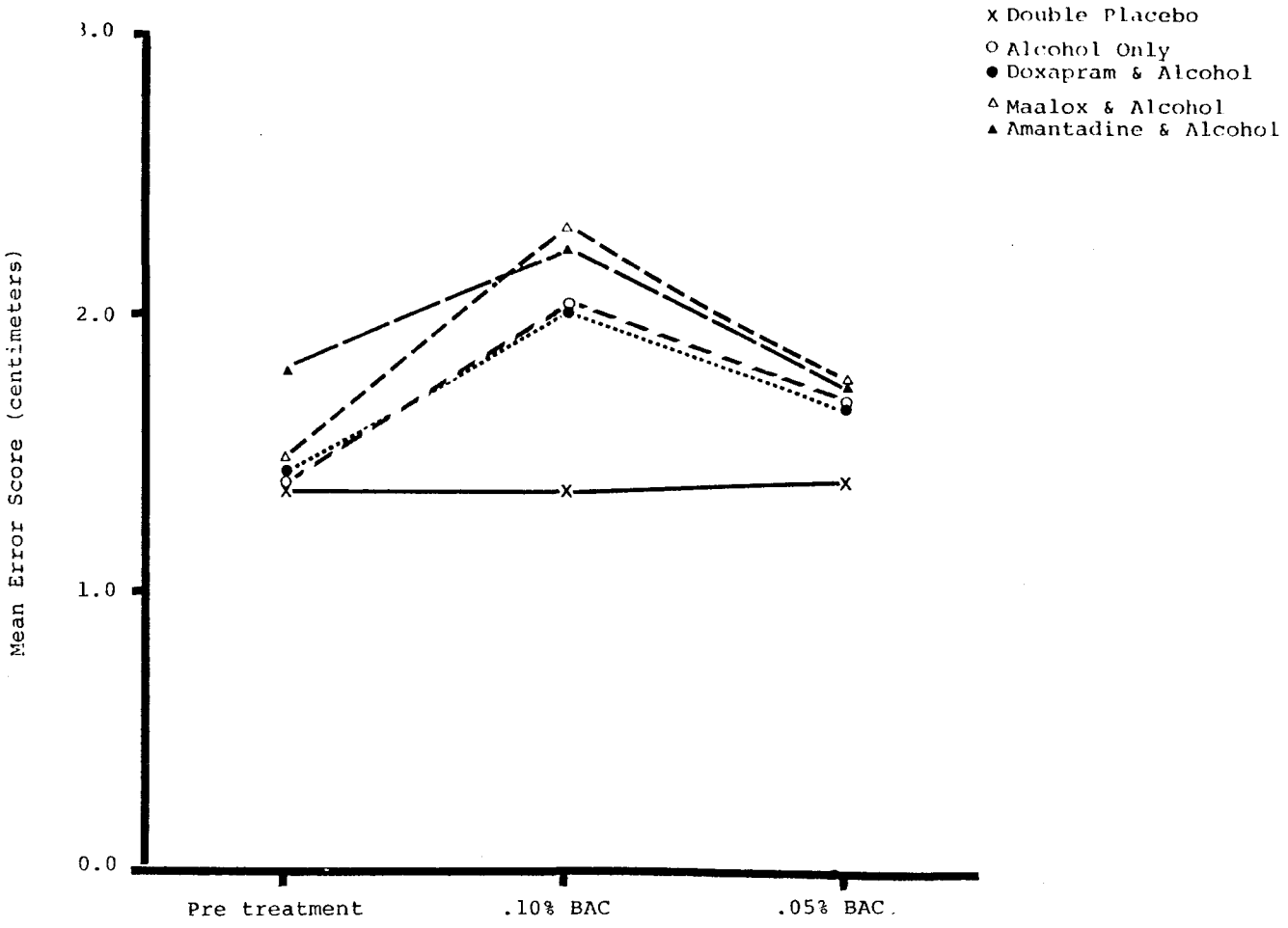

FIGURE 6

RESPONSE ERRORS TO PERIPHERAL SIGNALS
IN VISUAL SEARCH UNDER DIVIDED ATTENTION

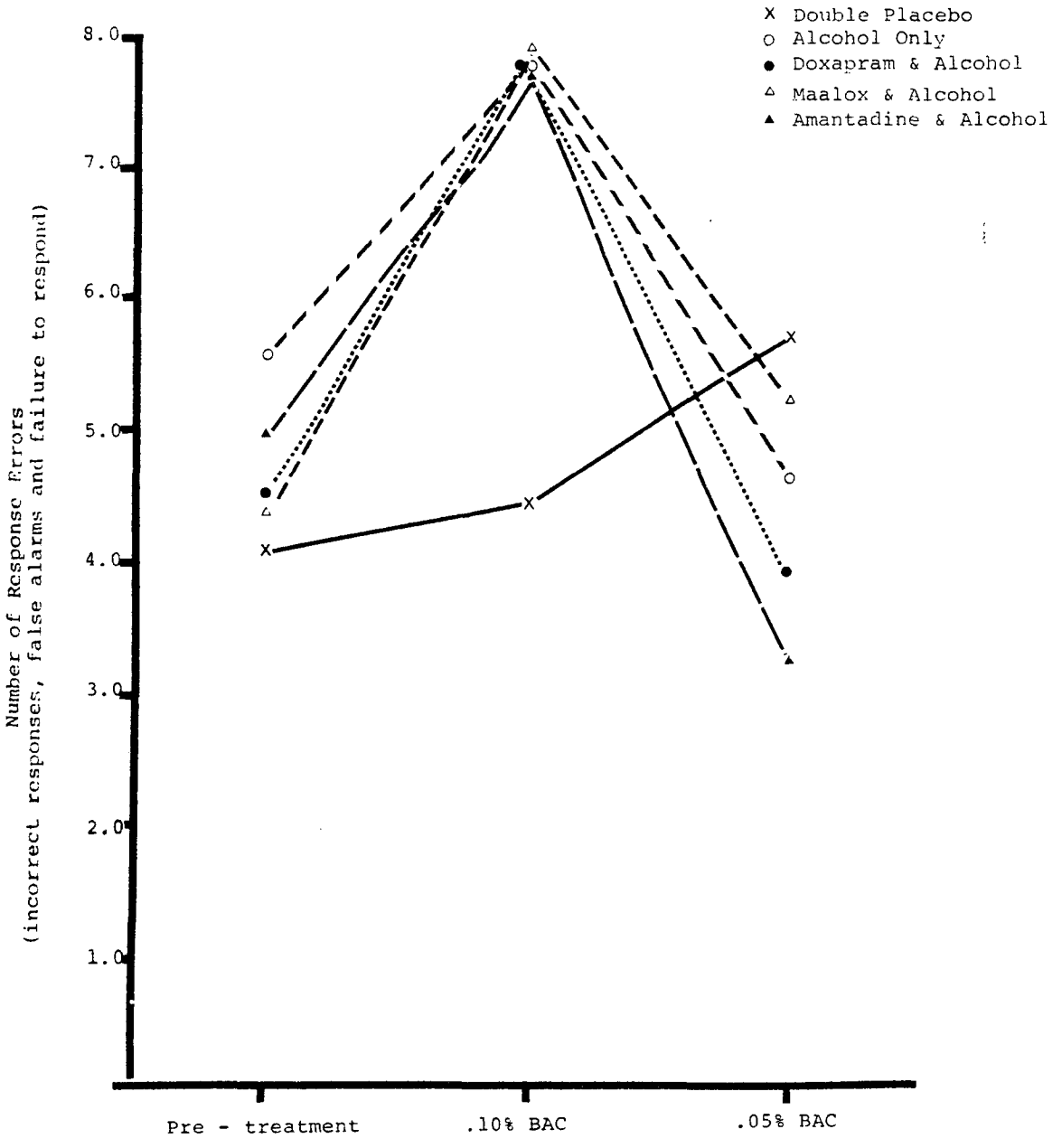

FIGURE 7

BODY SWAY

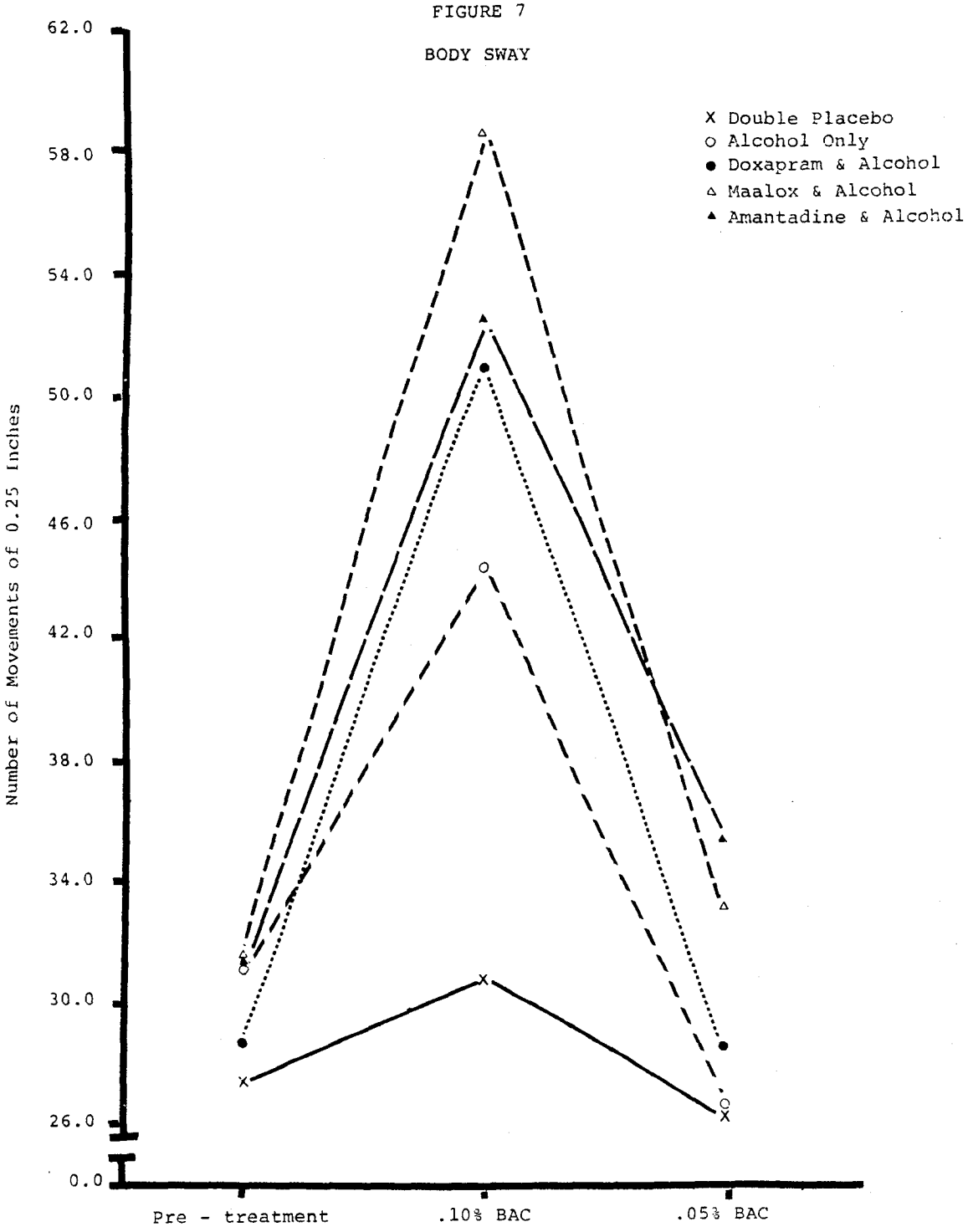

FIGURE 8

HAND STEADINESS: DURATION

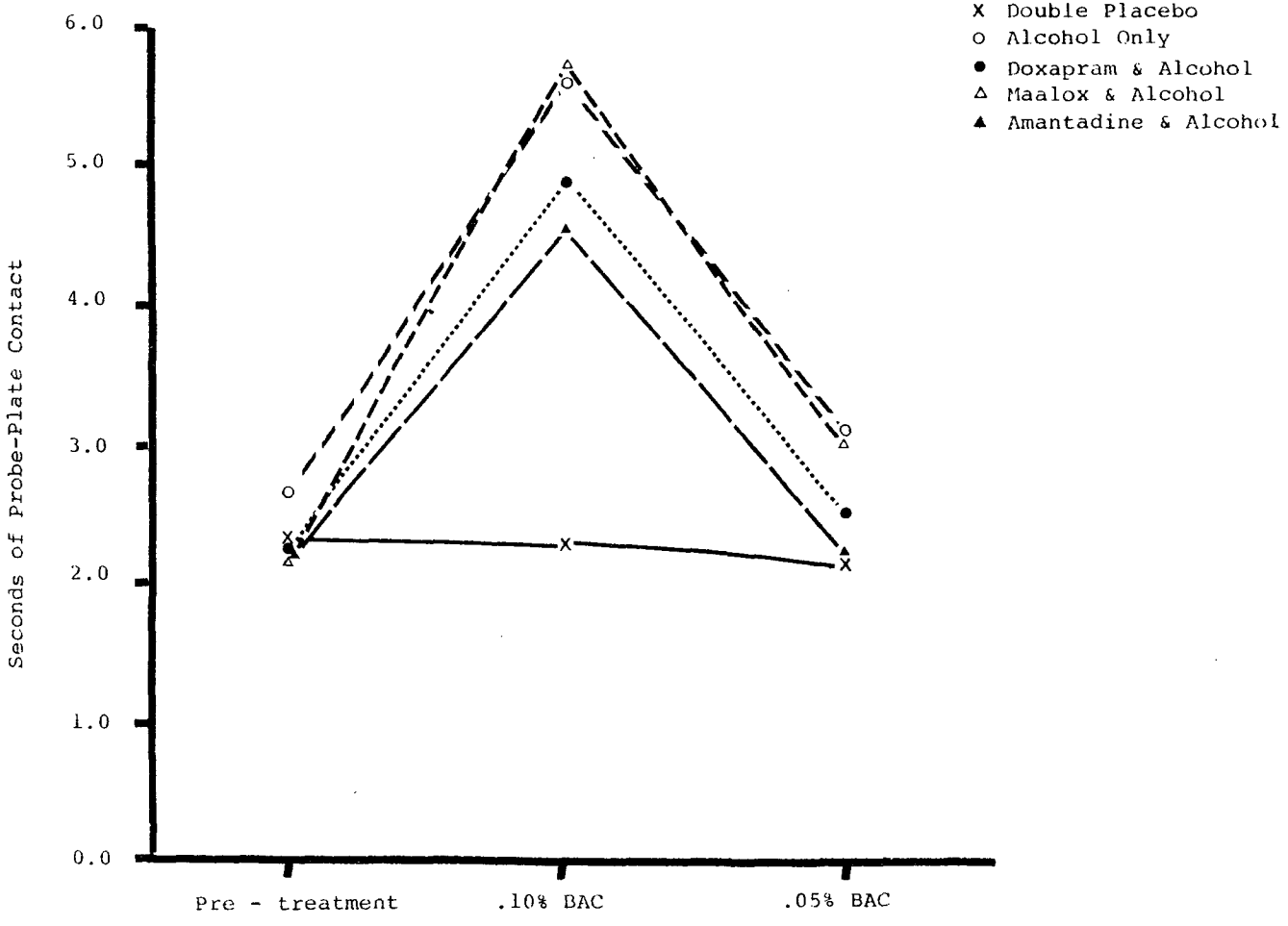

FIGURE 9

HAND STEADINESS: CONTACT FREQUENCY

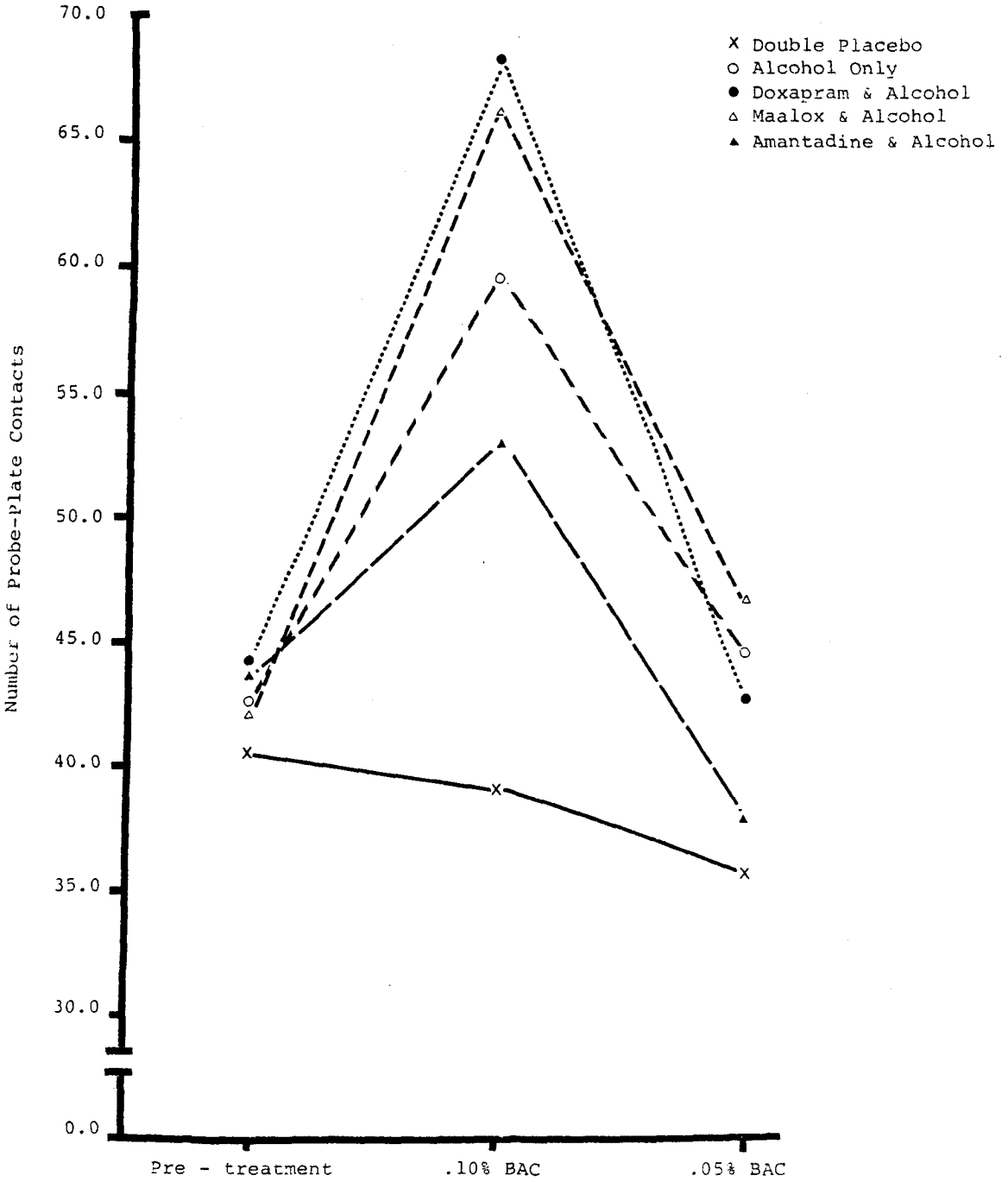

TABLE 2

CRITICAL TRACKING TASK

Mean Score (Lambda)

