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Comparison of Psychological Effects of Certain Centrally Acting Drugs in Man

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A number of recent studies have emphasized that the psychological effects of a given drug are not entirely a function of the drug's more classic "pharmacological properties." On the contrary, as pointed out by Lasagna et al., "the nature of the subject and the situation in which a drug is administered are important determinants of drug effects." [1] The point of view which Lasagna has presented is supported by the results of Hill et al.[2] and of Kornetsky.[3] These investigators have demonstrated that an informal, friendly attitude by the experimenter toward the subject affects the analgesic effect of morphine, and that reaction time is not decreased when subjects are motivated by electric shock.[4] Von Felsinger et al.[5] have concluded that those subjects who respond atypically to one drug are likely to respond atypically to other drugs. The present studies have been designed to obtain further data concerning the degree to which the psychological effects of certain drugs are dependent on the reaction pattern of the subject, and, therefore, independent of the specific pharmacological activity of the drug which has elicited these effects. An attempt has been made to test the hypothesis that the magnitude of drug-induced psychological effects is significantly related to the reactivity of the subject.

In addition to obtaining data concerning the questions raised in the previous paragraph, the present studies have been designed to compare certain of the psychological effects of several classes of centrally active agents; the drugs which were selected include secobarbital, meperidine, chlorpromazine, and lysergic acid diethylamide (LSD). These drugs were selected as representatives of the categories of narcotic, hypnotic, psychotomimetic, and "tranquilizing" agents. Data were obtained concerning the extent to which these agents produce impairment of performance on certain psychomotor and intelligence tests; it seemed that such data might be of value in arriving at conclusions concerning the degree to which the impairment produced by a "tranquilizing" drug, such as chlorpromazine, might differ from impairment produced by hypnotic and narcotic drugs, such as secobarbital and meperidine.

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Methods

Ten normal volunteers between the ages of 18 and 23 years, 6 males and 4 females, served as subjects. The subjects had had little or no previous experience with centrally acting drugs. Each subject received the following drugs at the dosages indicated: meperidine hydrochloride, 50 and 100 mg.; secobarbital sodium, 100 and 200 mg.; chlorpromazine hydrochloride, 200 and 400 mg.; LSD, 50γ and 100γ. This dosage was maintained throughout the course of the experiment, except that, at the completion of observations on four subjects, the chlorpromazine dose was reduced to 100 and 200 mg. This was necessitated by the severity of the postural hypotension produced by single 400 mg. doses of chlorpromazine. On any single testing day the subject received only one drug. There was a minimum of one day between drug administrations. The order of administration was a 10×10 Latin-square design, which included two placebos. In addition to being administered on regular experimental days, all performance tests were given to each subject prior to and at the end of the experimental period. All drugs, including placebos, were administered orally in identical capsules; the "double-blind" technique was employed throughout.

On each experimental day, as well as on the two control days, the following tests were given, starting 75 minutes after the ingestion of the drug:

1. Speed of addition (three digits)[6]
2. Speed of addition (nine digits)[6]
3. Modified digit symbol test[7,8]
4. Speed of copying numbers[9]
5. Pursuit rotor (a standard Gerbrand machine rotating at a rate of 30 rpm was used)
6. Tachistoscopic discrimination of circle size (two circles at a time were tachistiscopically (0.01 to 1.0 second's exposure) projected, and the subject was required to make a judgment as to which circle was the larger)
7. Tactual threshold determination (the skin on the index finger of the right hand was stimulated with finely graded nylon hairs, and the subject was asked to respond verbally when he felt something[10])
8. A 46-item symptom questionnaire,[11] administered to the subjects 30, 90, 150, and 210 minutes after ingestion of the drugs

An analysis of variance[12] was performed on the data for each test. The significance of the differences between the subjects' scores on each drug day and the mean of the two placebo scores was tested by the Dunnett *t*-test,[14] and the significance of differences in the effects of the drugs on the individual tests was determined by the Scheffé test.[15] In order to obtain some over-all estimate of drug effects and also to partial out the differences in original abilities of the subjects on the tests, the mean scores for each subject on each test were expressed as a percentage of the mean of his scores on the same test on the two control days. The mean of the transformed scores for all tests was obtained separately for each subject for each drug. The means for each drug were then obtained, and an analysis of variance was performed.

