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Drug, Doctor Warmth, and Clinic Setting in the Symptomatic Response to Minor Tranquilizers

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Abstract. An NIMH-PRB collaborative double-blind clinical trial, concerned with the importance of the "doctor variable" for drug treatment outcome, was conducted with 485 anxious neurotic outpatients receiving either chlordiazepoxide, meprobamate, or placebo. The participating clinics were located at the Johns Hopkins Hospital, Philadelphia General Hospital, and the Hospital of the University of Pennsylvania. The doctor variable selected for presentation was "doctor warmth". Data on the 169 patients completing the 4 week study according to protocol were analyzed using a factorial analysis of covariance procedure, and the main findings were as follows: 1. several main "drug" effects, present only at 2 weeks, indicated chlordiazepoxide to produce significantly more improvement than either meprobamate or placebo; 2. several main "warmth" effects, present only at 4 weeks, showed patients rating their physicians at the initial visit as "warm" to improve significantly more than patients rating their physicians as "non-warm"; and 3. several significant drug × clinic interaction effects at 4 weeks reflected the fact that while hardly any drug differences were seen in 2 clinics, at Philadelphia General Hospital, patients strongly favored chlordiazepoxide. "Drug" and "warmth" effects were particularly marked in initially sicker patients, and "warmth" appeared especially important in the improvement of initially sicker placebo patients.

Key-Words: Anxiety Neurosis — Chlordiazepoxide — Meprobamate — Placebo — Doctor Warmth.

Introduction

The importance of non-specific or non-drug factors for the outcome of drug treatment has been well established (Honigfeld, 1964; Lipman *et al.*, 1966; Rickels, 1968; Uhlenhuth *et al.*, 1959; Uhlenhuth *et al.*, 1969). This is particularly true when treating neurotic patients. As Hamilton

(1968) so succinctly stated "non-specific factors are important for *small treatments* and *small illnesses*". Confirmatory data have been presented by Cole and his co-workers (1968).

Several collaborative studies conducted by this group have been concerned with the importance of the "doctor variable" for drug treatment outcome, and more specifically with the doctor characteristic "drug enthusiasm".

In one of these studies (Uhlenhuth *et al.*, 1966), resident psychiatrists were trained to convey 2 different attitudes towards drug treatment in anxious psychoneurotic outpatients. This experimental manipulation of doctor attitudes was premised on the assumption that doctor medication enthusiasm represented an extremely important uncontrolled parameter which might differentially influence the therapeutic response of the patient, depending on whether the patient was receiving an active medication (i.e. meprobamate) or an inert placebo. One group of resident psychiatrists was trained to convey a therapeutic-enthusiastic approach toward the medication and another group was trained to convey an experimental-evaluative approach.

The study was carried out double-blind in 3 different outpatient clinics. The results may be summarized as follows. Therapeutic outcome was reliably influenced by both the medication and the kind of attitudes toward medication conveyed by the treating doctor, but differentially in the 3 participating clinics. In a further analysis of these data, Lipman *et al.* (1968) demonstrated that most significant interactions between medication, doctor attitudes, and clinics occurred in those areas of symptomatology not directly tied to the pharmacological action of meprobamate, whereas several "main drug effects" were found on anxiety and somatization. Despite extensive statistical exploration of our data, we were at a loss to fully explain the observed drug $\times$ set $\times$ clinic interaction. Conceptually, we felt that the "therapeutic-enthusiastic" role may have consisted of 2 loosely related characteristics, drug enthusiasm and therapeutic enthusiasm or warmth. Moreover, training a doctor to play a certain role may not produce the same end result as selecting physicians who have over the years established a certain fixed attitude in treating patients.

It seemed indicated, therefore, to re-examine the doctor characteristic "drug enthusiasm", this time, however, adding additional controls needed for a more exact interpretation of our data. Thus, in the present study, doctors were not trained, but selected according to their known (i.e. observed and expressed) attitudes toward drug treatment.

The specific aims of the present study may be presented as follows:

1. To assess over a 4 week treatment period, the relative efficacy of chlordiazepoxide, meprobamate and placebo in the treatment of anxious

psychoneurotic outpatients, when this treatment is conducted by experienced psychiatrists (main medication effects).

2. To determine whether patients who perceive their doctor as being more "enthusiastic" toward the prescribed medication, and patients who see their doctor as "warmer" show a reliably better therapeutic response than patients who perceive their doctor as less "enthusiastic" and less "warm". This may occur as a main doctor effect irrespective of type of medication, or as an interaction effect (conditioned by the particular medication taken by the patient).

The characteristic of "doctor warmth" is of particular interest to us, since drug attitudes and therapeutic warmth may, while showing some correspondence, still represent rather independent aspects of the doctor's treatment attitude which have only rarely been separated from each other.

Method

Design. This double-blind study was planned according to a $3 \times 2 \times 3$ factorial design with 3 medications (meprobamate, chlordiazepoxide, and placebo), 2 selected doctor types (tranquilizer enthusiastic [E] and tranquilizer skeptical or non-enthusiastic [NE]), and 3 participating clinics. Each patient was treated under the same condition for a period of 4 weeks and evaluated bi-weekly. The research procedures used were similar to those reported earlier by Uhlenhuth *et al.* (1966). Results were analyzed using a factorial covariance technique for the 2 and 4 week study periods.

Because we recognized that doctors may not be entirely consistent in the medication attitude they convey to each patient, and since our selection of doctors may not have been completely satisfactory, patient perception of doctor medication enthusiasm was measured after the initial treatment visit. Doctor warmth, found to be an important variable for psychotherapy by Truax and Carkhuff (1967), was also assessed by the patient after the initial interview. Both measures were based on a checklist developed by Dr. Mitchell Balter of the NIMH Psychopharmacology Research Branch. Three items of this checklist form the "doctor drug enthusiasm" cluster and 21 items the "doctor warmth" cluster. The items defining both clusters are given in Table 1.