TREATMENTS	PRE-DOSE	.10% BAC	.05% BAC
ALCOHOL PLACEBO + DRUG PLACEBO	2.29	2.37	2.41
ALCOHOL + DRUG PLACEBO	2.18	1.27	1.70
ALCOHOL + AMANTADINE	2.12	0.94	1.62
ALCOHOL + DOXAPRAM	2.36	1.17	1.67
ALCOHOL + MAALOX	2.08	0.96	1.66

TABLE 3

INFORMATION PROCESSING TASK

Mean Number of Letters Correct
Across All Intersimulus Intervals

TREATMENTS	PRE-DOSE	.10% BAC	.05% BAC
ALCOHOL PLACEBO + DRUG PLACEBO	2.63	2.70	2.77
ALCOHOL + DRUG PLACEBO	2.60	2.16	2.58
ALCOHOL + AMANTADINE	2.61	2.41	2.77
ALCOHOL + DOXAPRAM	2.64	2.23	2.58
ALCOHOL + MAALOX	2.63	2.15	2.54

TABLE 4

Mean Reaction Time in Seconds to Peripheral Visual Search Signals During the Divided-Attention Task.

TREATMENTS	PRE-DOSE	.10% BAC	.05% BAC
ALCOHOL PLACEBO + DRUG PLACEBO	3.24	3.23	3.20
ALCOHOL + DRUG PLACEBO	3.39	4.16	3.31
ALCOHOL + AMANTADINE	3.45	4.00	3.22
ALCOHOL + DOXAPRAM	3.11	3.82	3.11
ALCOHOL + MAALOX	3.20	4.12	3.44

TABLE 5

Mean Tracking Error in cm. During
