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DRUG–SET INTERACTION: THE EFFECT OF EXPECTATIONS ON DRUG RESPONSE IN OUTPATIENTS*

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This is a preliminary report on a collaborative research project conducted by the Psychopharmacology Service Center in collaboration with Johns Hopkins University and the University of Pennsylvania. The study is part of the Psychopharmacology Service Center's larger special program concerned with the effects of expectations upon drug response in patients and in normal subjects. The study has there main purposes:

(1) To determine whether meprobamate administered for a 6-weeks period at a fixed dosage is more effective than an inert placebo in the treatment of neurotic outpatients.

(2) To determine whether patients' expectations about the doctors' attitudes toward the medication being prescribed have a significant effect upon treatment course. Patient expectation (or "set", as we refer to this variable) was varied by training one group of doctors to maintain a positive, consistent, reasonably enthusiastic attitude toward the medication being used for their patients; another group of doctors was trained to manifest a more uncertain, "experimental" attitude about the efficacy of the medication being prescribed to their patients.

(3) To determine whether a significant drug–set interaction exists: *i.e.*, to test the hypothesis that a favorable set may potentiate the clinical response to an active drug.

BACKGROUND

The rationale underlying this research approach may be best understood by referring to Fig. 1.

It has long been observed that clinical response to drugs may be affected by the milieu or climate in which the medication is administered. The interpretation of this observation, however, presents a most interesting problem. Take, for example, a situation where a particular drug is administered in a setting where the staff consistent-

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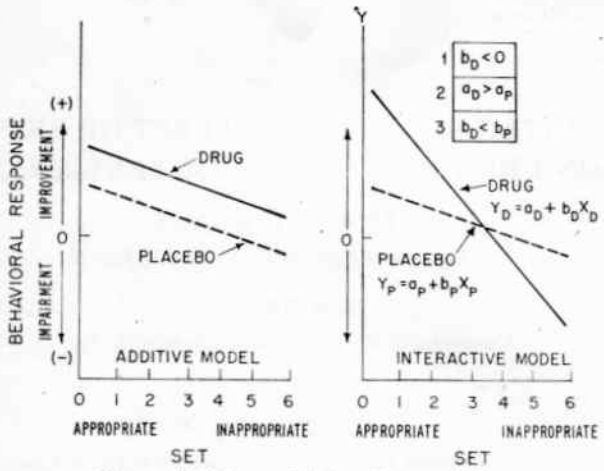

Fig. 1. Additive and interactive models.

ly conveys to the patients its faith in the treatment efficacy: it would not be surprising to find these patients showing better response to the medication than a comparable group of patients being administered the same medication in a setting where the staff may communicate certain doubts and reservations about the treatment efficacy. It is precisely this assumption which requires the use of placebo controls, so that one may hopefully assess the pharmacodynamic action of the drug above and beyond the influence of the particular expectations (along a continuum of appropriateness) which the patients may have. When a placebo control group is introduced into a research design, the universal assumption accepted by investigators is that an additive model obtains. This is shown on the left side of Fig. 1. Regardless of the level of set under which patients may be operating, by subtracting out the amount of response attributed to placebo the remainder may be attributed to the "true" drug action. In other words, at any level of set, however appropriate or inappropriate the set may be, it is assumed that the drug-placebo difference remains the same. Note in the figure that the two curves, one for the drug subjects, and one for placebo subjects, remain parallel across all levels of set so that the drug-placebo difference is constant. When the additive model is appropriate, the use of response to placebo administration as a base line for estimating the additional influence of the active drug is a valid and sufficient approach to estimating pure pharmacodynamic effects.

