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DRUGS AND PLACEBOS:

THE EFFECTS OF INSTRUCTIONS UPON PERFORMANCE AND MOOD UNDER AMPHETAMINE SULPHATE AND CHLORAL HYDRATE¹

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The experiment reports the effects of appropriate and inappropriate instructions and 2 drugs (.5 g chloral hydrate and 10 mg racemic amphetamine sulphate) on motor performance and mood measures. The Ss were 90 older men randomly assigned to 9 experimental groups. The design used was expansion of a model design involving Drug Disguised groups, Placebo groups (300 mg lactose), an Untreated group, and Amphetamine, Chloral Hydrate, and Neutral instructions. The drugs and placebos were given to the Ss in capsules, and all Ss received orange juice, which was also the vehicle for the disguise. The Untreated group received orange juice only. Instructions alone affected performance, but had little or no effect on mood. Instructions appropriate to the presumed drug effects produced performance deterioration on the simple motor tasks used. Instructions inappropriate to the presumed drug effects counteracted much of the drug produced decrement. A slight decrement in performance was found in the Placebo group which received Amphetamine instruction. Amphetamine treated Ss produced reports of greater comfort on the mood index than did chloral hydrate. On the other hand, the chloral hydrate instructions resulted in greater comfort than the Amphetamine instructions. There was no interaction between drug effects and instructional effects. The 2 Placebo groups did not differ significantly on the mood index. The effects of instructions on mood were found only when the drug was present. Several suggestions are offered for further research.

This study is the second report dealing with a model design for the analysis of drug effects (Ross, Krugman, Lyerly, & Clyde, 1962). The essential characteristic of the design is the addition to the standard test groups of a group to whom the drug is administered in *disguised* form. We contend that at least a fourfold arrangement—Drug group, Drug Disguised group, Placebo group, and

Untreated group—is essential in order to assess independently drug effects and placebo effects. The methodological problems of the quantitative and objective assessment of drug effects—including the problems of placebo effects—are attracting interest from a variety of viewpoints (Fisher, 1962; Gorham & Sherman, 1961; Hawkins, Pace, Pasternack, & Sandifer, 1961; Kast, 1961; Rinkel, 1963; Wendt, Cameron, & Specht, 1962; Wilson & Huby, 1961).

We have reported one experiment on the effects of amphetamine sulphate in an elderly male population. The results of that experiment, carried out with Neutral instructions, indicated a positive placebo effect on mood in

¹ This study has been supported in part by a grant from the Human Ecology Fund to the Veterans Administration. We express our thanks to John J. Randolph and Frank Vicino for their aid in gathering the data, to E. R. Swepston for medical assistance, and to R. Ledbetter for pharmaceutical cooperation.

a more "comfortable" direction, and a negative effect of the drug, when administered in the Disguised condition. These two effects appeared to cancel one another in those subjects who knew they had received a drug. The Untreated group gave results similar to the group which received the drug as a pill. Motor performances of both the Drug and the Drug Disguised groups were significantly poorer than those of the Placebo and Untreated groups.

The present experiment was designed to determine the specific effects of instructions (appropriate and inappropriate) and the effects of two drugs, which might be expected to produce different pharmacological and perceptual effects. The drugs selected for study were 10.0 milligrams of racemic amphetamine sulphate (a well-known "energizing" drug) and .5 gram of chloral hydrate (a standard sedative). Instructions were developed so that the "instructed" subject would be led to expect that the capsule he swallowed would yield effects usually produced by one or the other of the drugs. Groups similar to those in the previous experiment were used, in addition to an Untreated group and two Placebo groups which were given lactose (300 milligrams) capsules.

In addition to providing for comparisons of effects of the two drugs and the two sets of instructions and for the detection of placebo effects, this study will attempt to answer questions such as the following: Do instructions in the absence of a drug produce effects on mood and performance? Can specific instructions to the subject enhance the effect of the drug administered in the direction suggested

by the instructions? Can instructions inappropriate to the effects produced by the drug alter the effects of the drug in the direction suggested by the instructions?