The original selection for drug enthusiastic and drug non-enthusiastic (skeptical) doctors did not consistently agree with patient ratings of "doctor drug enthusiasm" or "doctor warmth" (Lipman *et al.*, 1970). Also, only moderate correlations existed in each clinic between "doctor drug enthusiasm" and "doctor warmth" as rated by the patient (JHH: $r = 0.66$, PGH: $r = 0.60$, and HUP: $r = 0.59$). We may thus conclude that doctor selection, patient rating of "warmth", and patient rating of

Table 1. *Patient's evaluation of doctor*
(PED)
Clinical Clusters

I.	*Doctor Warmth*—Friendly, careful, sure of himself, warm, patient, understands my problems, firm, experienced, encouraging, tender, pays close attention to details, optimistic, sincere, tells me how to help myself, easy to talk to, sympathetic, easy to understand, interested in me as a person, gives advice, likes me as a person, gives information.
II.	*Doctor Drug Enthusiasm*—Believes in medications, sure I will get better, confident that medicine will help me.
III.	*Buffer Items*—Unsympathetic, cold, unfriendly.

"drug enthusiasm" (at least at the initial visit) represent 3 fairly different ways of classifying our doctors.

Three separate sets of factorial covariance analyses were therefore performed. In the first set of analyses, each doctor was categorized as either drug enthusiastic or drug unenthusiastic. In the remaining 2 analyses the data of patients treated by the same doctor were not classified as a group but, rather, were redistributed over doctors depending on whether or not a patient rated his doctor as either above or below the clinic median on the dimension of "doctor drug enthusiasm" or "doctor warmth".

The results of the 3 analyses were in many ways quite similar, yet the original doctor selection variable (drug enthusiastic versus drug skeptical) had the least, and the patient perception of "doctor warmth" the greatest number of significant doctor attitude main and interaction effects. For this reason, and because "doctor warmth", based on 21 rather than 3 items, appeared to be more sensitively assessed than "doctor drug enthusiasm", we decided in this presentation to focus on the characteristic of "doctor warmth" as measured by the patient. All analyses of covariance to be reported in the present paper, therefore, have been conducted with patients in each clinic divided above and below the median on their scores for the "doctor warmth" variable.

Setting. The following 3 outpatient clinics employing an identical research protocol and procedures participated in the study: the Outpatient Department of the Henry Phipps Psychiatric Clinic of the Johns Hopkins Hospital (JHH), the Outpatient Psychiatric Clinic of the Philadelphia General Hospital (PGH), and the Outpatient Psychiatric Clinic of the Hospital of the University of Pennsylvania (HUP). They shared many features common to University affiliated community clinics in large cities, yet differed in a number of patient characteristics as discussed below.

Study Personnel. The research team at each clinic worked under the general supervision of a principal investigator in each city. At each clinic, the research team consisted of a research psychiatrist, an intake psychiatrist, experienced psychiatrists who served as study doctors, a social worker, a technician, and a secretary. Their functions are discussed in an earlier report (Uhlenhuth *et al.*, 1966).

Staff members of the Psychopharmacology Research Branch of NIMH made every effort to assure uniformity of procedure among the 3 clinics. They played key roles in planning the study, developed the manual of procedures, coded all medication, intermittently observed the procedures at the 3 clinics as the study progressed, and monitored the first interview transcripts as well as all other data collected.

Selection and Assignment of Study Patients. Psychiatric staff members of each clinic referred new patients to the study whom they saw during the course of their consultative work in the clinic or whose records were discussed during routine intake conferences. All study patients were then scheduled for an intake interview by the "study intake psychiatrist". It was the responsibility of this intake psychiatrist to see that all appropriate patients were sent to the research project. Patients were accepted for the study provided they were between the ages of 18 and 60, were new admissions to the clinic or at least had not visited the clinic for 6 months, and presented functional neurotic complaints including mainly overt evidence of manifest anxiety, with or without secondary depressive symptomatology. Patients on a stable program for a medical condition were also admitted, provided the regimen did not include a psychotropic or sedative drug.

Patients were excluded if they had visited the clinic within the past 6 months or had participated in one of our earlier collaborative studies (Lipman *et al.*, 1966; Uhlenhuth *et al.*, 1966); showed evidence of psychosis, organic brain syndrome, alcoholism, sociopathy, or severe depressive symptomatology; required ancillary therapy for their psychiatric condition; refused to stay off any non-study psychiatric medication either during the study or during the last 4 days prior to study onset (with the exception of occasional night time sedation); were unable to complete the necessary research forms; or would not keep their scheduled appointments.

All accepted patients were assigned at random within each clinic to 6 different treatment conditions (2 doctor attitudes and 3 drugs). Patients were assigned to successive code numbers according to a clinic master assignment sheet. They began treatment within one week of intake.

Dropping Patients from the Study. The research psychiatrist also determined when a patient had to be dropped from the study. Main

reasons were misdiagnosis, concomitant regular use of other psychiatric medication, dropping out of the study on the patient's own volition, refusal to take medication, and concurrent medical illnesses severe enough to necessitate study discontinuation.

Patients who deviated from prescribed dosage were continued in the study as long as they took some medication. However, they were identified as "deviators", if they took less than an average of 75% of medication daily during the 2 week interval between visits, or took less than 75% of medication on each of the 3 days prior to the next study visit.

Patient Population. A total of 485 patients entered the study. The present report deals with those 169 patients who completed the study according to protocol and who had all data needed for the present analyses. While 173 patients actually completed the study according to protocol, 4 of them had enough missing data to necessitate their exclusion from the analyses to be reported in this paper.

Another 115 patients also completed 4 weeks of treatment, but deviated from dosage according to the research protocol, and/or took additional psychotropic drugs. Dropouts accounted for 144 patients, or 30% of the total population, a percentage frequently found in controlled drug trials conducted with clinic outpatients. Finally, 53 patients were excluded from the study because of misdiagnosis, intercurrent medical illness, or refusal to take *any* medication. These latter patients probably should not have been assigned to the study in the first place.

Most dropout patients were interviewed by a social worker and these data as well as the data on dosage deviation were examined. Since we had previously found (Uhlenhuth *et al.*, 1965) that including patients who deviated from prescribed dosage in the analyses of outcome criteria together with patients completing the study as per protocol did slightly improve significance levels, we performed data analyses not only for completing patients alone, but also for completing and drug deviating patients combined. However, in the present study, the addition of deviating patients led to slightly fewer significant results, and we therefore decided to focus the present report only on data analyses conducted with the 169 patients who completed the study according to protocol.

