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Paradoxical Influence of a Therapeutic Side-Effect Interpretation

RONALD S. LIPMAN, PhD; LEE C. PARK, MD; AND KARL RICKELS, MD, CHEVY CHASE, MD

THE CLINICAL literature is replete with references to the importance of nonpharmacological factors which may influence the response of patients to pharmacotherapy. An excellent review of these "nonspecific" factors is provided in two recent articles by Honigfeld.[1,2] In the main, however, there have been relatively few studies [3-7] which have experimentally manipulated nonpharmacological variables thought to affect therapeutic outcome.

Since a number of studies have suggested that the psychological "meaning" of side-effects to the patient may reliably influence his clinical course, the present research has focused on evaluating the impact of two different side-effect interpretations on the clinical response of anxious neurotic outpatients. In this connection investigations by Kast,[8,9] by Kast and Loesch,[10,11] and by Rickels et al,[12] are particularly relevant. In studies with patients characterized by an anxiety and gastrointestinal somatization,[11] hypertropic arthritis,[9] and functional digestive disorders without organic pathology;[10] Kast and Loesch used atropine sulfate (0.6 mg, t.i.d.) to produce dry mouth, which was either "positively" (a signal of therapeutic effectiveness) or "negatively" (a sign of dangerous toxicity) interpreted to the patient sample. In general the positive interpretation of dry mouth enhanced clinical improvement, whereas the negative interpretation produced a worsening of the clinical picture. In a related study with depressed patients [8] who were diagnosed as either primarily withdrawn and passive or primarily agitated, an interaction between dry mouth interpretation and depressive type was reported. Withdrawn patients improved most when atropine-induced dry mouth was positively interpreted, whereas agitated patients showed greatest improvement under the negative dry mouth interpretation. It should be noted, however, that improvement was rated only by the treating physician who was not blind to the medication.

Rickels et al [12] employed a double-blind crossover design to evaluate the relative efficacy of imipramine vs placebo and meprobamate and benactyzine (Deprol) vs placebo for the treatment of depression in medical clinic and psychiatric clinic outpatient samples. Results indicated that the more passive, more somatically-focused patients of the medical clinic did better on the combination of benactyzine and meprobamate than imipramine while an opposite pattern held for their psychiatric clinic patients. In retrospect these results appear related to the different side-effects of the active medica-

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From Outpatient Studies, Psychopharmacology Research Branch, National Institute of Mental Health, Chevy Chase, Md (Dr. Lipman); The Johns Hopkins University School of Medicine, Baltimore (Dr. Park); and School of Medicine University of Pennsylvania and Philadelphia General Hospital, Philadelphia (Dr. Rickels).

Reprint requests to Program Head, Outpatient Studies, Psychopharmacology Research Branch, National Institute of Mental Health, Barlow Bldg, Rm 10B01, Chevy Chase, Md 20015 (Dr. Lipman).

tions; drowsiness with the combination of benactyzine and meprobamate and dry mouth with imipramine.

These latter two studies, as well as many others (see Honigfeld [2 (p 17)] for a list of references), also have an important bearing on the question of the most appropriate model for evaluating drug effects. The most frequently assumed model [3, (p 150)] is the additive one which conceptualizes the drug effect (defined as the difference in improvement between drug- and placebo-treated patients) as remaining constant regardless of the particular patient sample or the particular setting in which medications are administered. Many normal and outpatient studies suggest, however, that the additive model is less appropriate than an interactive model which specifies that an "appropriate" treatment situation (eg, a warm doctor who is enthusiastic regarding the use of psychotropic medication and is treating a patient who "believes" in the competence of the physician and the efficacy of the prescribed medication) may increase the drug effect, whereas an "inappropriate" situation (eg, a detached physician who uses medication without confidence for patients whom he consciously or unconsciously rejects as unsuited for more appropriate treatment procedures such as psychotherapy) may "inactivate" an otherwise effective medication. Fisher et al [3 (p 150)] has most clearly depicted these alternative models.

The present study comprises a double-blind one-week evaluation of four medications —chlordiazepoxide hydrochloride (Librium), chlordiazepoxide hydrochloride + atropine, atropine, and placebo—in which one half the patients were treated by doctors who communicated a positive therapeutic attitude toward dry mouth whereas the remaining patients were treated by these same doctors who were also trained to convey a "neutral" attitude toward the occurrence of dry mouth.

The major hypothesis of the study was that the difference in therapeutic improvement between patients receiving atropine medications (chlordiazepoxide + atropine, atropine) and nonatropine (chlordiazepoxide hydrochloride, placebo) medications under the positive set would be reliably greater than the magnitude of the difference in therapeutic response between patients receiving atropine and nonatropine medications under the neutral set. This hypothesized outcome is shown in Fig 1.

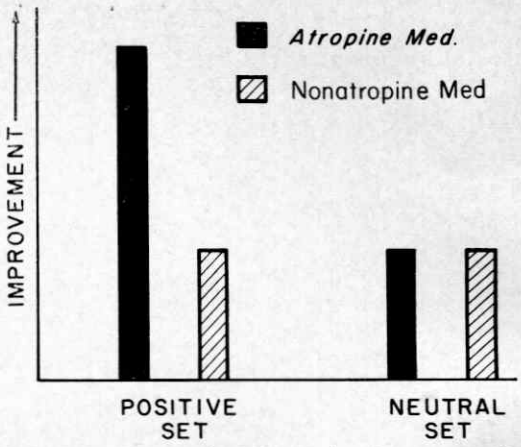

Fig 1.—Hypothesized interaction between medication and set.