METHOD

Design

The design, involving 90 subjects, is shown in Figure 1. This design resembles a 3×3 factorial, but it really is not. We regard it as three sets of "nested" 2×2 designs. The first 2×2 is the upper-left part of Figure 1 (Cells 1, 2, 4, and 5). This set is concerned with the drug versus instruction analysis. The second set includes Cells 1, 3, 7, and 9 (at the four corners of the figure) and involves the drug-placebo effects of amphetamine. It is similar to the design used in the first study, except that the two capsule groups were given instructions as to what to expect. The third set is composed of Cells 5, 6, 8, and 9, and is the corresponding design for chloral hydrate. These three 2×2 sets are not independent, of course, since each pair has one cell in common. (Each of the cells along the main diagonal is included in two of the segments.)

The major dependent variables were the same as used in the earlier study with the addition of a tapping test with both preferred and nonpreferred hands, using a telegraph key in a circuit with an electric counter. The subjects also made some human figure drawings and participated in some other time filling tasks while waiting for the drugs to take effect. Of the 90 subjects used only 4 had taken part in the first study, and these were from former non-drug groups (Placebo or Untreated).

All subjects received orange juice. Those who were given capsules were given the juice to "wash down" the pills. All subjects were told that the Psychology Service was making a taste survey of orange juice for the guidance of the kitchen staff of the Center and were given a rating scale on which they rated the flavor from Excellent to Very Poor. In addition to its motivating purpose for the No Capsule groups, this maneuver enabled us to reassure ourselves that the drugs were effectively disguised for the subjects who received the drugs unwittingly.

Subjects

The subjects were 90 men members of the Domiciliary at the Veterans Administration Center, Martinsburg. They were between 40 and 77 years old, with a median of 61 years. Each subject was randomly assigned to one of the nine experimental groups. Each subject was cleared medically for participation in the study, was free from major brain pathology or psychiatric disorder, and volunteered at an earlier date to serve in a study by the Psychology Service. The subjects represent a wide variety of occupational histories and educational attainments. Educational levels ranged from second grade to completion of medical school, with the median at the eighth grade.

		DRUG		
		Amphetamine Sulphate	Chloral Hydrate	Placebo
INSTRUCTIONS	Amphetamine	1 CAPSULE	2 CAPSULE	3 CAPSULE
	Chloral Hydrate	4 CAPSULE	5 CAPSULE	6 CAPSULE
	None	7 DRUG DISGUISED	8 DRUG DISGUISED	9 NOTHING

FIG. 1. Basic design of amphetamine/chloral hydrate experiment. ($N = 10$ in each cell. All groups received orange juice.)

Instructional Variable

Each subject was given one of the following sets of instructions pertinent to the group to which he was assigned. For groups which received capsules, the following general instructions were given:

You have taken a capsule which has been used by doctors with older people for many years. It is very well-known medically, and it is perfectly safe for you to take. The staff of the Domiciliary Clinic has checked your complete medical record and has certified that it [the capsule] cannot hurt you in any way.

Depending upon the specific instructional group to which the subject was assigned one of the following two additional sets of instructions was given:

Amphetamine instructions:

What it [the capsule] can do is to make you feel a little livelier than you feel now, or maybe more pepped up, or even a little tense. However you feel, don't worry about it, because the effects will last only a short time, and you will be perfectly all right when you are finished here today.

Chloral hydrate instructions:

This capsule may make you feel somewhat calmer than you feel now, or relaxed, maybe even a little drowsy or tired. However you feel, don't worry about it. The effects will last only a short time, and you will be perfectly all right when you are finished here today.