Table 2 lists some of the more relevant patient characteristics at each clinic elicited at the time of intake or at the first study visit. The typical study patient may be described as a relatively young, married female of less than high school education and of low social class (IV and V) whose complaints, while not severe, were longer than 6 months' duration and who was heavily drug pretreated primarily, however, by non-psychiatrists.

Clinic differences were found primarily on those patient characteristics related to socio-economic class and race (e.g. education, marital status,

Table 2. *Patient characteristics*[a]

Characteristic	Clinic		
	JHH ($N = 64$)	PGH ($N = 63$)	HUP ($N = 42$)
Sex			
Male	21	19	18
Female	43	44	24
** Race			
White	44	11	24
Negro	20	52	18
Age (mean)	33	30	33
Marital Status			
Single	6	11	11
Married	45	32	24
Separated, divorced, widowed	13	20	7
** Education			
> High school	10	4	13
High school graduate	15	19	14
Part high school	14	16	9
Junior high school or less	24	24	6
** Social Class			
I—III	14	4	8
IV	23	18	20
V	27	41	12
Duration of present complaint			
< 6 months	25	23	13
6—12 months	15	8	7
> 1 year	24	32	22
* Took psychotropic drugs before			
Yes	59	55	30
No	5	8	12
Number of drugs taken past few years			
0—1	17	21	11
2	16	20	11
3 or more	26	14	8
Tranquilizers taken			
Yes	46	38	21
No	13	17	8
How long off drugs			
On drug now	25	20	18
<1 month	19	20	7
<1 year	11	8	4
>1 year	5	6	1
Patient's main treatment goal			
Resolve inner conflicts	19	9	13
Relief of psychic symptoms	27	44	23
Relief of physical symptoms	16	10	6
Help with reality problem, outside pressure, ambiguous	2	0	0

Table 2 (continued)

Characteristic	Clinic		
	JHH ($N = 64$)	PGH ($N = 63$)	HUP ($N = 42$)
** Treatment patient expects			
Psychotherapy	19	2	6
Guidance/advice	5	12	19
Medical treatment and drug therapy	24	47	13
Psychotherapy and drug therapy	16	2	4
** Treatment recommended			
Drug therapy	9	26	2
Psychotherapy	8	7	19
Both	47	29	20
Guidance/advice	0	1	1
** Attitude toward taking drug			
Very eager, somewhat eager	43	26	10
Neither	13	33	22
Somewhat reluctant, very reluctant	8	4	10
** Patient feels he will improve			
Not at all	3	7	6
A little bit	39	46	35
Quite a bit	22	9	1
Dr.'s feeling with patient			
Extremely comfortable	18	18	6
Moderately comfortable	38	43	34
Generally uncomfortable	8	2	2
* Dr. likes patient			
Much more than most, a little more than most	23	11	17
As much as most	31	41	23
A little less than most, much less than most	10	11	2

[a] N varies due to missing data. — * $p < 0.05$; ** $p < 0.01$.

treatment expectations, most suitable treatment, etc.). In regard to initial psychopathology (see Table 3), PGH patients tended to be the least sick on most psychopathology measures, somatization being an expected exception, as PGH patients were also of lowest social class and strongest medical orientation.

These clinic differences in patient characteristics are very much in agreement with those found in our 2 earlier collaborative studies (Lipman *et al.*, 1966; and Uhlenhuth *et al.*, 1966). As before, PGH patients were of lowest and HUP patients of highest social class.

Table 3. *Mean pre-study psychopathology scores for the 3 clinics at first treatment visit*

Characteristic	Clinic		
	JHH	PGH	HUP
Initial distress ratings by patient (SCL) (Range: 0 = none, 3 = extreme psychopathology)			
Factors:			
I (General neurotic feeling)	1.21	0.97	1.24
II (Somatization)	0.86	0.85	0.66
III (Performance difficulty)	1.04	0.94	0.91
IV (Depression)	1.15	0.91	0.89
V (Fear-anxiety)	1.28	1.15	1.22
Target Symptoms[a]	26.70	19.54	24.07
Initial distress ratings by doctor[b] (Range: 1 = none, 7 = extreme psychopathology)			
Overall Psychopathology	4.70	3.36	4.57
Degree of Anxiety	5.05	3.08	4.38
Degree of Depression	4.16	2.50	4.24

[a] $p < 0.05$ (analysis of variance).
[b] $p < 0.01$ (analysis of variance).

Study Doctors. At each of the 3 participating clinics, experienced psychiatrists, 2 drug enthusiastic [E] and 2 drug skeptical [NE] were selected to serve as study doctors. This selection was influenced by: a) the psychiatrist's reputation in the psychiatric community; b) a knowledge of the psychiatrist's training and practice; and c) a personal interview with the psychiatrist. While no attempt was made to inform the participating psychiatrists of the reason for their selection, these reasons nevertheless became obvious to all of them.

In general, all study doctors were told that we were interested in obtaining the participation of experienced psychiatrists with established attitudes toward treatment modalities, and that we wanted them to be as "natural" as possible in their relationships with clinic patients. They were not trained for the study and only a minimum of necessary contraints were placed upon their patient contact behavior.