Secondary hypotheses of the study were: (1) Psychotropic medications (chlordiazepoxide hydrochloride, chlordiazepoxide hydrochloride + atropine) will produce a reliably better therapeutic response than nonpsychotropic medications (atropine, placebo). (2) Patients receiving the positive set will evidence reliably more improvement than patients receiving the neutral set.

Three clinics participated in the study to increase the size of the patient sample. In a prior study conducted at these same three clinics,[13] it was found that the influence of medication (meprobamate vs placebo) and doctor medication role ("Enthusiastic" vs "Skeptical") influenced patient response differently as a function of the clinics. Thus, while we have not hypothesized that clinic differences would reliably influence the out-

TABLE 1.—*Design of the Study (Eight Patients per Cell)*

	Set		Set		Set	
Medication	Pos	Neut	Pos	Neut	Pos	Neut
Chlordiazepoxide, hydrochloride						
Chlordiazepoxide hydrochloride + atropine						
Atropine						
Placebo						
	JHH		PGH		HUP	

TABLE 2.—*Incidence of Patient Reported Dry Mouth by Atropine and Nonatropine Medication*

Medication	Report: Dry Mouth	Report: No Dry Mouth	Total	Dry Mouth %
A. Positive Set				
Atropine	44	8	52	84.6
Nonatropine	19	25	44	43.2
	63	33	96	
$\chi^2=16.35$; $P<0.001$.				
B. Neutral Set				
Atropine	33	17	50	66.8
Nonatropine	28	26	54	51.9
	61	43	104	
$\chi^2=1.60$; *NS*.				

TABLE 3.—*Distribution of Study Doctors' Medication Guesses for Atropine and Nonatropine Patients*

Medication	Dr. Guessed: Atropine	Dr. Guessed: atropine	Total	Dry Mouth %
A. Positive Set				
Atropine	30	20	50	60.0
Nonatropine	8	34	42	19.0
	38	54	92	
$\chi^2=14.14$; $P<0.001$.				
B. Neutral Set				
Atropine	15	33	48	31.3
Nonatropine	10	39	49	20.4
	25	72	97	
$\chi^2=1.66$; *NS*.				

come of the present study, we were aware of this possibility.

General Plan

The study was designed as a $2 \times 2 \times 2 \times 3$ factorial. The variables comprising the design were: (A) psychotropic (chlordiazepoxide hydrochloride, chlordiazepoxide hydrochloride + atropine) vs nonpsychotropic (atropine, placebo) medicine; (B) atropine (chlordiazepoxide hydrochloride + atropine, atropine) vs nonatropine (chlordiazepoxide hydrochloride, placebo) medication; (C) positive side-effect interpretation vs neutral side-effect interpretation; and (D) clinics. The original plan called for eight patients to complete the one-week treatment period according to protocol in each of 24 cells. Table 1 depicts this design. Dependent criterion measures as rated by the patient and by his treating doctor were to be analyzed by either analysis of covariance or analysis of variance, depending on whether initial distress level ratings or only change ratings were available.

Setting

The three outpatient psychiatric clinics that contributed patients were: the Outpatient Psychiatric Clinic of the Philadelphia General Hospital (PGH), the Outpatient Department of the Henry Phipps Psychiatric Clinic of The Johns Hopkins Hospital (JHH), and the Outpatient Psychiatric Clinic of the Hospital of the University of Pennsylvania (HUP). These clinics followed an identical protocol.

A more comprehensive description of these clinics has been presented elsewhere.[13] It should be noted that these clinics were known to differ with regard to the socioeconomic levels and racial backgrounds of their patients.

Study Personnel

Working under the general supervision of a psychiatrist who served as principal investigator, the research team at each clinic consisted of a research psychiatrist, intake psychiatrists, psychiatric residents who served as study doctors, a social worker, and secretary-technicians.

The research psychiatrist and principal investigator shared responsibility for the clinical welfare of the patient and for the day-to-day conduct of the study. Intake psychiatrists had major responsibility for referring patients to this study. The two study doctors at each clinic were responsible for conveying two different side-effect roles to their patients, for dispensing medication and checking on the medicine the patient took during the treatment week, and for making distress level and improvement ratings. Social workers had responsibility for contacting and conducting interviews with those patients who started treatment but failed to return for their second scheduled visit. The secretary-technicians scheduled patient visits, administered patient forms and checked them for completeness, kept all other study forms properly filed, and also checked these forms for their completeness.

Staff members of the Psychopharmacology Service Center played major roles in the planning and data analysis phases of the study. They developed a detailed protocol of procedure for data collection, helped train the study doctors to conduct uniform interviews in their different roles, observed the clinic operations from time to time, checked on the completeness of data collection, and coded medication for use by the clinics.

Selection and Assignment of Patients.—The major responsibility for screening patients to this study was assigned to a senior psychiatrist at each clinic. Preliminary referrals were made by the many psychiatric consultants at each clinic who were informed of the study selection criteria and encouraged to refer patients to the study intake psychiatrist by the clinic chief.

Patients were accepted for the study provided they satisfied the following criteria: (A) men between 18 and 45 years; (B) women between 18 and 55 years; and (C) new admissions to the

clinic with functional psychoneurotic complaints including overt evidence of manifest anxiety.