To determine the relationship between objective and subjective psychological effects, the strength of the relationship between the mean over-all per cent score on the objective tests and the number of positive responses on the symptom questionnaire were correlated by means of the rank-difference method (ρ).[13]

Results

The analysis of variance results for each test produced a significant F ratio for both drug and individual variance but no significant variance for days. The summaries of these analyses are shown in Table 1. Table 2 shows the mean scores obtained for each drug on each test. LSD had significant effects on performance on the addition test (both three and nine digits for 100/γ of LSD), the digit symbol test, and the tachistoscopic discrimination of circle size. Two hundred milligrams of secobarbital sodium had significant effects on the digit symbol and pursuit rotor tests. Two hundred milligrams of chlorpromazine hydrochloride significantly affected performance on the digit symbol and pursuit rotor tests. With the exception of 200 mg. of secobarbital sodium, 100γ of LSD produced significantly more impairment than any of the drugs. Two hundred milligrams of secobarbital sodium produced more impairment than LSD on the three-digit addition test. In no other test were the effects of the high doses of the drugs significantly different from one another. A more comprehensive picture of the

TABLE 1.—*Summary of Analyses of Variance for All Tests*

		Addition (3 Digits)		Addition (9 Digits)		Speed of Copying		Digit Symbol Test	
Source of Variance	*df*	Mean Sq.	*F*	Mean Sq.	*F*	Mean Sq.	*F*	Mean Sq.	*F*
Individuals	9	6824.68	71.2*	2829.70	62.1*	3118.76	27.5*	967.14	24.6*
Drugs	9	738.78	7.7*	342.60	7.5*	241.91	2.1†	425.16	10.8*
Days	9	175.40	1.8	47.69	1.1	73.47	0.6	68.44	1.7
Residual	72	95.88		45.58		113.37		39.28	
Total	99								

		Pursuit Rotor		Visual Discrimination		Tactual Perception	
Source of Variance	*df*	Mean Sq.	*F*	Mean Sq.	*F*	Mean Sq.	*F*
Individuals	9	216.75	23.8*	690.98	83.9*	182.17	7.6*
Drugs	9	97.21	10.7*	24.69	3.0*	71.80	3.0*
Days	9	10.42	1.1	5.98	0.7	20.06	0.8
Residual	72	9.10		8.24		24.03	
Total	99						

* $P < 0.01$.
† $P < 0.05$.

TABLE 2.—*Mean Raw Score for Each Drug on Each Test*

	LSD		Meperidine		Secobarbital		Chlorpromazine*	Placebo	
	50 γ	100 γ	50 Mg.	100 Mg.	100 Mg.	200 Mg.	200 Mg.	1	2
Addition (3 digits), digits per min.	64.5†	50.4†	77.9	74.2	75.4	66.3	76.1	74.1	75.5
Addition (9 digits), digits per min.	37.6	25.0†	42.3	41.9	44.5	37.0	39.6	42.6	42.1
Speed of copying, digits per min.	86.7	75.6	84.4	84.4	85.0	73.6†	74.8	86.1	84.2
Digit symbol, total correct	53.0	41.1†	59.6	56.4	55.3	49.9†	50.0†	57.1	58.3
Pursuit rotor, sec.	19.2	18.5	22.0	19.7	19.6	15.6†	15.9†	20.1	21.5
Visual discrimination, incorrect	9.3	10.8†	6.3	7.6	7.0	9.4	7.8	6.5	6.5
Tactual perception, no. correct	53.3	51.7	55.6	57.5	56.3	52.8	52.8	56.5	52.9

* Since only six subjects received 100 mg. and only four received 400 mg., these results are not reported on the individual tests.
† $P<0.05$ (between score and mean of two placebos).