The characteristics of the study doctors are described in Table 4. All psychiatrists were male, either board certified or board eligible, with several years of experience, primarily in private practice, and they differed as predicted on the MacAndrew-Rosen (1964) drug attitude scale. Study doctors were given relatively few instructions. They were encouraged to keep only brief notes during the interview, to complete the research forms after their interview with the patient, and in general not

Table 4. *Characteristics of study doctors for each clinic*

Clinic	JHH					PGH				HUP			
Dr. Drug Attitude	E			N–E		E		N–E		E		N–E	
Doctor	1	2	3	4	5	1	2	3	4	1	2	3	4
Age	43	47	37	34	41	39	41	36	31	54	40	42	39
Experience (in years)	15	9	10	6	12	15	17	8	5	8	16	18	10
MacAndrew scale[a]													
Attitude toward drug use	0.76	—	0.56	−0.52	0.30	0.63	0.69	0.58	0.36	0.84	0.52	0.11	0.40
Attitude toward psychotherapy	0.48	—	0.62	0.18	0.37	0.17	0.24	0.48	0.51	0.57	0.12	0.55	0.60
Patient evaluation of													
Doctor warmth—pre visit (mean)[b]	2.70	2.94	3.41	2.57	2.68	2.70	2.85	2.80	3.12	2.97	2.35	2.75	2.38
Doctor drug enthusiasm—pre visit (mean)[b]	2.94	3.04	3.56	2.72	2.65	2.73	2.58	2.65	3.04	3.10	2.50	2.56	2.44
Patients seen													
completers	17	8	3	19	19	21	13	22	8	17	4	19	3
Total	42	20	8	35	50	82	25	81	25	42	13	48	14

[a] Higher score, more favorable attitude.
[b] Higher score, more doctor warmth and drug enthusiasm.

to spend more than 30 minutes during the first visit and not more than 20 minutes during subsequent visits with their patients. The study doctor explained the presence of the tape recorder to his patients only if he felt the need to do so, and in such instances would usually introduce the tape recorder as an aid for following the treatment process.

All study doctors were asked to refrain from "dynamic interpretations", and to focus on the somatic and psychological symptoms which brought the patient to the treatment situation. The drug names were not mentioned to the patient, but on inquiry, a patient was assured that he was being treated with a mild tranquilizer and that the drug would be available for him as long as he needed it. Also, again only on inquiry, the doctor or technician explained the research forms as "clinic routines", allowing for periodic reassessment of treatment.

Medication. The medication consisted of identical pink, No. 2 capsules, containing either 200 mg of meprobamate, 5 mg of chlordiazepoxide, or inert placebo. The prescribed dosage was 2 capsules q.i.d. (1600 mg meprobamate or 40 mg chlordiazepoxide daily). Each patient was given only one medication for the entire treatment period.

At every treatment visit the doctor gave the patient 3 bottles (50 capsules per bottle) of medication, enough for an additional week in case the patient missed an appointment. He reminded the patient to take his medicine regularly and to return the bottles with the remaining medications at his next visit, at which time the doctor inquired into dosage deviation and the technician counted the remaining capsules and entered this count in the patient's research records.

After every interview, except the first one, the study doctor was asked to guess whether the patient had been taking meprobamate, chlordiazepoxide, or placebo. He also indicated how confident he felt about his guesses.

Clinical Criterion Measures[1]

1. Patient Symptom Checklist (SCL): This 64-item checklist, based on a scale developed earlier by Parloff *et al.* (1954) was completed at each visit by the patient prior to his interview with his therapist. Its 4 clinical clusters (Lipman *et al.*, 1968) and 5 factors (Williams *et al.*, 1968), were chosen as improvement criteria.

2. Patient Target Symptoms (TS): A group of "target symptoms" was identified at the first treatment visit. A symptom reported by the patient on his symptom checklist and independently by his doctor on a similar checklist that he filled out after his visit with the patient, was defined as a "target symptom". The patient's TS score at each visit was

1 For a fuller discussion of these measures, see Uhlenhuth *et al.* (1966).

obtained by summing his responses to the same group of symptoms, defined as target symptoms at the first visit.

3. Patient's Global Rating of Change: At 2 and 4 weeks, the patient recorded the overall change in his clinical status on a 7-point scale ranging from "very much worse" (7) to "very much better" (1).

4. Miscellaneous Information: The study doctor and technician independently inquired into dosage deviations and the doctor recorded any volunteered side effects which the patient attributed to medication and guessed what medication the patient was receiving.

Results

Completion Rate. In Table 5 the total study population is divided into patients completing the study according to protocol (completers) and used in all data analyses; patients completing the study period but deviating significantly from research procedures, particularly medication intake (deviators); patients dropping out on their own (dropouts); and patients who were dropped by the doctor because of misdiagnosis (misdiagnosis). As can be seen, at PGH, significantly more patients were in the "warm" meprobamate than in the "warm" chlordiazepoxide and placebo groups ($x^2 = 7.55$, df 2, $p < 0.05$). This occurred partly as a result of the median split on this score, and partly because of differential dropout rates.

Table 5 also indicates that: a) The lower socio-economic PGH patients deviated from protocol ($x^2 = 6.39$, df 2, $p < 0.05$) and dropped out ($x^2 = 4.84$, df 2, $p < 0.10$) more frequently than patients in the other 2 clinics; and b) Chlordiazepoxide patients tended to have the lowest dropout rate ($x^2 = 4.69$, df 2, $p < 0.10$). Differential dropping out of treatment as a function of population (clinic) as well as medication thus may have biased our clinical results, at least to some extent.

Side Effects. All side reactions reported voluntarily by the patient on each of the 3 medications are reported in Table 6. The number of patients reporting these side reactions are given in parentheses. Since the occurrence of side effects was not significantly influenced by either doctor characteristics or clinics, side effects are discussed only in terms of their relation to medication. At 2 and 4 weeks, more side reactions were reported with chlordiazepoxide and meprobamate than with placebo ($p < 0.10$ and $p < 0.20$ respectively) and, as was observed by us earlier (Rickels *et al.*, 1967), the incidence of side effects as well as the number of patients reporting side effects decreased from the 2 to 4 week evaluation period. The main side effect was drowsiness; it occurred slightly more frequently in patients on chlordiazepoxide than in patients on meprobamate.