Patients were excluded when they: (A) showed evidence of overt psychotic symptomatology (schizophrenia, manic-depression), sociopathy, alcoholism, central nervous system impairment, or relatively pure neurotic depression; (B) required ancillary therapy for their psychiatric condition, a medical regimen which included a psychotropic or sedative drug such as phenobarbital for management of peptic ulcer or reserpine for control of hypertension; (C) evidenced a history of glaucoma, urinary retention due to prostatic hypertrophy (men not selected above age 45), had taken belladonna alkaloids or synthetic anticholinergics for long periods of time (these exclusion criteria represent routine precauations for atropine administration); (D) were unable to reliably complete the required study forms; (E) were not able to keep the scheduled treatment appointments; and (F) refused to stop taking psychotropic drugs for at least four days prior to their first treatment appointment with their study doctor.

Those patients accepted for the study were randomly assigned to treatment conditions. Patients were given consecutive code numbers in their order of acceptance for the study. This code number determined the medication, set, and doctor for each patient.

Training Study Doctors.—At each clinic two psychiatric residents were selected to serve as study doctors. Each resident conveyed both the positive and neutral role, thus controlling for doctor personality and general attitudinal variables which might otherwise have confounded the interpretation of role differences.

Study doctors were given descriptions of each role to study and were asked to commit certain key phrases to memory. They also listened to a tape illustrating a fictitious patient interview under the positive and neutral roles. They practiced conducting interviews of both types with each other and with staff members of the Psychopharmacology Service Center. When these "sample" interviews adhered to prototype, each doctor was assigned a "practice" patient. The research psychiatrist monitored these interviews very closely, observing the session through a one-way mirror and listening to the doctor-patient interaction (the interview rooms were wired so that sound was piped to the observation room). A checklist, which listed the critical aspects of both roles, was also employed by the research psychiatrist for these and all subsequent interviews.

Major deviations from the prescribed roles, such as a negative dry mouth statement in the positive role or linking dry mouth with improvement in the neutral role, would serve to invalidate the interview and the data from the patient would be deleted from the study. Actually, the "practice" interviews were judged to be acceptable, as were all subsequent "study" interviews.

TABLE 4.—*Patient Classification by Clinic*

Classification	JHH	PGH	HUP	Total
Accepted for treatment	80	79	61	220
1. Patients' data analyzed	71	77	56	204
A. Adhered to protocol	59	63	39	
B. Deviated from protocol	12	14	17	
1. Insufficient medication	8	7	6	
2. Other medication	1	1	1	
3. Insufficient + other medication	1	1	4	
4. No-shows	2	5	6	
2. Patients' data not used				16
A. Data lost in mail	1	—	—	
B. Misdiagnoses	4	1	3	
C. Miscellaneous	3	1	—	
D. No-shows (follow-up not possible)	1	—	2	

Major Experimental Variables

Medication.—The selection of 0.5 mg (t.i.d.) of atropine sulfate was based on the work of Kast and Loesch,[11] a personal communication with Dr. Adrian Ostfeld (1963) who has published only on his experience with higher dosages of atropine, and a pilot study in which staff members of the participating clinics and of the Psychopharmacology Service Center ingested atropine at this dosage for a three-week period. This background information provided assurance that 1.5 mg of atropine daily would produce a reliable experience of dry mouth in a very large percentage of our patient sample without producing other debilitating side effects. Further, Goodman and Gilman[14 (p 544)] indicate that this atropine dosage does not produce an accompanying psychotropic effect.

The combination of chlordiazepoxide hydrochloride with atropine was deemed compatible by our pharmacologists and by Dr. John Pepper, then the Assistant Medical Director of Hoffmann-LaRoche, Inc.

The four study medications were packaged in identical pink No. 5 capsules containing 10 mg of chlordiazepoxide hydrochloride, 10 mg of chlordiazepoxide hydrochloride plus 0.5 mg of atropine, 0.5 mg of atropine, or placebo. Patients were instructed to take one capsule three times a day for the treatment week and to return the medication bottles (which contained 30 capsules) with the unused medication at their next visit. Unused medication was counted by the technician. The study doctor independently inquired into dosage and other psychotropic medication the patient may have taken.

Medications were identified by code numbers (assigned at random) known only to personnel at the Psychopharmacology Service Center. In case of clinical emergencies (none occurred), the research psychiatrist had access to sealed envelopes which contained the medications corresponding to each code number.

Positive and Neutral Sets.—The positive and neutral roles conveyed by the study doctors, al-