The No Capsule groups received instructions which emphasized that they were a Control group or an Untreated group in a drug experiment. They were told that we were going to use their scores on these tests as a basis or standard of comparison so that we could compare their scores to the scores of those subjects who took a drug. They were told that this was the way we could find out what the drug effects were really like. The fact that they were a Control group which did not receive a drug (capsule) was stressed at least four times in the instructions. The subject was also asked if he understood why we did not give him a drug. Unless an adequate verbal statement of understanding was elicited, the experimenter gave the instructions over again with suitable modifications. The instructions were given until the subject could make a verbalization of the necessity for having an untreated, i.e., no drug group in the experiment. It was found necessary to use such instructions because the subjects were aware of the fact that some people were receiving drugs, i.e., capsules, when they came to see the experimenter.

Experimental Procedure

After random assignment to one of the conditions of the experiment, at least 1 hour elapsed before a subject was subjected to any formal measurements. At the start of this period, the subject was interviewed, given his set of instructions, and the appro-

priate capsule-juice or juice arrangement. He was then asked to complete the orange juice quality questionnaire, and a brief, innocuous "reading habits" questionnaire, and an attitude scale. After an hour had elapsed, the subject was administered the Clyde (1960) Mood Scale a handedness questionnaire, a figure drawing test, the paper-and-pencil tapping test, the H-Bar crossing test (see Ross et al., 1962, for descriptions of these tests), the telegraph key tapping test, and a second attitude scale. The administration of these measures started at the end of 1 hour after drug administration and occupied varying amounts of time from 1 to 2 hours. The specific order described above was followed, and each subject was tested individually.

The Mood Scale was administered as previously described (Ross et al., 1962). Although subjects were given no instructions concerning speed, i.e., they were free to work as fast or as slowly as they chose, the examiner recorded the number of seconds taken to complete the Mood Scale items. The handedness questionnaire was derived from the manual of the Harris Test of Laterality. Instructions for the figure drawing were to "make it a whole person, not just a head and shoulders." The paper-and-pencil tapping test was the same as previously utilized and described, as was the H-Bar test. The instructions used for the telegraph key tapping test were as follows:

I want to see how fast you can tap with your right hand and with your left hand. At the end of each period when you tap, you will be given a rest period. Try to relax. Rest with your wrist and arm on the table and hold the key with your thumb and first finger [demonstrated]. You will be able to tap much faster if you use your wrist and hand. These two boxes [Counter and Stimulus Controller] will click, but you should go right on working. Begin to tap when I say "go," and stop when I say "stop." Remember to tap as fast as you can.

RESULTS

Orange Juice Test

The mean "flavor ratings" for the two groups who received the drugs disguised in orange juice did not differ significantly from those of the Control group. We consider, therefore, that the drugs were effectively concealed.

Performance Measures

Performance test means are listed in Table 1. Low values are associated with good performance except in the case of telegraph tapping. The number of errors was recorded for the tapping and H-Bar tests, but their incidence was so small and the resulting distributions so skewed that we made no analysis of these

TABLE 1
PERFORMANCE TEST RESULTS

Group	Drug given	Instructions	Tapping time ^a	H-Bar time ^a	Mood Scale time ^a	Telegraph tapping
1	Amphetamine	Amphetamine	133.3	179.5	721.6	529.0
2	Chloral Hydrate	Amphetamine	120.2	139.4	692.7	540.7
3	Placebo	Amphetamine	130.6	169.4	962.6	559.3
4	Amphetamine	Chloral Hydrate	109.8	128.0	641.7	549.9
5	Chloral Hydrate	Chloral Hydrate	162.3	164.7	876.3	474.4
6	Placebo	Chloral Hydrate	111.4	143.6	597.4	556.3
7	Amphetamine	None	121.5	154.6	734.4	557.2
8	Chloral Hydrate	None	132.4	137.7	877.4	524.7
9	Nothing	None	115.5	144.1	651.3	558.4

^a In seconds.

data. The results were first subjected to analysis of variance. Three analyses were made for each measure: one for each of the 2×2 segments of the design, or 12 analyses in all. These analyses are not presented here for reasons of space. As a summary analyses, the numbers in each column were replaced by ranks (because of differences in scale units among the four measures), Friedman's (1937) chi square analysis was applied, and the null hypothesis was rejected at the .05 level.