External Events. At each visit, patients were asked whether any important positive or negative external events occurred in their lives

Table 5. *Patient status at end of study*[a]

Patient classification	JHH						PGH						HUP					
	Mep		Chlordiaz		Placebo		Mep		Chlordiaz		Placebo		Mep		Chlordiaz		Placebo	
	W	N–W	W	N–W	W	N–W	W	N–W	W	N–W	W	N–W	W	N–W	W	N–W	W	N–W
Completers[b]	8	10	13	9	11	13	16	6	8	15	7	11	5	8	7	9	8	5
Deviators	4	6	5	2	4	6	8	10	8	11	5	8	6	5	6	7	8	4
Dropouts	4	7	2	8	9	4	12	7	8	4	5	16	2	5	1	2	4	4
Number of patients	16	23	20	19	24	23	36	23	24	30	17	35	13	18	14	18	20	13
Misdiagnosis	6	2	1	4	2	0	1	5	3	4	6	5	1	4	1	1	2	3

[a] Total $N = 437$ because 44 patients are missing "Doctor Warmth" data.
[b] Excludes 4 patients not included in data analysis because of missing data.
W = Warm; N–W = Non-warm

Table 6. *Side effects on meprobamate, chlordiazepoxide and placebo*

Period	0—2 Weeks			2—4 Weeks		
Type of side effects	Meprobamate $N = 50$[a]	Chlordiazepoxide $N = 57$	Placebo $N = 51$	Meprobamate $N = 52$	Chlordiazepoxide $N = 61$	Placebo $N = 55$
Behavioral	16 (15)[b]	17 (15)	8 (6)	9 (8)	14 (13)	5 (5)
Central nervous system	4 (2)	2 (2)	1 (1)	0 (0)	3 (2)	0 (0)
Autonomic nervous system	5 (4)	5 (5)	3 (2)	2 (2)	5 (5)	3 (2)
Allergic	1 (1)	1 (1)	2 (1)	1 (1)	0 (0)	1 (1)
Total side effects	26 (16)	25 (20)	14 (8)	12 (10)	22 (15)	9 (6)

[a] N is reduced due to missing side effects data.
[b] Figures in parentheses give patient N.

during the past 2 week period. Data found at the 2 week evaluation period confirmed results previously reported by Lipman *et al.* (1965), namely, that chlordiazepoxide patients reported significantly more positive events than placebo patients ($x^2 = 12.64$, $p < 0.01$); and the same trend was seen comparing chlordiazepoxide with meprobamate patients ($x^2 = 4.78$, df 2, $p < 0.10$). These differences, however, were not found at the 4 week evaluation period.

Medication Guesses. It is worth noting that while "doctor warmth" had no effect on medication guesses, at 2 weeks doctors guessed both drugs, chlordiazepoxide as well as meprobamate, more often correctly than they did placebo ($x^2 = 6.07$, df 2, $p < 0.05$), while at 4 weeks this differential guessing became insignificant ($x^2 = 4.41$, df 2, $p < 0.20$).

Clinical Results. The main results of our 2 and 4 week analyses of covariance are summarized in Tables 7 and 8. Table 7 gives the post-treatment group means for all treatment cells adjusted for differences in initial distress level, and Table 8 gives the corresponding F ratios. For main clinic and clinic × warmth interaction effects, F ratios are not reported since none reached significance (the highest F ratios being 2.74 and 1.65 for clinic and clinic × warmth, respectively).

Reviewing Table 8, one is struck by the relative lack of significant findings, quite in contrast to our earlier collaborative study (Uhlenhuth *et al.*, 1966; Lipman *et al.*, 1968), in which several significant triple interactions between drug, doctor role, and clinic, as well as a number of significant main effects were observed. In the present study no significant triple interactions occurred at 2 weeks and only 2 at 4 weeks. Some trends

Table 7. *Adjusted means by treatment condition for patients completing study*

Period			2 Weeks			4 Weeks		
Medication			Mep	Chlor-diaz	Plac	Mep	Chlor-diaz	Plac
Rating[a]	Clinic	Role						
Anx.	JHH	W	0.87	0.86	0.63	0.81	0.87	0.78
		N−W	0.87	0.83	0.96	0.73	0.89	0.97
	PGH	W	0.96	0.44	0.90	0.95	0.50	0.64
		N−W	1.04	0.65	0.96	1.05	0.71	0.86
	HUP	W	0.88	0.71	0.82	0.87	0.81	0.71
		N−W	0.73	0.66	0.96	0.81	0.69	1.03
Depr.	JHH	W	0.81	1.01	0.61	0.50	1.01	0.61
		N−W	0.88	0.87	0.96	0.89	0.98	0.94
	PGH	W	0.90	0.72	0.62	0.84	0.82	0.52
		N−W	0.94	0.78	0.92	1.00	0.90	0.88
	HUP	W	0.99	0.88	1.00	0.88	0.95	0.79
		N−W	0.98	0.74	1.13	0.90	0.92	1.02
Ang.-Host.	JHH	W	0.52	0.98	0.47	0.42	0.88	0.60
		N−W	0.74	0.72	0.74	0.62	0.64	0.80
	PGH	W	0.84	0.46	0.73	0.70	0.50	0.45
		N−W	0.78	0.58	0.89	0.62	0.73	0.78
	HUP	W	0.57	0.46	0.67	0.66	0.67	0.45
		N−W	0.70	0.51	0.64	0.63	0.81	0.83
Obs.-Comp.	JHH	W	0.65	0.75	0.44	0.42	0.68	0.59
		N−W	0.56	0.63	0.67	0.53	0.68	0.70
	PGH	W	0.67	0.51	0.79	0.60	0.45	0.51
		N−W	0.69	0.63	0.70	0.62	0.57	0.73
	HUP	W	0.71	0.78	0.63	0.81	0.83	0.52
		N−W	0.56	0.89	1.08	0.50	0.80	1.07
Target Symptom	JHH	W	14.61	19.25	12.76	11.42	18.86	14.96
		N−W	18.81	16.34	18.90	15.83	16.62	19.09
	PGH	W	21.15	14.70	17.36	19.80	13.36	15.05
		N−W	20.19	15.48	21.04	19.55	15.19	20.00
	HUP	W	19.34	16.30	16.06	19.69	17.90	13.15
		N−W	16.91	14.35	21.54	17.04	16.34	21.25
Factor I General neurotic feeling	JHH	W	0.83	1.20	0.58	0.57	1.08	0.78
		N−W	0.96	0.96	1.05	0.94	0.96	1.02
	PGH	W	0.99	0.76	0.94	0.91	0.82	0.70
		N−W	1.02	0.90	1.11	1.06	1.03	1.12
	HUP	W	1.07	0.89	1.01	1.06	1.00	0.75
		N−W	0.95	0.79	1.15	0.87	1.05	1.36
Factor II Somatization	JHH	W	0.80	0.60	0.52	0.66	0.56	0.66
		N−W	0.75	0.81	0.70	0.59	0.74	0.76
	PGH	W	0.82	0.35	0.68	0.83	0.41	0.44
		N−W	0.85	0.56	0.68	0.90	0.54	0.62
	HUP	W	0.67	0.68	0.69	0.72	0.79	0.50
		N−W	0.53	0.59	0.62	0.50	0.55	0.58