TABLE 5.—*Patient Characteristics by Clinic at Intake*

Characteristics *	Clinic JHH	PGH	HUP	Characteristics *	Clinic JHH	PGH	HUP
Sample size †	71	75	56	Treatment recommended ¶			
Previous OPD admission ‡§				Drug therapy	10	16	8
0	44	53	30	Psychotherapy	24	4	25
1	19	21	17	Both	37	55	21
2+	8	1	9	Neither	0	0	1
Previous hospitalization				Missing data	0	0	1
Yes	5	11	9	Sex ‖			
No	66	64	47	Male	14	24	20
Duration of present complaints				Female	57	51	36
0-6 mo	37	17	11	Race ¶			
7-12 mo	14	13	8	White	51	21	29
12+ mo	20	45	37	Negro	18	54	22
Took psychotropic drugs before ¶				Age			
Yes	64	60	38	Range	19–55	16–53	18–58
No	7	15	18	Mean	31.4	31.9	34.0
No. of drugs taken during				Marital status ¶			
past year ¶				Single	10	22	13
0 and 1	9	29	21	Married	45	29	32
2	18	23	12	Separated, divorced, widowed	16	24	11
3+	36	7	6	Head of household ‖			
Missing data	1	1	0	Yes	23	40	28
How long off drugs ¶				No	48	35	28
On drug now	35	24	11				
Off drug from 0-6 mo	26	28	24	Education ¶			
More than 6 mo	2	8	4	0-7 yr	2	6	0
Never on drug	7	15	17	7-9 yr	18	23	8
Missing data	1	0	0	10-11 yr	31	25	18
Patient's main treatment goal ¶				High-school graduate or beyond	20	21	30
Resolve inner conflicts	21	10	19	Social class ¶			
Relief of psychic symptoms	33	33	27	V	30	47	13
Relief of somatic symptoms	11	30	7	IV	31	20	24
Help with reality problem	3	0	1	III, II, I	5	7	18
Treatment by outside pressure	3	1	0	Missing data	5	1	1
Ambiguous	0	1	2	Degree of pathology ¶			
Treatment patient expected ¶				1 (no pathology)	2	4	3
Psychotherapy	25	7	18	2	20	13	17
Guidance or advice	15	5	20	3	30	16	15
Medication	30	60	10	4	16	25	11
None	1	1	1	5-8 (8 = extreme pathology)	3	16	10
Combinations	0	2	0	Missing data	0	1	0
Missing data	0	0	7				

* To conserve space, the following variables which did not reveal clinic differences have been omitted from Table 5: Type of drugs previously taken, family size, patient's ordinal sibling position, patient compliance with drug wash-out period, number of neurotic behaviors shown at first treatment visit, treating doctor's feeling of comfort and liking of patient, mean intensity of initial symptom distress, number of somatic TS and mean intensity of psychic symptoms; additionally, categories have been pooled for presentation purposes.

† Two patients had missing background data.

‡ χ^2 was employed to test clinic differences.

§ $P<0.10$.

‖ $P<0.05$.

¶ $P<0.01$.

though differing with regard to the degree of side-effect preparation and the side-effect interpretation, shared many features. At the initial treatment visit all doctors elicited the symptoms that were distressing the patient and delved into the history of the patients' complaints. These symptoms were then summarized and inquiry was made into the past use of medication by the patient. Medication was then prescribed in the same manner for all patients: "I have some medicine that I want you to take for your condition." All patients were told how to take the medication (three times a day before meals), cautioned not to miss dosages, and cautioned not to take any other medicine for their "nerves." The importance of keeping their next scheduled appointment was also stressed.

The crucial difference between the roles was introduced at this point in the interview. With those patients assigned to the positive set, the doctor handled the possibility of dry mouth as follows: "You may get a dry mouth from the medicine. If you do get the dry mouth, it will be very noticeable and the dry mouth will persist. *The dry mouth is a good sign!* It shows that the medicine is working effectively. Do you have any question about the dry mouth?"

When seeing a patient in his positive role, the doctor was trained to stress the correlation be-

tween dry mouth and clinical improvement whenever the opportunity presented itself in the subsequent course of the interview. For example, if the patient inquired whether the doctor felt the medication would help, the doctor would indicate that he could look for dry mouth and improvement going hand-in-hand. At any rate, the doctor would always again stress the contingency between noticeable dry mouth and improvement in a review period before the end of the interview.

In playing the neutral role, the doctor would only once and casually indicate to the patient: "This medicine may make your mouth dry but this is nothing to be worried about."

Doctors were instructed to avoid engaging in psychotherapy with their patients and all interviews were limited to a maximum of 30 minutes.

The second interview was identical for both roles and consisted of the study doctors evaluating the current symptom status of the patient and inquiring into medication taken during the prior week.

A number of procedures were employed to check the role performance of the doctor and the patient's perception of the side-effect communication.

From an "objective" viewpoint it was clear that the study doctors correctly communicated the positive and neutral roles to their patients. This was carefully checked for each interview by the research psychiatrist. Since it was considered of crucial importance that the patient "subjectively" register the set correctly, at the end of the second patient visit, within the context of a disposition interview, a psychiatrist interviewed the patient with regard to what the treating doctor had told him about the medicine, about side effects of the medicine, and finally about dry mouth if the patient had not already mentioned dry mouth in response to the initial more open-ended questions. The patient's perception of the meaning of dry mouth was also probed. On the basis of these data it was determined that 78.4% and 89.5% of patients correctly perceived the positive and neutral roles, respectively. That is, they indicated that the doctor mentioned dry mouth and, further, that dry mouth was linked with therapeutic efficacy (positive set) or, alternatively, was nothing to worry about (neutral set).

Patient Experience of Dry Mouth.—In addition to correctly perceiving the meaning of dry mouth, it was also crucial, particularly in the positive set, that dry mouth be differentially experienced by patients receiving the atropine medications as contrasted with patients receiving the nonatropine medications.