On the other hand, a number of clinicians have suggested the view that the two variables, set (or milieu) and drug, are not simply additive in their combined effect, but rather a particularly appropriate set may potentiate* a given drug response, and conversely a highly inappropriate or unfavorable set may indeed inhibit drug action. One example of an interactive model is shown on the right of Fig. 1. In a simple

* The term "potentiate" is used here in its pharmacological sense. Two independent variables (*e.g.*, chemicals), when applied in combination or immediate sequence, may yield one of four results: when both factors independently work in the same direction with the net result being the sum of their separate effects, we may speak of *synergism*; when both factors work in the same direction to elicit a response greater than the sum of their independent actions, the term *potentiation* is appropriate. For two variables which independently act in opposite directions, a similar distinction can be made between *antagonism* (the algebraic sum) and inhibition.

additive model, the ultimate behavioral response is always predictable from the simple sum of the two independent effects: if a favorable milieu is capable of producing a certain amount of improvement in placebo subjects, and the drug also has a favorable effect, then the sum of these two effects determines the outcome. In the interactive model, however, the outcome is not predictable simply from knowing what the drug and the set effects may be independently. Given the interactive model shown, notice that if a drug-placebo comparison were to be made under a highly appropriate set (for example, something like zero or one on the horizontal axis), the drug would be seen to produce much greater improvement than the placebo. However, if the experiment, had been carried out under a somewhat neutral set (around three on the horizontal axis), then the drug-placebo comparison would yield no differences at all. Finally, in the rather unlikely situation that a study were carried out under a highly inappropriate set, relative to the placebo the drug would appear to be producing impaired behavioral response.

Thus the meaning of drug–set interaction becomes defined as follows: in terms of experimental operations, if a drug-placebo comparison is made at two or more levels of set, interaction is inferred whenever the drug-placebo differences are not equal under different sets. If three or more levels of set are included in the research design and if one can assume linearity of regression (as assumed in these models), then interaction will be seen by showing that the slope (or regression coefficient) for drug subjects under varying degrees of set is significantly different from the slope for placebo subjects.*

RESEARCH DESIGN

Studies at Denison University and at Seton Hall using normal subjects strongly indicate that, under certain conditions, an interactive model may be considerably more appropriate than an additive model. It has often been noted that new forms of therapy are enthusiastically received on the basis of early uncontrolled clinical impressions, only to be laid to rest by subsequent controlled evaluation. If some genuine interaction effect should exist between physician-milieu and drug action, this could help account for many apparent discrepancies between the findings of hardheaded researchers and those of equally hardheaded clinicians. In uncontrolled clinical trials, the patients may be exposed to a quite different "attitudinal" atmosphere: they more often see themselves as being "treated" rather than "researched", and this may provide a highly favorable setting for drug action. In many controlled experiments, the patients become definitely aware that they are participating in a research project (implying "Let's see if the drugs will help you"), and such a perception could tend to inhibit drug action. This problem can be thought of as the *Heisenberg Principle of the Behavioral Sciences*, where the very act of setting up certain controls can alter the phenomenon sufficiently to yield quite different results. In the present study, our intent is to determine whether a meprobamate-placebo comparison for patients being treated by an enthusiastic physician is the same or different from a meprobamate-

* The factorial design which includes different combinations of medication and set provides the basis for answers to three discrete questions: (a) Is there a drug effect? (b) Is there a set effect? (c) Does the drug effect depend upon the level of set (or—the identical statement—does the set effect depend upon the level of drug)?

placebo comparison for patients being treated by a more skeptical doctor.

The design of the present study is as follows (Table I): three participating psychiatric outpatient clinics* followed an identical protocol. At each clinic selected neurotic

TABLE I

STRUCTURE OF THE 2 × 2 FACTORIAL DESIGN CARRIED OUT AT 3 SEPARATE OUTPATIENT CLINICS

(Experimental design of medication)

Set	*Clinics*					
	PHIPPS		*PGH*		*PENN*	
	Meprobamate	*Placebo*	*Meprobamate*	*Placebo*	*Meprobamate*	*Placebo*
T	20	20	15	15	15	15
E	20	20	15	15	15	15

patients were randomly assigned to one of four treatment combinations: meprobamate or placebo administered by a "Therapeutic" (T) doctor, meprobamate or placebo administered by an "Experimental" (E) doctor. At each clinic two psychiatric residents were trained to convey a "therapeutic" attitude, and two other residents were trained to convey an "experimental" attitude. Thus, as can be seen from the table, half of the patients in the project received meprobamate and half received placebo; half of the patients were exposed to a T doctor, and half were exposed to an E doctor. The numbers shown in each of the cells represent the number of patients we originally hoped to complete at each clinic under the assigned combination of medication and set.