Table 7 (continued)

Period			2 Weeks			4 Weeks		
Medication			Mep	Chlor-diaz	Plac	Mep	Chlor-diaz	Plac
Rating	Clinic	Role						
Factor III	JHH	W	0.73	0.82	0.56	0.56	0.79	0.67
Perfor-		N—W	0.81	0.95	1.02	0.72	1.15	0.91
mance	PGH	W	0.89	0.67	0.78	0.79	0.70	0.43
difficulty		N—W	1.01	0.83	0.96	1.01	0.93	0.87
	HUP	W	0.93	0.93	0.72	1.19	0.88	0.62
		N—W	0.76	0.98	1.13	0.66	1.10	1.32
Factor IV	JHH	W	0.74	0.96	0.70	0.46	1.16	0.55
Depression		N—W	0.81	0.86	0.82	0.84	0.96	0.92
	PGH	W	0.94	0.70	0.52	0.84	0.92	0.51
		N—W	0.83	0.69	0.86	0.91	0.89	0.74
	HUP	W	0.90	0.88	0.98	0.70	0.81	0.72
		N—W	1.06	0.79	1.18	1.00	0.87	0.89
Factor V	JHH	W	0.93	1.04	0.87	0.73	1.03	1.09
Fear-		N—W	0.95	0.88	1.06	0.85	1.01	1.08
anxiety	PGH	W	1.06	0.52	1.06	1.01	0.64	0.85
		N—W	1.02	0.80	1.10	1.03	0.87	0.96
	HUP	W	1.16	0.80	0.98	1.13	0.88	0.88
		N—W	0.92	0.81	1.36	0.97	0.85	1.39
Global	JHH	W	3.50	3.69	2.64	2.75	2.15	2.91
Improve-		N—W	3.20	2.67	3.46	3.10	3.22	3.23
ment	PGH	W	3.75	1.62	3.00	2.38	1.88	2.43
		N—W	3.50	2.73	3.64	2.83	3.33	2.54
	HUP	W	3.60	3.28	2.75	3.00	4.28	2.12
		N—W	3.62	2.44	4.00	3.25	2.78	4.40

[a] In all ratings, lower score means more improvement.

were seen for a "drug × warmth" interaction, and several significant "drug × clinic" interactions were found.

Of the 3 possible main effects, only doctor "warmth" and "drug" but not "clinic" significantly influenced improvement rate[2].

The main findings provided by these factorial analyses indicate significant "drug" effects at 2 weeks and significant "warmth" effects at 4 weeks. At 2 weeks, chlordiazepoxide patients were significantly more improved than either placebo or meprobamate patients. These

2 In the global rating of improvement performed by the doctor, significant main "drug", "clinic", and "drug × clinic" interaction effects were obtained at 2 weeks. At 4 weeks, however, only "warmth" effects were found in this rating, as well as in a physician global psychopathology rating and a physician measure of change in the 3 most important complaints for each patient.

Table 8
Results of covariance analysis by treatment condition for patients completing study

Treatment condition	Rating	Period			
		2 Weeks		4 Weeks	
		F	$p <$	F	$p <$
D×W×C	Anx.	0.60	—	0.32	—
	Depr.	0.18	—	0.30	—
	Ang.-Host.	1.17	—	1.09	—
	Obs.-Comp.	1.95	—	1.74	—
	TS	0.57	—	0.88	—
	Factor I	0.80	—	1.36	—
	Factor II	0.28	—	0.47	—
	Factor III	0.50	—	2.51	0.05
	Factor IV	0.26	—	0.40	—
	Factor V	0.71	—	0.81	—
	Global	1.34	—	4.33	0.01
D×W	Anx.	0.94	—	1.44	—
	Depr.	2.60	0.10	2.00	—
	Ang.-Host.	0.85	—	1.72	—
	Obs.-Comp.	2.20	—	2.64	0.10
	TS	2.63	0.10	2.60	0.10
	Factor I	2.25	—	2.30	—
	Factor II	0.89	—	0.85	—
	Factor III	2.42	0.10	3.55	0.05
	Factor IV	1.12	—	2.01	—
	Factor V	0.74	—	0.29	—
	Global	2.60	0.10	0.21	—
D×C	Anx.	2.41	0.10	2.55	0.05
	Depr.	1.59	—	1.44	—
	Ang.-Host.	3.47	0.025	0.95	—
	Obs.-Comp.	2.22	0.10	1.60	—
	TS	1.73	—	2.83	0.05
	Factor I	2.27	0.10	0.95	—
	Factor II	2.38	0.10	3.57	0.01
	Factor III	1.34	—	1.89	—
	Factor IV	1.19	—	1.43	—
	Factor V	1.15	—	1.54	—
	Global	1.55	—	0.59	—
Drug	Anx.	4.36	0.025	1.56	—
	Depr.	0.50	—	1.74	—
	Ang.-Host.	0.51	—	0.72	—
	Obs.-Comp.	0.60	—	1.32	—
	TS	1.74	—	0.36	—
	Factor I	0.06	—	0.78	—
	Factor II	3.08	0.05	2.02	—
	Factor III	0.00	—	1.89	—
	Factor IV	0.42	—	3.01	0.10
	Factor V	2.90	0.10	1.02	—
	Global	3.91	0.025	0.01	—

Table 8 (continued)

Treatment condition	Rating	Period			
		2 Weeks		4 Weeks	
		F	$p <$	F	$p <$
Warmth	Anx.	0.41	—	0.75	—
	Depr.	0.68	—	5.53	0.025
	Ang.-Host.	0.23	—	2.50	—
	Obs.-Comp.	0.54	—	1.87	—
	TS	0.40	—	1.20	—
	Factor I	0.57	—	6.33	0.025
	Factor II	0.15	—	0.00	—
	Factor III	5.95	0.025	12.05	0.001
	Factor IV	0.03	—	2.24	—
	Factor V	0.06	—	0.28	—
	Global	0.02	—	7.39	0.01