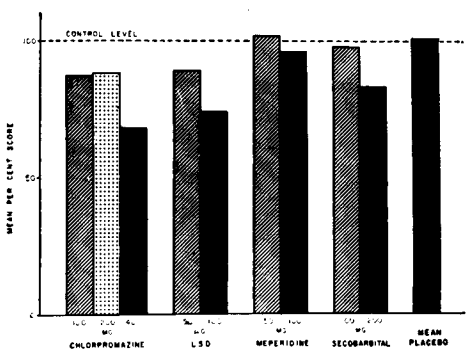

Fig. 1.—Mean per cent over-all score for each drug.

comparative effects of the drugs is shown in Figure 1. The summary of the analysis of variance for these data is shown in Table 3.

Since it was not expected that any of the drugs would produce an over-all increase in performance, single-tailed Dunnett *t*-tests were employed to determine the significance of the difference between the effects of each drug and of the mean of the two placebos. The effects of 200 mg. of secobarbital sodium; 100, 200, and 400 mg. of chlorpromazine hydrochloride, and 50γ and 100γ of LSD differed significantly from those of the placebos ($P<0.05$). High doses of secobarbital, meperidine, LSD, and chlorpromazine produced more impairment than low doses of the same drugs ($P<0.05$).

An analysis of the effects of the three doses of chlorpromazine (6 subjects received 100 mg.; 10 received 200 mg., and 4

TABLE 3.—*Summary of the Analysis of Variance for Over-All Per Cent Scores*

Source of Variance	*df*	Sum Sq.	Mean Sq.	*F*	*F*
Tests	6	2.130	0.3550	T / TXS	2.58*
Drugs	8	6.591	0.8239	D / DXS	10.06†
Subjects	9	3.280	0.3644	S / DXSXT	12.23†
Tests×drugs	48	5.082	0.1059	DXT / DXSXT	3.55†
Drugs×subjects	72	5.927	0.0819	DXS / DXSXT	2.75†
Subjects×tests	54	7.419	0.1374	SXT / DXSXT	4.61†
Drugs×subjects×tests	432	12.867	0.0298		
Total	629	43.296			

* $P<0.05$.
† $P<0.01$.

received 400 mg.) by means of the *t*-test showed that 400 mg. of chlorpromazine hydrochloride produced significantly more impairment of performance, at ($P<0.01$), than did 200 mg. on speed of addition (three and nine digits), digit symbol, pursuit rotor, visual discrimination, and tactual threshold tests. Two hundred milligrams of chlorpromazine hydrochloride produced a significantly greater degree of impairment in performance than did 100 mg. on only the digit-symbol test ($P<0.05$).

The analysis of the responses to symptom questionnaire (mean number of symptoms for four periods after receiving the drug) is summarized in Figure 2; the analysis of variance is shown in Table 4. Although all the drugs produced an average increase in reported symptoms, only 50γ and 100γ of LSD, 200 mg. of secobarbital sodium, and 400 mg. of chlorpromazine hydrochloride produced a statistically significant increase in the number of symptoms over the mean for the two placebos.