INDEPENDENT VARIABLES

Table II summarizes the nature of the two independent variables involved, each variable being studied at two different levels. For the pharmacological variable

TABLE II

SUMMARY OF THE INDEPENDENT VARIABLES, WITH TWO LEVELS OF EACH VARIABLE

1. *Drug*
   - 2 capsules meprobamate (@ 200 mg) q.i.d.
   - 2 capsules placebo q.i.d.

2. *Set*
   - "T" Doctors
   - "E" Doctors

* The three clinics are Henry Phipps Psychiatric Clinic of Johns Hopkins University (Phipps), the Neuropsychiatric Clinic at Philadelphia General Hospital (PGH), and the Functional Clinic at the University of Pennsylvania (Penn.).

patients received two capsules of meprobamate q.i.d. (1600 mg), or two placebo capsules q.i.d. For the psychological variable, patients were exposed to either a T doctor or an E doctor.

The basic criteria for the T role are shown in Table III. Notice that the T doctor consistently attempted to convey confidence in the efficacy of the drug. Care was taken to keep T patients from recognizing that they were participating in a research project, and the emphasis was completely upon the situation as being treatment-oriented, whether we succeed in all T patients is doubtful, however. The T doctor also utilized the probability of the occurrence of drowsiness as a side effect of meprobamate to prepare the patient for the eventuality of the side effect. Thus, the T doctor in the initial interview would inform the patient that the medication being given him sometimes produces mild drowsiness and then stresses to the patient that should this appear this was a favorable sign of the drug's efficacy.

TABLE III
BASIC COMPONENTS OF T ROLE

1. Doctor conveys confidence in the efficacy of the drug: patient perceives situation as *treatment-oriented.*
2. Doctor prepares patient for subsequent "side effect" (drowsiness), and interprets the appearance of this effect as a favorable sign of the drug's efficacy.

In contrast, the E doctors consistently attempted to convey uncertainty about the efficacy of the drug (Table IV). The doctor would point out that he hoped that the medication he was prescribing would help the patient's symptomatology but one could not be sure and although it was known that the medication was a safe medication, it was necessary to carry out this research project to find out whether the medication would or would not be of any help to the patient. The E doctors made no mention of any possible drowsiness.

TABLE IV
BASIC COMPONENTS OF E ROLE

1. Doctor conveys uncertainty about the efficacy of the drug: patient perceives situation as *research-oriented.*
2. Doctor does not mention any possible side effect.

ROLE VALIDATION

Since the success of the study stands or falls on the assumption that the doctors were conveying differential attitudes to the patients, it was important to attempt to determine how valid our training procedures were. To obtain information on this point, we ran a pilot study using 24 patients, 8 patients at each clinic, 4 of whom were exposed to E docters and 4 to T doctors. Immediately following the initial interview between the doctor and the patient, the patient was interviewed by a research psychiatrist who attempted to elicit from the patient his general perception of his doctor's attitude toward

medication. These interviews were tape recorded, subsequently transcribed, and rated blindly by three independent judges. Due to recording difficulties data were available on only 20 patients. Table V shows the results of these ratings when the judges were asked "From the patient's viewpoint how certain is his doctor of the drug efficacy?" The ratings were made on a five-point scale ranging from extremely uncertain to extremely certain. As can be seen from Table V, each of the three raters judged that the T patients perceived their doctors as being more certain about the drug's efficacy than did the E patients. To this extent then, we had some indication that the doctors were indeed conveying differential attitudes to their patients.