To check on the differential occurrence of dry mouth as a function of medication, the disposition interview also focused on this area. Data for the positive and neutral sets are presented in Table 2. Patients exposed to the positive set who received the atropine medications more reliably experienced dry mouth (84.6%) than patients not

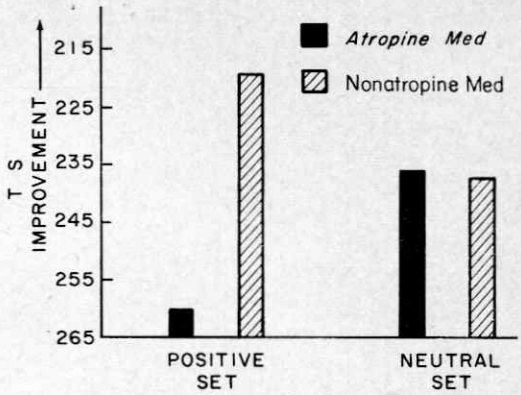

Fig 2.—Observed interaction between medication and set.

TABLE 6.—*Patient Characteristics by Clinic at First Treatment Visit*

Characteristic	Clinic JHH	PGH	HUP
Attitude toward drug *†			
Very eager	0	1	0
Somewhat eager	14	5	16
Neutral	42	55	27
Somewhat reluctant	14	13	11
Very reluctant	1	1	2
Doctor's role performance			
Excellent	27	22	8
Moderately well	42	53	48
Poorly and very poorly	2	0	0
Patient's degree of pathology			
1 (no pathology)	0	0	1
2	4	1	14
3	10	21	20
4	19	26	11
5-8 (8 = extreme pathology)	37	27	10
Missing data	1	0	0
Median	5	4	3
No. psychic TS			
Range	0-15	0-17	0-21
Mean	6.48	6.05	8.55
Mean intensity—somatic symptoms			
Range	1.19-3.32	1.03-3.58	1.19-3.10
Mean	1.96	1.98	1.81

* χ^2 was employed to test clinic differences.
† $P<0.05$.
‡ $P<0.01$.
§ $P<0.10$.

TABLE 7.—*Effects Derived From the 2 × 2 × 2 × 3 Variance Analyses*

1. Psychotropic × atropine × set × clinic
2. Psychotropic × atropine × clinic
3. Psychotropic × atropine × set
4. Psychotropic × set × clinic
5. Atropine × set × clinic
6. Psychotropic × atropine
7. Psychotropic × clinic
8. Psychotropic × set
9. Atropine × clinic
10. Atropine × set
11. Set × clinic
12. Psychotropic
13. Atropine
14. Set
15. Clinic

TABLE 8.—*Results of Variance and/or Covariance Analyses*

		Patient Ratings					Dr Ratings		
		SCL	TS	Anx	Dep	Glo	TS	Anx	Glo
Psychotropine & atropine × DM	F							2.89	
	P							<0.10	
Psychotropine × set × clinic	F	2.97	4.89	3.39	4.53	2.47	6.99		
	P	<0.10	<0.01	<0.05	<0.025	<0.10	<0.001		
Atropine × set	F	4.82	8.36	3.46	3.15	3.95	2.96		4.33
	P	<0.05	<0.005	<0.10	<0.10	<0.05	<0.10		<0.05
Atropine × clinic	F		4.09						
	P		<0.025						
Psychotropine	F		3.83			14.18			4.97
	P		=0.05			<0.001			<0.05
Atropine	F	3.39	7.45						
	P	<0.10	<0.01						

TABLE 9.—*Adjusted Means for the Psychotropic vs Nonpsychotropic Effect*

Criterion	Chlordiazepoxide Hydrochloride	Non-Chlordiazepoxide Hydrochloride
TS	2.31	2.44
Glo	2.92	3.64
Glo (Dr.)	3.03	3.38

receiving atropine medications (43.2%). Under the neutral set the incidence of dry mouth did not differ as a function of medication.

Study doctors also guessed whether or not the patient was receiving atropine at the end of the second treatment visit. Although they were specifically instructed not to probe this area with their patients, data presented in Table 3 indicate that reliably more dry mouth was mentioned in the atropine than nonatropine groups under the positive set ($\chi^2 = 14.15$, $P<0.001$). The relatively lower percentage of dry mouth indexed by this technique (compare Tables 2 and 3) reflects the more spontaneous nature of patient reports.

Finally, dry mouth was included as an item in the symptom checklist (SCL) which was independently checked by the patient and by his treating physician. Analysis of covariance on this item yielded an F of 23.83 ($P<0.001$) and an F of 15.93 ($P<0.001$) for patient and doctor ratings associated with the comparison of atropine and nonatropine groups, with adjusted means in the expected direction.

Major Dependent Variables.—*Patient.*—The following five patient criterion measures were collected: (1) SCL;* (2) target symptoms (TS); (3) anxiety (Anx); (4) depression (Dep); and (5) global improvement (Glo). These measures are described more fully elsewhere.[13]

Doctor.—Three doctor measures were analyzed: TS, Anx, and Glo.[13]

Results

Of those patients accepted for this study at intake, 220 kept their first treatment appointment. Of this group, 161 patients completed the treatment week with "adherence" to protocol, whereas 43 deviated from protocol by either taking (A) less than 16 capsules of the prescribed medicine, (B) other psychotropic medicine, (C) a combination of (A) and (B) above, or (D) not keeping their second treatment visit so that a social worker follow-up was necessary. Table 4 provides a complete specification of the patient classification by clinic.