The general findings in regard to the performance measures are that both drugs interfere with speed of performance, whether given disguised or openly, whether given with appropriate or inappropriate instructions. With instructions which are *consistent* with the presumed drug effect (i.e., instructions expected to *reinforce* the drug effect), performance is poorest. Instructions which are *inappropriate*

to the drug effect give rise to performance which is approximately equivalent to that of the Control (no treatment) group. The uninstructed subjects (i.e., those who received the drugs in disguised form) earned scores which fell between those who received appropriate instructions and those who received inappropriate instructions. The best performances occurred when the amphetamine subjects were given instructions more appropriate to Chloral Hydrate, while the poorest occurred when Chloral Hydrate subjects were given Chloral Hydrate instructions. This effect was most striking in the case of tapping time where there was a difference of 50.5 seconds between the means of these two groups.

There is a considerable placebo effect in the case of Amphetamine instructions, i.e., the Amphetamine instructed Placebo subjects

TABLE 2
MOOD SCALE MEANS FOR TREATMENT GROUPS

Group	Drug given	Instructions	Friendly	Energetic	Clear-thinking	Aggressive ^a	Jittery ^a	Depressed ^a	Total index
1	Amphetamine	Amphetamine	52.5	50.9	52.4	53.7	53.5	54.4	317.4
2	Chloral Hydrate	Amphetamine	50.9	46.2	47.2	53.6	51.3	51.3	300.5
3	Placebo	Amphetamine	52.5	51.0	48.1	50.5	53.9	51.7	307.7
4	Amphetamine	Chloral Hydrate	52.7	52.1	49.9	57.5	56.3	55.0	323.5
5	Chloral Hydrate	Chloral Hydrate	51.9	46.6	49.4	54.8	55.3	51.2	309.2
6	Placebo	Chloral Hydrate	52.5	50.5	51.3	50.1	53.6	50.4	308.4
7	Amphetamine	None	53.1	50.1	50.1	51.1	49.8	49.9	304.1
8	Chloral Hydrate	None	55.5	50.5	50.2	52.2	51.7	48.1	308.2
9	Nothing	None	52.3	46.7	48.0	51.1	46.2	50.0	294.3

^a Scales reversed (see text).

showed impairment of performance as compared with the Control group (except in the telegraph tapping task). The Chloral Hydrate instructed Placebo subjects performed at about the same level as the Control subjects.

It is interesting to note that of the four performance measures considered separately, the one which is most sensitive to drug effects and to instruction effects is the time taken by the subject to complete the Mood Scale. In the variance analyses of the three 2×2 portions of the design, this measure differentiated the two drugs ($p < .05$, better performance under amphetamine than under chloral hydrate); drug instruction interaction ($p < .001$, compensatory effect of *inappropriate* instructions); Amphetamine drug-no drug difference ($p < .05$, better performance under

TABLE 3

ANALYSIS OF VARIANCE OF MOOD SCALE MEANS FOR DRUG VERSUS INSTRUCTION CONDITIONS

Source	SS	df	MS	F
Scales	112.71	5	22.54	11.7**
Treatments	49.97	3	16.67	8.6**
Drugs	40.56	1	40.56	21.0**
Instructions	9.13	1	9.13	4.7*
Interaction	.28	1	.28	<1.0
Remainder	28.94	15	1.93	
Total	191.62	23		

* $p < .05$.
** $p < .01$.

amphetamine than under no drug); Amphetamine instruction interaction ($p < .001$, subjects receiving amphetamine in capsule or disguised performed *better* than Amphetamine instructed Placebo subjects, but *poorer* than Control group); Amphetamine instruction-no instruction difference ($p < .001$, Amphetamine instructed subjects performed poorer than subjects with no instructions); and Chloral Hydrate drug-no drug effect ($p < .001$, subjects receiving chloral hydrate poorer than subjects not receiving that drug). The greatest mean difference between any two groups was that between the two Placebo groups (963 seconds for the Amphetamine instructed subjects versus 597 seconds for the Chloral Hydrate instructed subjects).