the Divided-Attention Task

TREATMENTS	PRE-DOSE	.10% BAC	.05% BAC
ALCOHOL PLACEBO + DRUG PLACEBO	1.38	1.39	1.43
ALCOHOL + DRUG PLACEBO	.40	2.06	1.72
ALCOHOL + AMANTADINE	1.81	2.26	1.77
ALCOHOL + DOXAPRAM	1.42	2.03	1.68
ALCOHOL + MAALOX	1.50	2.34	1.78

TABLE 6

Mean Number of Response Errors in Visual Search
During the Divided-Attention Task

TREATMENTS	PRE-DOSE	.10% BAC	.05% BAC
ALCOHOL PLACEBO + DRUG PLACEBO	4.13	4.47	5.73
ALCOHOL + DRUG PLACEBO	5.60	7.80	4.67
ALCOHOL + AMANTADINE	5.00	7.73	3.27
ALCOHOL + DOXAPRAM	4.53	10.71	3.85
ALCOHOL + MAALOX	4.40	7.93	5.27

TABLE 7

BODY SWAY

Mean Number of 0.25 Inch Movements in Both Planes

TREATMENTS	PRE-DOSE	.10% BAC	.05% BAC
ALCOHOL PLACEBO + DRUG PLACEBO	27.50	30.86	26.29
ALCOHOL + DRUG PLACEBO	30.96	44.47	26.63
ALCOHOL + AMANTADINE	31.42	52.31	35.34
ALCOHOL + DOXAPRAM	28.53	50.95	28.45
ALCOHOL + MAALOX	31.69	58.36	33.13

TABLE 8

HAND STEADINESS

Duration of Probe-Plate Contact (secs.)