In another study[15] it was found that including the data of patients who took less than the prescribed amount of medication actually increased the reliability of drug-placebo comparisons so that the data of the 43 "nonadhering" patients, after an examination by χ^2 for psychotropic vs nonpsychotropic improvement differences, were also included in the final data analysis of the present study.

* Prior to the start of the study, the items of the SCL were categorized into those that might reflect atropine improvement (eg, pains in the stomach, throwing up, etc), atropine side-effects (eg, dry mouth, stuffy nose, etc), and nonatropine related. Criterion data are reported from the nonatropine related items.

TABLE 10.—*Adjusted Means for the Psychotropic × Set × Clinic Interaction*

	HOP				PGH				UPA			
	Pos		Neut		Pos		Neut		Pos		Neut	
Criterion	A *	B †	A *	B †	A *	B †	A *	B †	A *	B †	A *	B †
SCL	1.96	1.89	1.88	2.00	2.00	1.89	1.93	1.98	1.90	2.07	1.93	1.75
TS	2.43	2.34	2.23	2.50	2.36	2.37	2.24	2.52	2.24	2.75	2.33	2.15
Anx	0.21	0.45	0.39	0.46	0.32	0.27	0.10	0.45	0.02	0.61	0.30	−0.36
Dep	0.07	0.29	−0.07	0.34	0.13	0.29	0.07	0.48	−0.21	0.52	0.14	−0.67
Glo	2.94	3.47	3.22	4.05	2.69	3.35	2.82	3.28	2.77	4.60	3.08	3.13
TS (Dr.)	2.31	2.02	2.03	2.55	2.16	2.07	1.85	2.14	1.93	2.50	2.19	1.78

* Indicates chlordiazepoxide hydrochloride.
† Indicates nonchlordiazepoxide hydrochloride.

Tables 5 and 6 summarize some characteristics of those patients that were employed in the final data analyses. The main effects and interactions yielded by the 2 × 2 × 2 × 3 analyses of variance or covariance are presented in Table 7. In order to simplify the reader's task, only those effects which proved reliable are shown in Table 8.

An examination of Table 8 reveals the presence of two reliable main effects and two reliable interactions. The main effects are psychotropic vs nonpsychotropic and atropine vs nonatropine. The interaction effects are atropine × set and psychotropic —nonpsychotropic × clinic × set.

Adjusted means for these main effects and interactions on those criterion measures which yielded significant P values are presented in Tables 9-12. An inspection of Table 9 reveals that patients receiving the chlordiazepoxide hydrochloride medications generally showed more improvement than patients receiving the nonchlordiazepoxide hydrochloride medications.

In addition to the above criterion data, the following previously reported data [16,17] also supported the efficacy of chlordiazepoxide hydrochloride.

1. At the end of the second treatment visit, the patient evaluated his treatment doctor (PED) on a 24-item checklist containing such adjectives as warm, friendly, interested in me as a person, sure of himself, etc.† A 4-point scale ranging from "not at all" to "extremely" was employed and a total mean "doctor likability" score was obtained ($F = 6.54$, $P<0.025$).

2. During the disposition interview in which future treatment plans were formulated with the patient, they were asked whether or not they wanted to continue taking the prescribed medication ($F = 8.94$, $P<0.005$).

3. During the course of the disposition interview patients were asked to indicate the degree of help they had received from the medicine. A 4-point scale was employed ($F = 6.32$, $P<0.025$).

4. At one of the clinics the treating doctors elicited "significant" or "important" life situation events which may have occurred during the treatment week. Classification was made into three categories: "positive," "negative," or "no change" ($\chi^2 = 6.94$, $P<0.05$).

† The PED developed by Dr. Balter of the Biological and Psychopharmacology Research Branch.

TABLE 11.—*Adjusted Means for the Atropine vs Nonatropine Effect*

Criterion	Atropine	Nonatropine
SCL	1.98	1.89
TS	2.47	2.27

TABLE 12.—*Adjusted Means for the Atropine × Set Interaction*

	Positive		Neutral	
Criterion	Atropine	Nonatropine	Atropine	Nonatropine
SCL	2.04	1.84	1.91	1.92
TS	2.60	2.19	2.34	2.33
Anx	0.50	0.10	0.22	0.24
Dep	0.33	0.03	0.01	0.15
Glo	3.51	3.05	3.16	3.38
TS (Dr.)	2.22	2.12	2.04	2.29
Glo (Dr.)	3.40	3.05	3.06	3.33

Although no reliable clinic interactions were found on these measures, a consistent psychotropic vs nonpsychotropic × set × clinic interaction did obtain on most other criterion measures (Tables 8 and 10). This interaction indicates that the relative superiority of the chlordiazepoxide hydrochloride medications varied reliably as a function of the particular doctor-role the patient was exposed to at the different clinics (Table 10). In this connection, the pattern of improvement at Hopkins and Philadelphia General Hospital tended to be fairly similar with

TABLE 13.—*Adjusted Means by Cell for the Various Patient and Dr. Criterion Measures (The N per Cell Is Given in the Parentheses)*

Patient Measures

SCL

	JHH		PGH		HUP	
	Pos	Neut	Pos	Neut	Pos	Neut
Chlordiazepoxide hydrochloride + atropine	2.09 (10)	1.93 (11)	2.05 (9)	2.04 (9)	1.99 (7)	1.87 (6)
Chlordiazepoxide hydrochloride	1.80 (8)	1.81 (7)	1.93 (7)	1.85 (13)	1.80 (6)	1.98 (7)
Atropine	1.86 (7)	1.92 (10)	2.03 (12)	2.07 (8)	2.17 (8)	1.57 (7)
Placebo	1.92 (8)	2.09 (10)	1.67 (8)	1.91 (10)	1.96 (7)	1.91 (8)