In fact, this Mood Scale time score discriminated the groups more effectively than did any one of the six scale scores derived

TABLE 4

ANALYSIS OF VARIANCE OF MOOD SCALE MEANS FOR THE AMPHETAMINE GROUPS

Source	SS	df	MS	F
Scales	27.07	5	5.41	2.11
Treatments	45.55	3	15.18	5.93**
Drug-No Drug	15.84	1	15.84	6.19*
Pill-No Pill	29.70	1	29.70	11.60**
Interaction	.01	1	<.01	—
Remainder	38.42	15	2.56	
Total	111.04	23		

* $p < .05$.
** $p < .01$.

from the items themselves. This was the only one of the four tasks which permitted the subject to work at his own pace rather than "as rapidly as you can." We interpret these findings to be a consequence of the human organism's capacity to compensate to some degree when faced with a challenging task. We suggest that studies of the effects of drugs upon performance should include situations where the critical requirements of the tasks as well as the drug can be "disguised."

Mood Measures

Means of the six scores from the Mood Scale are shown in Table 2. Separate analyses of variance were performed for each score, 3 for each 2×2 segment of the design, or 18 analyses in all, but are not reported here since they are so numerous. As in the earlier study, we reversed the scoring direction for the last three scales (Aggressive, Jittery, and Depressed) so that high values can be interpreted as "comfortable." Then analysis of variance was applied to the means of the six scales for each of the 2×2 segments of the design. These are presented in Tables 3, 4, and 5.

TABLE 5

ANALYSIS OF VARIANCE OF MOOD SCALE MEANS FOR CHLORAL HYDRATE GROUPS

Source	SS	df	MS	F
Scales	56.32	5	11.26	2.53
Treatments	25.45	3	8.48	2.83
Drug-No Drug	8.76	1	8.76	1.97
Pill-No Pill	9.75	1	9.75	2.19
Interaction	6.93	1	6.93	1.56
Remainder	66.70	15	4.45	
Total	148.47	23		

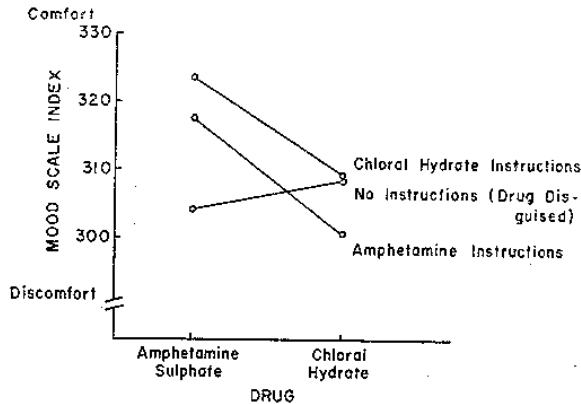


FIG. 2. Effects of instructions and drugs on Mood Scale index.

Drug Instruction Effects

In the first analysis, involving the drug instruction segment of the design (Cells 1, 2, 4, and 5 in Figure 1), a significant drug effect was discovered: Subjects who received amphetamine, whether they knew it or not, reported themselves as more comfortable than those who received chloral hydrate (see Table 3). There was also a significant difference resulting from the two drug instructions. Those subjects receiving instructions appropriate to chloral hydrate, regardless of which drug they had taken, were more comfortable than those who were led to expect an amphetamine experience. There was no interaction between the two effects; i.e., the magnitude of the differences in drug effect are independent of which of the two instructions were used, and vice versa. This is illustrated in Figure 2, in which we have arbitrarily added the six scale means into a single crude "comfort-discomfort" index and plotted values for these drug instruction combinations, adding for comparison the corresponding data from Cells 7 and 8 for the groups who received the drugs in disguised form.