TREATMENTS	PRE-DOSE	.10% BAC	.05% BAC
ALCOHOL PLACEBO + DRUG PLACEBO	2.32	2.31	2.15
ALCOHOL + DRUG PLACEBO	2.67	5.61	3.11
ALCOHOL + AMANTADINE	2.25	4.57	2.27
ALCOHOL + DOXAPRAM	2.28	4.94	2.54
ALCOHOL + MAALOX	2.20	5.76	3.02

TABLE 9

HAND STEADINESS

Mean Number of Probe-Plate Contacts

TREATMENTS	PRE-DOSE	.10% BAC	.05% BAC
ALCOHOL PLACEBO + DRUG PLACEBO	40.62	39.18	35.77
ALCOHOL + DRUG PLACEBO	42.78	59.55	44.68
ALCOHOL + AMANTADINE	43.64	52.75	39.65
ALCOHOL + DOXAPRAM	44.31	68.46	42.43
ALCOHOL + MAALOX	42.07	66.33	46.71

drugs upon the absorption of alcohol and the resulting peak BAC, it was possible to test the effects of the drugs as inhibitors of alcohol-induced behavioral impairment by behavioral testing at equivalent BAC levels for all treatments.

There are no statistical significance levels indicated on the figures and tables. This is due to the performance of a variety of analyses involving the same data, so that no simple method of presenting all the statistical analyses can be placed on the figures without misleading the viewer. Tables 10, 11, 12 and 13 present summaries of the statistical analyses. Reference should be made to these tables when examining figures and tables 2 through 9. In addition, another reason for not placing the statistical analysis levels on each separate figure and table is that these single levels are misleading for estimating the true probability of obtaining the results for the entire experiment. For example, in making comparisons between the combined drug-alcohol treatments with the alcohol-alone treatment, there are 3 drug comparisons, 9 response measures and 3 testing periods, for a grand total of 81 comparisons. If each possible comparison is assessed at a .05% level individually, it is anticipated that 3 plus or minus comparisons would be found statistically significant by chance. If, instead of listing each comparison separately and giving a misleading impression, one presents the comparisons by sets where one can observe the total set of comparisons as in tables 10 through 13, it is possible to understand the irrelevance of the occasional chance finding of statistical significance.

Figure 2 and table 2 present the mean lambda scores on the critical tracking task. The larger the score the better the performance. Figure 3 and table 3 present the mean number of correctly reported letters across all interstimulus intervals on the rate of information processing task. The larger the score the better the performance. Figure 4 and table 4 present the reaction time in seconds responding to the peripheral signals for the visual search aspect of the divided-attention task. The larger the score the worse the performance. Figure 5 and table 5 present the mean error in centimeters on the compensatory tracking aspect of the divided-attention task. The larger the score the worse the performance. Figure 6 and table 6 present the mean number of response errors (false alarms, incorrect responses and failures to respond) in the visual search aspect of the divided-attention task. The larger the score the worse the performance. Figure 7 and table 7 present mean number of quarter inch movements in the body sway task. The larger the score the worse the performance. Figure 8 and table 8 present the mean duration in seconds of contact between the probe and plate in the hand steadiness task. The larger the score the worse the performance. Figure 9 and table 9 present the mean number of contacts between the probe and plate during the hand steadiness task. The larger the score the worse the performance.

TABLE 10

DRUG EFFECTS ON PERFORMANCE SCORES

Statistical Significance from the Latin Square Anova

(Compares All 5 Drug Conditions)

TIME	Critical Tracking Task	Information Processing Rate	Reaction Time Divided-Attention	Tracking Error Divided-Attention	Response Errors Divided-Attention	Standardized Scores Divided-Attention	Body Sway	Hand Steadiness Contact Duration	Hand Steadiness Contact Frequency
.10% BAC	* * *	* * *	* * *	* * *		* * *	* * *	* * *	* * *
.05% BAC	* * *	* * *	*	* *		* *	* *	* * *	*

Key: * p <.10

** p <.05

*** p <.01

TABLE 11

DRUG EFFECTS ON PERFORMANCE SCORES

Statistical Significance from the Latin Square Anova

Planned Comparisons
F (1,52)

TIME	Critical Tracking Task	Information Processing Rate	Reaction Time Divided-Attention	Tracking Error Divided-Attention	Response Errors Divided-Attention	Standardized Scores Divided-Attention	Body Sway	Hand Steadiness Contact Duration	Hand Steadiness Contact Frequency
	D M A	D M A	D M A	D M A	D M A	D M A	D M A	D M A	D M A
PRE-TREATMENT	*			**		*		*	
.10% BAC	* *	***					*		
.05% BAC		***					* **	* ***	

Planned Comparisons of the 3 Drug Alcohol Conditions with the Alconol Only Condition.