TS

	JHH		PGH		HUP	
	Pos	Neut	Pos	Neut	Pos	Neut
Chlordiazepoxide hydrochloride + atropine	2.59 (10)	2.26 (11)	2.57 (9)	2.37 (9)	2.35 (7)	2.29 (6)
Chlordiazepoxide hydrochloride	2.23 (8)	2.19 (7)	2.08 (7)	2.15 (12)	2.11 (6)	2.37 (7)
Atropine	2.32 (7)	2.44 (10)	2.72 (12)	2.68 (8)	2.90 (8)	1.93 (7)
Placebo	2.35 (8)	2.56 (10)	1.84 (8)	2.40 (10)	2.57 (7)	2.34 (8)

Anx

	JHH		PGH		HUP	
	Pos	Neut	Pos	Neut	Pos	Neut
Chlordiazepoxide hydrochloride + atropine	0.33 (10)	0.34 (11)	0.58 (9)	0.23 (9)	0.21 (7)	0.17 (6)
Chlordiazepoxide hydrochloride	0.06 (8)	0.46 (7)	−0.01 (7)	−0.03 (13)	−0.20 (6)	0.41 (7)
Atropine	0.36 (7)	0.40 (10)	0.56 (11)	0.56 (8)	0.90 (8)	−0.60 (7)
Placebo	0.53 (8)	0.51 (10)	−0.12 (8)	0.36 (10)	0.27 (7)	−0.14 (8)

Dep

	JHH		PGH		HUP	
	Pos	Neut	Pos	Neut	Pos	Neut
Chlordiazepoxide hydrochloride + atropine	0.33 (10)	−0.09 (11)	0.22 (9)	0.34 (9)	−0.18 (7)	−0.13 (6)
Chlordiazepoxide hydrochloride	−0.26 (8)	−0.05 (7)	0.01 (7)	−0.11 (13)	−0.24 (6)	0.37 (7)
Atropine	0.22 (7)	0.27 (10)	0.41 (11)	0.46 (8)	0.86 (8)	−1.16 (7)
Placebo	0.35 (8)	0.41 (10)	0.13 (8)	0.50 (10)	0.13 (7)	−0.24 (8)

Glo

	JHH		PGH		HUP	
	Pos	Neut	Pos	Neut	Pos	Neut
Chlordiazepoxide hydrochloride + atropine	2.90 (10)	3.36 (11)	3.00 (9)	2.78 (9)	3.29 (7)	2.83 (6)
Chlordiazepoxide hydrochloride	3.00 (8)	3.00 (7)	2.29 (7)	2.85 (13)	2.17 (6)	3.29 (7)
Atropine	3.43 (7)	3.80 (10)	3.58 (12)	3.13 (8)	5.00 (8)	2.71 (7)
Placebo	3.50 (8)	4.30 (10)	3.00 (8)	3.40 (10)	4.14 (7)	3.50 (8)

TABLE 13.—*Adjusted Means by Cell for the Various Patient and Dr. Criterion Measures (The N per Cell Is Given in the Parentheses)*—Continued

Dr. Measures

TS

	JHH		PGH		HUP	
	Pos	Neut	Pos	Neut	Pos	Neut
Chlordiazepoxide hydrochloride + atropine	2.32 (10)	2.00 (10)	2.04 (9)	1.87 (8)	2.05 (5)	2.09 (5)
Chlordiazepoxide hydroehloride	2.29 (8)	2.08 (7)	2.31 (7)	1.84 (10)	1.81 (5)	2.28 (6)
Atropine	2.12 (7)	2.51 (10)	2.22 (12)	2.32 (9)	2.55 (7)	1.19 (7)
Placebo	1.93 (8)	2.59 (9)	1.82 (7)	2.31 (8)	2.45 (7)	2.29 (8)

Anx

	JHH		PGH		HUP	
	Pos	Neut	Pos	Neut	Pos	Neut
Chlordiazepoxide hydrochloride + atropine	0.82 (10)	0.62 (10)	0.18 (9)	−0.12 (8)	0.31 (5)	−0.22 (5)
Chlordiazepoxide hydrochloride	0.17 (8)	0.84 (7)	−0.16 (7)	0.10 (11)	−0.38 (5)	0.19 (6)
Atropine	0.18 (7)	0.59 (10)	0.27 (12)	0.39 (9)	0.54 (7)	−0.54 (7)
Placebo	0.16 (8)	0.33 (9)	−0.19 (7)	0.18 (8)	1.04 (7)	−0.01 (8)

Dep

	JHH		PGH		HUP	
	Pos	Neut	Pos	Neut	Pos	Neut
Chlordiazepoxide hydrochloride + atropine	−0.01 (10)	0.07 (10)	0.44 (9)	0.31 (8)	0.31 (5)	0.07 (5)
Chlordiazepoxide hydrochloride	0.53 (8)	0.42 (7)	−0.37 (7)	0.31 (11)	−0.89 (5)	0.08 (6)
Atropine	0.14 (7)	0.52 (10)	0.36 (12)	0.38 (9)	0.40 (7)	−0.47 (7)
Placebo	−0.27 (8)	0.14 (9)	0.15 (7)	0.44 (8)	0.70 (7)	0.02 (8)