Judging from the results of the two Drug Disguised groups (which are not significantly different from each other), we would expect that chloral hydrate would produce an experience at least as comfortable as that produced by amphetamine when averaged over both sets of instructions, but this did not happen. Related to this is the paradoxical finding that while amphetamine resulted in a more comfortable mood report, the *instructions* which we presumed to be appropriate

for amphetamine apparently operated in such a way as to produce reports of *less* comfort.

There are several possible interpretations of these phenomena. For example, subjects who know that they have received a drug may introspect and report mood in a different manner than those who do not know that they have received a drug. Further, the instructions which we gave may not have been the most appropriate for those particular drugs under the conditions in which they were used.

Drug-Placebo Effects—Amphetamine

In the analysis of the second 2×2 segment (Groups 1, 3, 7, and 9) concerning the drug-placebo effects of amphetamine, we find that subjects who received the drug, knowingly or unknowingly, report themselves as more comfortable than those not receiving the drug, and subjects receiving a capsule are more comfortable than those who did not ingest a capsule (see Table 4). This appears to be inconsistent with the results of our earlier study, in which amphetamine produced reports of *less* comfort than placebo. This difference apparently can be reconciled only as a function of the expectation of the amphetamine and placebo subjects in the present study, since the instructions are the only essential elements in which the two experiments differ.

Drug-Placebo Effects—Chloral Hydrate

In the analysis of the Chloral Hydrate-Placebo portion of the study (Groups 5, 6, 8, and 9) no significant effects appeared on either the drug-no drug or the capsule-no capsule dimensions (see Table 5). This leads us to two conclusions: The significant drug effects reported in the drug versus instruction analysis above were functions mainly of the effectiveness of amphetamine (in contrast to the apparently relative ineffectiveness of chloral hydrate); the chloral hydrate dose used (500 milligrams) is not equivalent to the amphetamine dose so far as its impact upon reported mood is concerned.

DISCUSSION

The finding that amphetamine impairs speed of motor performance may appear to

be contradictory to the widely held view that this drug is beneficial in elevating mood and enhancing performance. Our results in both this and the earlier study indicate no performance improvement. Rather a *decrement* in performance is found under the drug (unless counteracting instructions are given). This effect may be a function of the advanced ages of our subjects. Some reports in the literature, however, conclude that amphetamine has beneficial effects only in cases where there is an existing performance impairment produced by conditions such as fatigue or sleep loss. According to this view, since our subjects were presumably rested and favorably motivated, enhancement of performance would not be expected. (See the review by Weiss and Lattes, 1962, for a discussion of this and alternative hypotheses.)

Comparisons of the results of the Placebo groups indicate that the expectations induced by the instructions affected the performance measures (better performance with Chloral Hydrate instructions), but had no differential effect upon reports of mood. It is not clear why this should be the case. A possible explanation may be that the Mood Scale is less sensitive to such manipulation than are the performance measures, even though the instructions were designed to have effect upon the subject's mood as well as performance. The instructions used affected mood reports *only when a drug was present*.

The greater degree of expressed comfort in the Placebo groups as compared with the Controls is consistent with the findings in the earlier study. This effect of increased comfort may arise from a nonspecific expectation of "goodness" of outcome induced by the hospital setting, the therapeutic goal of hospital staffs, etc.

Comparing the two groups which received the drugs in disguised form (with no instructions) we find no significant differences, in either mood or performance, attributable to differential effects of the two drugs. These drugs at the dose levels used were effective *only when instructions were used*. It appears that the drugs may give rise to nonspecific stimuli, perhaps certain internal perceptions,

which need to be "interpreted." These interpretations are guided by or related to the expectancies produced by the instructions.

It is important to stress that our findings and interpretations are applicable only to the specific drugs, dose levels, tasks, and population used in this study. Other experiments employing different parameters may yield different patterns of outcome. We hope to gain further insight into these findings and interpretations from data which we are gathering on younger subjects in the medical setting, and we have plans for studying drug and instructional effects in nonmedical settings.

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