The Mean Square Error term used for this 2-condition F-test was obtained from the 5-condition comparison F-test.

D: Comparison of (Alcohol Only) with (Doxapram + Alcohol)

M: Comparison of (Alcohol Only) with (Maalox + Alcohol)

A: Comparison of (Alcohol Only) with (Amantadine + Alcohol)

Key: * p <.10

** p <.05

*** p <.01

TABLE 12

DRUG EFFECTS ON PERFORMANCE SCORES

Statistical Significance from the Latin Square Anova

Dunnett's t-Test

(Compares 4 Conditions)

TIME	Critical Tracking Task			Information Processing Rate			Reaction Time Divided-Attention			Tracking Error Divided-Attention			Response Errors Divided-Attention			Standardized Scores Divided-Attention			Body Sway			Hand Steadiness Contact Duration			Hand Steadiness Contact Frequency		
	F	t		F	t		F	t		F	t		F	t		F	t		F	t		F	t		F	t	
		D	M A		D	M A		D	M A		D	M A		D	M A		D	M A		D	M A		D	M A		D	M A
PRE-TREATMENT	*																										
.10% BAC				***																					**		
.05% BAC				***			*												*			**					

F: (3,38) Comparison of (Alcohol Only) with (Alcohol + Doxapram), (Alcohol + Maalox), (Amantadine + Alcohol).

t: Comparison of (Alcohol + Drug condition) with (Alcohol Only)

D: Comparison of (Alcohol Only) with (Doxapram + Alcohol)

M: Comparison of (Alcohol Only) with (Maalox + Alcohol)

A: Comparison of (Alcohol Only) with (Amantadine + Alcohol)

Key: * p <.10

** p <.05

*** p <.01

TABLE 13

SESSION EFFECTS ON PERFORMANCE SCORES

Statistical Significance from the Latin Square Anova

(Compares All 5 Drug Conditions)

TIME	Critical Tracking Task	Information Processing Rate	Reaction Time Divided-Attention	Tracking Error Divided-Attention	Response Errors Divided-Attention	Standardized Scores Divided-Attention	Body Sway	Hand Steadiness Contact Duration	Hand Steadiness Contact Frequency
PRE-TREATMENT	***	***	***		***	*		***	
.10% BAC	**	***	***			***		**	
.05% BAC	**	***	***			***	**	***	***

Key: * p <.10

** p <.05

*** p <.01

Visual inspection of these figures and tables suggests that the presence of alcohol produces an impairment in performance on all tasks. However, as will also be seen in the statistical analysis and discussion below, nothing suggests that the presence of drugs in combination with alcohol mitigates the alcohol-induced impairment. These impressions and analysis are clearest at the .10% BAC testing period. The development of acute tolerance on the declining blood alcohol curve obscures both alcohol and drug effects at .05% BAC.

Table 10 summarizes a Latin square analysis of variance comparing all five treatments; alcohol placebo plus drug placebo, active alcohol plus drug placebo, active alcohol in combination with the three active drugs. For the overwhelming majority of comparisons, significance is found in the post-dose situation at either .10% or .05%. However, this comparison merely indicates that the active treatments, either alcohol alone or alcohol in combination with drugs, affect skills performance differently than the placebo-placebo treatment. It demonstrates the effectiveness of the experimental test battery in detecting the effects of alcohol.

Table 11, another statistical summary, has dropped the placebo-placebo condition, to consider whether any of the drugs in combination with alcohol treatment differ from alcohol alone. These were planned comparisons determined prior to the experiment as the only relevant issue on performance. As noted above, the alcohol-placebo versus active alcohol-alone comparison merely demonstrates that the alcohol treatment produces decrements in performance of these tasks.

The analysis of table 11 tests whether the drug treatment offsets the impairment produced by alcohol. The statistical analysis presented in table 11 maximizes the possibility of uncovering a difference between the treatments. Given the large number of such treatment comparisons summarized in table 11, the overall type 1 error is underestimated. In table 12 a more conservative statistical procedure is presented.

Nevertheless, in spite of a procedure which emphasizes detection of any trend towards finding a treatment effect, little evidence of such effects are present. In comparisons between each of the drugs in combination with alcohol and alcohol alone, there were no significant differences found for the response variables of reaction time for visual search under divided attention, tracking error under divided attention, combined errors during visual search under divided attention, the standardized score which represents the overall divided attention task, nor on the number of plate-probe contacts for the hand steadiness task.