Table 5 presents the results of the correlation of the over-all objective scores and the subjective scores (symptom questionnaire) for each drug. As the data indicate, there was no significant correlation of the objective effects and the subjective effects

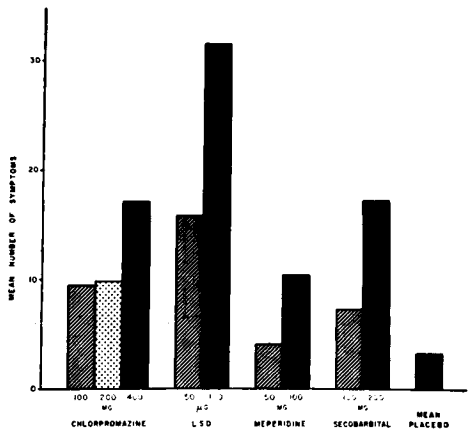

Fig. 2.—Mean number of symptoms on the symptom questionnaire for each drug.

of any one of the drugs taken individually, with the exception of 200 mg. of secobarbital sodium. One hundred micrograms of LSD produced a negative, but not significant, correlation (the greater the subjective effect, the less marked the objective effects). However, the mean objective effects correlate with the mean subjective effects ($\rho=0.84$) for all drugs at a statistically significant level. Thus, there is no discrepancy between objective and subjective effects when a correlation between drugs rather than between subjects is computed.

TABLE 4.—*Summary of the Analysis of Variance for the Symptom Questionnaire*

Source of Variance	*df**	Sum Sq.	Mean Sq.	*F*
Drugs	7	5,891.4	844.628	16.50†
Subjects	9	1,031.2	114.577	2.25‡
Residual (D×S)	63	3,212.65	50 994	
Total	79	10,135.25		

* The smaller number of degrees of freedom in this analysis was due to the combining of the two placebos and the use of only 200 mg. of chlorpromazine.
† $P<0.01$.
‡ $P<0.05$.

TABLE 5.—*Correlations (ρ) Between Objective (Over-All Score) and Subjective (Symptom Questionnaire) Effects of the Various Drugs*

Placebo*	LSD		Meperidine		Secobarbital		Chlorpromazine
	50 γ	100 γ	50 Mg.	100 Mg.	100 Mg.	200 Mg.	200 Mg.
0.46	0.39	−0.36	−0.03	0.12	0.53	0.66†	0.54

* Mean of two placebos.
† $P<0.05$.

Comment

Although most of the drugs produced impairment in performance of the tests used in the present study, the large individual variability resulted in statistically significant impairment of performance on only a few tests by each drug.

Since LSD affected performance on more tests than any of the other drugs, it was somewhat surprising to find that it did not significantly affect performance on the pursuit rotor test. This suggests that LSD has little effect on motor coordination but has considerable effect on perceptual and intellectual processes. However, chlorpromazine (200 mg. or less) and secobarbital do not seem to affect simple intellectual tasks (speed of addition) but do affect more complex intellectual tasks (digit symbol test) and motor coordination (pursuit rotor). The over-all analysis of variance suggests that the drug-test interactions are significant (Table 3, Test×drugs, $F=3.55$). In studies by Abramson [16] and Jarvik and their associates,[17] it was found that LSD at doses up to 100γ did not significantly affect performance on the pursuit rotor, hand steadiness, or manual reaction time. Verbal reaction time (time to read a series of words), attention, and concentration were significantly affected by the same doses of LSD. An opposite result was reported by Landis and Clausen.[18] They found impairment of performance on some motor tests, but they did not find impairment of flicker-fusion threshold in schizophrenics after LSD. There have been no reported studies of the effects of secobarbital on the tests employed in the present study; however, some studies on the effects of amobarbital indicate that at low dose levels there is very little effect on intellectual functioning (Arkola [19] and Slater and Sargant [20]), but greater effect on motor performance as measured by reaction time and the tracing of a pathway with stylus (Hill and Belleville [21]). Although secobarbital did not significantly affect visual discrimination in the present study, Ideström [22] has reported that moderate (0.30 gm/70 kg. of body weight) single doses of barbiturates produce an increase in the flicker-fusion threshold. It is unlikely that flicker fusion and discrimination for circle size measure the same aspect of visual function. The results obtained with chlorpromazine in the present study are in opposition to the findings of Lehmann and Hanrahan,[23] who reported that chlorpromazine in doses large enough to produce somnolence had no detrimental effect on a variety of psychological tests.