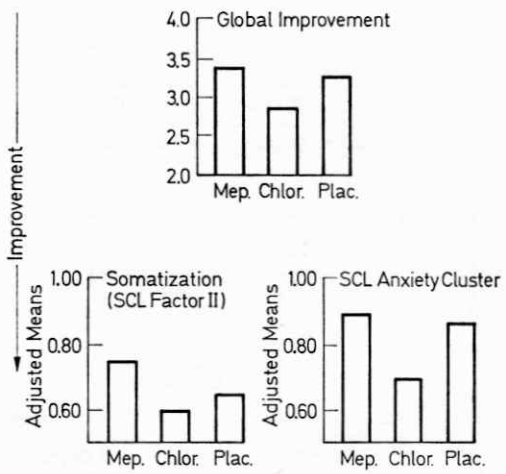

Fig. 1. 2 week drug effects for global improvement, the SCL somatization factor, and anxiety cluster

differences are graphed in Fig. 1 for the anxiety cluster, for the somatization factor, and for global improvement.

This difference in medication response partially disappeared, however, at the 4 week evaluation period, giving way to several drug × clinic interactions. As can be seen in Fig. 2, drug differences at this period are present only at PGH, with chlordiazepoxide producing most improvement. For the 3 clinics combined, only a marginally significant main drug effect in the depression factor (Factor IV) was observed at 4 weeks, with chlordiazepoxide producing the least and placebo the most improvement.

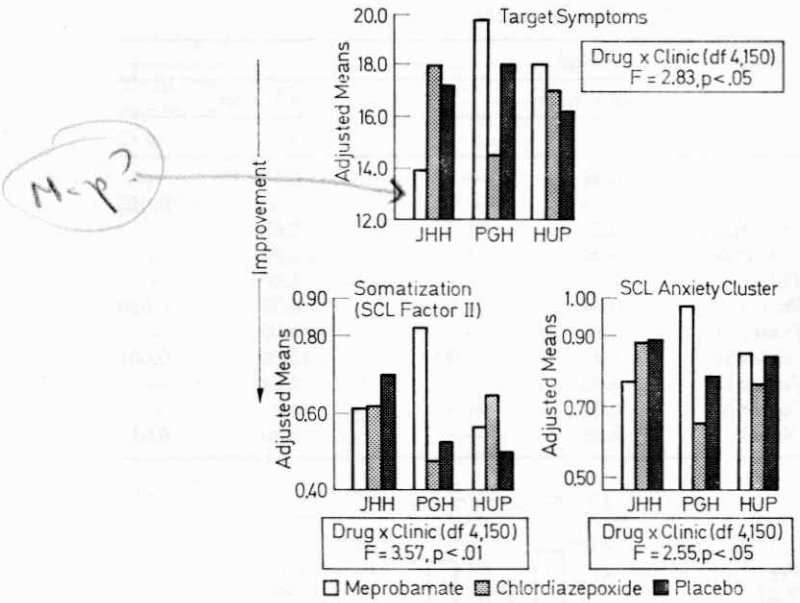

Fig. 2. Drug × cinic interactions (adjusted means) after 4 weeks of treatment

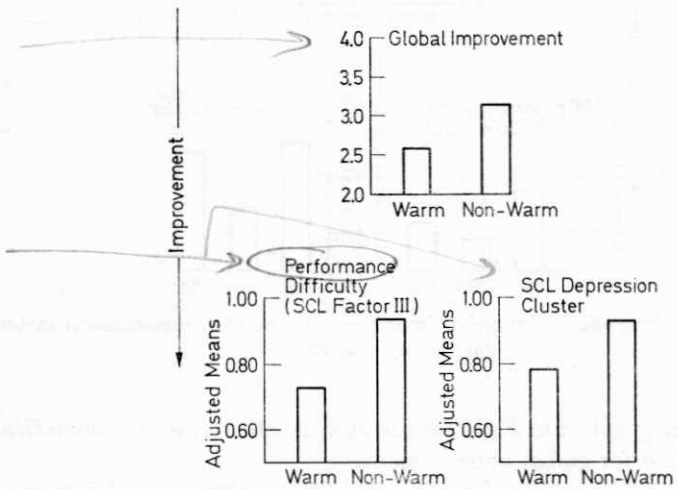

Fig. 3. 4 week warmth effects for global improvement, the SCL performance difficulty factor, and depression cluster

Doctor "warmth" effects occurred, with one exception, only after 4 weeks of treatment, with those patients improving most who initially described their doctor as "warm". This finding is illustrated for the

depression cluster, for the performance difficulty factor, and for global improvement in Fig. 3. Warmth exerted its most marked effect on the placebo response, and its least marked effect on the chlordiazepoxide response.

Regression analyses indicated that drug as well as warmth effects observed in this study were more marked in initially sicker patients. They also indicated that patients generally tended to improve more the sicker they were initially, with this effect being most pronounced in chlordiazepoxide and placebo patients. The same effect of initial distress level upon the response to chlordiazepoxide, meprobamate and placebo has been observed by McNair *et al.* (1965). Rickels and Clyde (1967) also confirmed this finding for chlordiazepoxide.

Further data analyses indicated that only the "warm" but not the "non-warm" placebo patients contributed to the initial level effect observed in placebo patients. Thus "doctor warmth" seemed to be a particularly important factor in the improvement of initially sicker placebo patients, while its effect on the response of both meprobamate and chlordiazepoxide patients varied as a function of the different outcome criteria used.

While the analysis of covariance model assumes homogeneity of regression, it has recently been shown by Peckham (1968) that non-homogeneity of regression slopes does not unduly bias the F-test of analysis of covariance. The present data, in which heterogeneity of slopes was obtained, were also checked using a repeated measure analysis of variance procedure. These analyses confirmed the major findings of the covariance analyses presented here.

Discussion

Both the present study and an earlier collaborative study conducted by the authors (Uhlenhuth *et al.*, 1966), serve to illustrate the complexities confronting the clinical researcher who attempts to study and define drug effects in neurotic outpatient populations.