In the few instances where statistical significance appeared, the majority of cases found the performance under the combined drug-alcohol treatment poorer than under alcohol alone. Such instances included the trend towards significance at the .1% level for both Maalox and Amantadine on the critical tracking task, and the significant differences found on the body sway task for Maalox and Amantadine. The only instances where the drug-alcohol treatment represented better performance than the alcohol alone was for Amantadine on the information processing task and the duration of probe-plate contacts in the hand steadiness task.

Thus it appears, given the number of comparisons which were undertaken (and presented in table 11), the number of instances of statistical significance for improved performance under drugs would have been anticipated by chance alone.

To repeat, examination of these comparisons of the antagonizing effects of drugs on alcohol impairment suggests that there is no adequate evidence to indicate alcohol antagonism associated with any of these drugs. On the majority of response measures, no effect of alcohol was found. On some response measures, impairment was increased and only on two response measures (information processing rate and duration of hand steadiness) was evidence found to suggest that Amantadine offset some of the alcohol impairment, such evidence being likely at chance level.

As noted in the introduction, the drugs selected were chosen from many possible candidates in what is essentially a preliminary investigation of the issues. It would have, indeed, been extremely fortunate if these candidates were the successful ones, but clearly it will require more than one study to assess the availability of a possible antagonist to alcohol impairment. In that sense the results are not unexpected. The effects of Doxapram as an anti-absorbant agent is clearly encouraging. It may well be that the results with respect to Amantadine are truly reliable rather than an artifact of the number of significance tests performed, but only a replication can determine that.

As noted above, a difficulty with multiple planned comparisons is that the statistical significance level associated with each comparison is inflated. A more conservative statistical test is the Dunnett's t test which was used to compare each of the alcohol plus drug conditions to the alcohol treatment alone. Table 12 indicates that none of the Dunnett's t comparisons exhibited statistical significance on any response measure for any drug. The conservative conclusion is that no drug has demonstrated antagonism of the impairment of alcohol.

Table 13 summarizes the session effects comparisons from the Latin square analysis of variance. These tested whether significant changes of performance over the five sessions occurred independently of drug treatment. For the majority of measures, there were highly significant changes. Examination of the data indicates that the majority of performance measures exhibited better performance over time as a function of learning or practicing skills performance on the tasks, session by session. These results were anticipated. Complex skills performance such as the experimental tasks typically show learning curves that extend over years of training, as does driving itself. The experimental design and analysis ensures that such learning trends or session effects do not intrude on the significance of the treatment comparisons.

CONCLUSIONS AND RECOMMENDATIONS

This study failed to find any evidence that the three drugs examined in combination with alcohol altered the degree of behavioral impairment associated with that alcohol intake. No significant changes in the degree of impairment produced by alcohol were found after any of the drugs. This should not be taken as evidence that such alcohol antagonist may not exist. As information is obtained about the neuropharmacological pathways of alcohol CNS action, alcohol antagonist drugs are likely to be found in the future. In fact, there is evidence from stimulants such as caffeine that alcohol antagonists do exist. However, these three drugs, namely, Amantadine, Doxapram and Maalox, are not alcohol antagonists.

Of more immediate practical importance was the portion of the study which examined the effect of drugs on the absorption of alcohol. One drug, Doxapram, clearly had a substantial effect on the absorption rate of alcohol, producing a delay in absorption which lasted almost two hours and resulted in a considerably decreased peak blood alcohol concentration. Such a finding is of considerable importance since it suggests a practical possible use of drugs to lower the blood alcohol concentrations of individuals with a given alcohol intake and thus reduce their level of impairment.

Recent studies under a companion NHTSA contract (DOT-HS-8-01999) have demonstrated that the ingestion of food prior to alcohol consumption will dramatically reduce attained BAC's. This demonstration that a drug has similar properties in reducing BAC level is of considerable importance. In comparison to food, drugs have the advantage of being easily carried by the drinker, can be more readily ingested and, moreover, can be taken repetitively to maintain the decreased absorption rate.

Recommendations which derive from this study are twofold, dealing with the twofold nature of the study. Additional activity to uncover alcohol antagonist properties of drugs will, undoubtedly, require more fundamental knowledge regarding the neuropharmacological pathways of alcohol effects. On the other hand, the evidence presented by this study, that drugs interfere with alcohol absorption, offers a more immediate potential for uncovering alcohol impairment countermeasures by suggesting further research into drug anti-absorption agents. As noted above, drugs have many advantages in practice, and studies in this area might well uncover drugs which have even greater ability than food to suppress the normal absorption rate. This would have an immediate effect on the level of BAC and thus on the likelihood of alcohol-related traffic impairment.

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