The analysis of variance of the over-all mean per cent scores (Table 3) gave a significant F ratio for all the sources of variance. The significant subject variance suggests that those subjects whose performance was most impaired by one drug are those whose performance was most impaired by the other drugs. However, this subject responsivity is not linear, since the drug×subject interaction was also significant. To test the extent of this responsivity or reaction pattern of the subjects, the Kendall coefficient for concordance was computed.[24] This yielded slight but positive evidence for the presence of a phenomenon of this type ($w=0.35$; $P<0.01$ level). This was also true, but to a less degree, for the symptom questionnaire data. ($w=0.26$; $P<0.05$ level). These results indicate that there is some factor independent of the drug, as well as some factor dependent on an interaction with specific drugs, which accounts for a portion of the total variance. This factor may be a function of personality, as suggested by von Felsinger, Lasagna, and Beecher, or it may be a function of specific pharmacological sensitivity and/or other physiological differences on the part of individual subjects.

The importance of placebo effects in the study of drugs has been emphasized by many investigators. However, in the present experiment the results of the tests done after administration of a placebo showed no significant placebo effect. The results obtained on the symptom questionnaire were an exception in that on this subjective test

there were a number of positive responses following placebo administration. Since the symptom questionnaire was not administered during the control period, the responses of placebo-treated subjects to the symptom questionnaire could not be interpreted as placebo effects.

The significant correlation between objective and subjective effects of the drugs indicates that the drugs which caused the greatest objective impairment in functioning also had the most marked subjective effects. However, the general lack of significant correlation between subjective and objective effects produced by each drug in the individual subjects (Table 5) indicates that, although a subject may feel he is greatly affected by a drug, there may be little or no actual impairment in his functioning. The opposite also holds true; many of the subjects who did not show drug effects on the symptom questionnaire were greatly impaired in their ability to carry on the tests. This suggests that there may be a dichotomy between the objective and subjective effects of a drug, making it impossible to predict accurately the extent of one type of effect from the extent of the other.

It is of interest that of the four drugs studied meperidine was the only one that produced pleasant effects in the majority of subjects. Many of the subjects said they would like to receive that "pleasant" drug again. Most of the subjects found that 200 mg., or more, of chlopromazine and 100γ of LSD produced unpleasant effects. The chlorpromazine made them feel faint, nauseated, dizzy, and very sleepy. The LSD made them feel anxious, tense, and in some instances depressed.

Summary

Ten normal volunteers were given various doses of lysergic acid diethylamide (LSD), meperidine, secobarbital, and chlorpromazine. The order of drug administration was a 10×10 Latin square, which included two placebos.

All drugs were administered orally, and the "double-blind" technique was employed throughout. Seventy-five minutes after ingesting the drug, subjects were given a variety of psychological tests, which included intellectual, motor, and perceptual tasks.

The following conclusions were drawn from the data:

The effects of drugs on psychological performance in man are due not only to the specific pharmacological activity of the drug, but also to the specific reactivity of the subject and to an interaction of the two.

There is not a significant correlation between the objective and the subjective psychological effects of a given drug. However, the drugs that produce the greater mean objective effect also produce the greater mean subjective effect.

Two hundred milligrams of secobarbital sodium; 100, 200, and 400 mg. of chlorpromazine hydrochloride, and 50γ and 100γ of lysergic acid diethylamide significantly impair performance on a variety of psychological tests. Meperidine hydrochloride in 50 and 100 mg. doses does not impair performance on the same psychological tests.

LSD had significant effects on intellectual and perceptual tasks but did not cause significant impairment of motor tasks, whereas chlorpromazine and secobarbital affected motor tasks but in general did not cause statistically significant impairment of performance on simple intellectual and perceptual tasks.

Two hundred milligrams of chlorpromazine does not impair performance significantly less than does 200 mg. of secobarbital sodium.

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