The primary set of $3 \times 2 \times 3$ factorial analyses indicated several significant main "drug" effects at 2 weeks, several significant main "doctor warmth" effects at 4 weeks, and some significant interaction effects at both evaluation periods, but primarily at 4 weeks.

At 2 weeks patients on chlordiazepoxide improved more than patients on meprobamate or placebo on the anxiety cluster and somatization factor of the SCL and on the patient global improvement rating. This difference among medications partially disappeared during the second treatment period. These 2 week findings are in a broad sense similar to the findings reported by Lipman *et al.* (1968), who observed in an

earlier study conducted by this research group, that main drug effects, indicating significantly more improvement with meprobamate than with placebo, occurred primarily on those dimensions of psychopathology closest to the anticipated pharmacological action of the drug under study (i.e. anxiety and somatization).

The main "doctor warmth" effect occurred at 2 and 4 weeks in Factor III (performance difficulty), and also occurred at the 6 week period as a main treatment role (set) effect in the above mentioned study (Lipman *et al.*, 1968). "Doctor warmth" in the present study and "therapeutic role" in the earlier study produced the most improvement.

The several significant main "doctor warmth" effects at 4 weeks indicate a strong influence of the "doctor warmth" variable on improvement. This influence, however, was mainly on those symptomatology dimensions more distal to the anticipated pharmacological action of both drugs (i.e. depression, general neurotic feeling, performance difficulty).

The main drug effect seen at 2 weeks gave way to several drug × clinic interactions at 4 weeks, again on those symptomatology dimensions closest to the anticipated pharmacological action of the drugs (i.e. anxiety and somatization). The 3 significant drug × clinic interactions occurring at 4 weeks, graphically illustrated in Fig. 2, clearly indicate that the major contribution to these findings comes from PGH, where patients on chlordiazepoxide improved the most and patients on meprobamate the least. Differences in drug effects are certainly much smaller in the other 2 clinics.

Several marginal drug × clinic effects observed at 2 weeks give some indication that the main "drug" effect in favor of chlordiazepoxide observed at this period was contributed primarily by PGH patients.

The most surprising finding of this study is the lack of any main meprobamate effects. This finding is certainly contrary to the results observed in our first collaborative study (Uhlenhuth *et al.*, 1966; Lipman *et al.*, 1968), in which similar improvement criteria and research procedures were employed, and in which several significant meprobamate-placebo differences in favor of meprobamate occurred. Our present data are also contrary to earlier studies conducted by Rickels *et al.* (1959, 1964, 1969) with similar patients. Yet, McNair *et al.* (1965), for example, were also unable to demonstrate any superiority of meprobamate over placebo in anxious neurotic outpatients.

Even if one considers that meprobamate may be slower acting than chlordiazepoxide, which may partially explain our 2 week results, it is difficult to explain our inability to show any general drug effects, either for meprobamate or for chlordiazepoxide, at the 4 week evaluation period. Our inability to differentiate between placebo and chlordiazepoxide at 4 weeks is certainly contrary to most reports in the literature (cf. McNair

et al., 1965). Our 2 week chlordiazepoxide results are, however, in accord with earlier research conducted by this group (Lipman *et al.*, 1966).

It is possible that our treatment situation, in which experienced psychotherapists were observed and the improvement of their patients monitored, caused the therapist to provide additional psychotherapy to patients who were not improving, thus rendering the drug effect less marked. The finding that the variable "doctor warmth" tended to exert its strongest effect on the placebo response seems to lend further support to this contention.

Certainly other explanations for the lack of consistent main drug effects in this study should also be considered. Patient characteristics present in this study may differ from characteristics found in other studies, and indeed they do differ from those in the first collaborative meprobamate study, conducted in the same clinics and with similar research procedures, on several dimensions.

Compared to our first collaborative study, patients in the present study were more acutely ill ($x^2 = 16.43$, $p < 0.001$), yet, interestingly, more drug pretreated ($x^2 = 22.97$, $p < 0.001$). The implications of these differences in predictor variables should be considered. With regard to placebo response, it has been shown that acuteness of illness is related to positive placebo response and prior drug treatment is related to negative placebo response (Rickels *et al.*, 1966). Certainly, the combination of *more* acute illness and *more* drug pretreatment would seem to point to a more drug resistant population in the present study than the population available several years ago in our first collaborative study. Thus, our present poor drug results may well be partially explained by drug "resistance" or "tolerance" (Covi *et al.*, 1969), and possibly, a higher dosage would have produced better results within the present population.

Along these lines, it should be noted that meprobamate treated patients in our earlier collaborative trials showed more global improvement at 2 weeks (2.83 vs. 3.36) and at 4 weeks (2.45 vs. 2.81) than did meprobamate patients in our present study. By contrast, the placebo response was roughly equivalent at 2 and 4 weeks (3.06 vs. 3.22 and 2.76 vs. 2.87) in both studies.

One final reservation in interpreting our data should be considered. The data on which the present report is based come from a rather select group of neurotic patients, since only 169 of 485 patients who entered the study actually completed treatment according to protocol and were included in the present data analyses. In addition, deviating and dropout patients were most frequent at PGH, i.e. in the population which contributed most heavily to the present main "drug effects" at 2 weeks. As Table 5 indicates, "warm" and "non-warm" patients are rather unequally

distributed between the 3 medications at PGH. The results of the present study may, therefore, have been biased by these factors.

There are several lessons to be learned from this study. Drug treatment of neurotic symptoms is strongly influenced by non-drug factors; how else can we explain the observed clinic differences in outcome, and how else can we explain the discrepancies between our present and our earlier results? Results found with a particular neurotic clinic population, therefore, are not necessarily applicable to all other neurotic populations. The present study indicates, however, that of many non-drug factors, the doctor variable "warmth" appears to have an important influence on drug and placebo treatment outcome in anxious neurotic, psychiatric clinic outpatients.

Thus, in order to increase our understanding of many divergent results reported in clinical trials using similar populations and drugs, a more concerted effort must be directed toward the elucidation of non-drug factors which affect treatment outcome. Hopefully such efforts will provide us with meaningful and consistent predictors of therapeutic efficacy.

Appendix

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