TABLE V

RESULTS ON ROLE VALIDATION

	Mean ratings		
	T patients (12)	*E patients (8)*	*P*
Rater A	3.36	2.12	< 0.05
Rater B	4.08	3.25	< 0.02
Rater C	4.08	1.71	< 0.01

From the patient's viewpoint, how certain is his doctor of the drug's efficacy?
0 . . . ⟶ . . . 5
Extremely uncertain ⟶ Extremely certain

MEASURING CLINICAL CHANGE

The dependent variables used in this project are shown in Table VI. The project extended over a 6-week treatment period. At each of the four biweekly interviews, a series of measures to detect clinical improvement were used. Prior to each interview the patient would rate himself on (1) a symptom check list*, (2) an adjective check list designed to measure anxiety and depression**, (3) the Clyde Mood Scale, also an

TABLE VI

SUMMARY OF DEPENDENT VARIABLES

Patient rates self	*Doctor rates patient*
1. Symptom check list	Symptom check list
2. Anxiety and depression adjective check list	Anxiety and depression adjective check list
3. Clyde Mood Scale	Clyde Mood Scale
4. Global "improvement"	Global "improvement"
Drop-out rates	

* Adapted from the John Hopkins Symptom Distress Check list.
** Adapted from previous outpatient drug research carried out by Drs. M. Lorr and D. McNair at the Outpatient Psychiatric Research Laboratory, Veterans Administration.

adjective check list to measure other aspects of subjective response, (4) a seven-point scale of global improvement (which was not administered until the patient's second interview). A comparable form of each of these four measures was similarly rated by the doctor following each interview. In addition to these specific indices of clinical improvement, drop-out rate constituted a fifth dependent variable. By "drop-out rate" we are referring to those patients who voluntarily do not continue treatment for the required 6-weeks period.

ANALYSIS OF DROP-OUTS

The major results of this project are still under analysis, but we would like at this time to indicate the results on drop-out rates. Of a total of 238 patients who began the study, 27.8% did not voluntarily complete 6 weeks of treatment (an additional 25% of our intake were dropped for technical reasons). An obvious question here is how these voluntary drop-outs (or as we refer to them, "no-shows") were distributed over the four treatment combinations (Table VII). The data indicate that for subjects who were receiving placebo, drop-out rate was essentially uninfluenced by the type of doctor: whether patient had an E doctor or T doctor, if he received placebo, the drop-out rate was a uniform 31.7%. However, for those patients who were receiving meprobamate, drop-out rate is differentially affected by the type of doctor. For meprobamate patients who had T doctors only 16.4% failed to complete 6 weeks of treatment, whereas for meprobamate patients with E doctors, 32.1% did not complete treatments.*

TABLE VII

"NO-SHOWS" UNDER DIFFERENT TREATMENT COMBINATIONS (%)
(Pooled data from three clinics, based upon totals of 66 "No-shows" and 171 "Shows")

	Meprobamate	*Placebo*
T	16.4	31.7
E	32.1	31.7

These data then are entirely consistent with an interactive model, in the following sense: using drop-out rate as a criterion, one would not have been able to differentiate the drug from the placebo if only E doctors had been employed in the project; with T doctors, however, one can readily detect a meprobamate-placebo difference, in that placebo patients drop out more frequently than do meprobamate patients ($X^2 = 3.1$, $p < 0.05$). Another way of viewing the interaction is to note that the drop-out rate for patients who are given meprobamate by T doctors is almost 50% less than the drop-out rate for patients under any of the other treatment combinations.

* A direct statistical test of the interaction hypothesis for enumeration data such as "Shows" and "No-shows" can be approached by partitioning a total chi-square into its three components. Using this test, with only 66 "No-shows" in the analysis, the interaction effect is significant between the 0.10 and 0.05 confidence levels.

SUMMARY

We have briefly reported the design and rationale of a collaborative clinical experiment concerned with the interactive effects of medication and "milieu" (broadly speaking) upon the clinical response of neurotic outpatients. Thus far, analysis of a single criterion—drop-out rate—suggests that response to meprobamate is in part a complex function of patient expectations. Since the clinical meaning of a "drop-out" may be somewhat ambiguous, it remains to be seen whether similar interactive effects will emerge on more direct criteria of clinical improvement.