Glo

	JHH		PGH		HUP	
	Pos	Neut	Pos	Neut	Pos	Neut
Chlordiazepoxide hydrochloride + atropine	3.30 (10)	2.90 (10)	3.44 (9)	2.75 (8)	3.20 (5)	2.40 (5)
Chlordiazepoxide hydrochloride	3.25 (8)	3.14 (7)	2.71 (7)	3.00 (11)	2.40 (5)	3.50 (6)
Atropine	3.29 (7)	3.60 (10)	3.25 (12)	3.22 (9)	4.00 (7)	3.14 (7)
Placebo	3.25 (8)	3.56 (9)	3.00 (7)	3.50 (8)	3.43 (7)	3.38 (8)

Librium and nonchlordiazepoxide hydrochloride-treated patients showing roughly comparable improvement under the positive set, while the chlordiazepoxide hydrochloride-treated patients showed more improvement than the nonchlordiazepoxide hydrochloride-treated patients under the neutral set. At the University of Pennsylvania, by contrast, chlordiazepoxide hydrochloride medications produced a better response in the positive set but a poorer response in the neutral set than the chlordiazepoxide hydrochloride medications.

Contrary to expectations, the atropine medications generally produced less therapeutic improvement than the nonatropine medications (Table 11), with this therapeutic disadvantage being particularly marked under the positive as compared with the neutral set (Table 12). This atropine

× set interaction is both highly reliable and consistent with the pattern of adjusted means, being strikingly uniform across the different criterion measures. Figure 2 shows this interaction. We have here as clear-cut an invalidation of the major hypothesis of this study (compare Fig 1 with Fig 2 in terms of the direction of the interaction) as one could "hope for."

The adjusted means and patient *N* per cell for all criterion measures are given in Table 13.

Comment

The present finding of a general therapeutic superiority of the chlordiazepoxide hydrochloride vs nonchlordiazepoxide hydrochloride medications agrees with the Veterans Administration findings of chlordiazepoxide's effectiveness over a one-week period.[18,19]

The PED and life-situation events data reflect a more positive "person" perception on the part of chlordiazepoxide hydrochloride-treated patients. Taken together, these data provide support for the hypothesis that chlordiazepoxide not only influences symptomatic improvement, but also influences the "perceptual-processing" components of neurosis.

It will be recalled that a reliable psychotropic × set × clinic interaction was present on most criterion measures. In this connection the improvement pattern at the University of Pennsylvania was distinctly different than at the other two clinics (Table 10). In a prior study conducted at these same clinics the pattern of response to meprobamate and placebo as a function of doctor medication role ("Enthusiastic" vs "Skeptical") was also reliably influenced by the clinic setting.[13] In that study, however, Philadelphia General Hospital was the most "different" clinic.

While it is clear that the participating clinics differed along many dimensions (Tables 5 and 6), it is most difficult to understand how these clinic differences might account for the psychotropic × set × clinic interaction. While any combination of patient (race, social class, treatment expectations, etc), doctor (personality, therapeutic orientation, etc), and general clinic "milieu" differences could, perhaps, have contributed to observed outcome variations, we are at a loss, even on a "post hoc" basis, to offer a satisfactory explanation, since our sets were focused on the atropine-nonatropine dimension and not on the psychotropic-nonpsychotropic dimension. At any rate, we should stress the point that the confusion of results in the literature regarding the efficacy or nonefficacy of the minor tranquilizers becomes most "believable" when different patterns of outcome are obtained in clinics following an identical protocol.

Contrary to the findings of Kast[9] and Kast and Loesch,[10,11] the results of the present study indicate that a "positive" treatment of dry mouth detracted from clinical improvement relative to a "neutral" treatment of dry mouth. Since this result was entirely unexpected, no provision was provided in the protocol to probe the "meaning" patients attached to the different sets and to the dry mouth experience. One can only speculate, therefore, with regard to the mechanism or mechanisms underlying the poor therapeutic response of atropine-treated patients under the positive set. Since side-effects have a generally negative connotation in the public mind, it is quite possible that preexisting beliefs about side reactions were a more important factor in influencing patient response than was the therapeutic interpretation of dry mouth offered by the treating doctor. Park and Covi report an analogous finding: despite the treating doctors telling patients that they were receiving placebos, ". . . six or 14 patients did not believe the capsules did not contain active drug, with three of them experiencing 'side effects.' . . ."[20 (p 342)] In this connection it seems plausible that the positive set reinforced already existing patient concern by focusing them on the likely occurrence of an unpleasant side effect. It is clear that this focusing on dry mouth in the positive set did sensitize patients to the dry mouth experience. It was also interesting to observe that patients receiving the atropine medications under the positive set also reported more side effects generally (the most typical atropine side effects such as dry mouth and stuffy nose

were excluded from this analysis) than did the nonatropine patients (44.9% vs 21.4%; $\chi^2 = 4.55$, $P<0.05$). Under the neutral set, by contrast, no reliable difference was obtained (31.4% vs 28.3%). It seems likely that the dry mouth experience reinforced the patient's focus on unpleasant somatic effects and any somatic change (drug-related or nondrug-related) was attributed to the medication. The therapeutic response of the patient probably reflects the psychological subtraction of perceived unpleasant side-reactions from the therapeutic effect of the treatment.

The diametrically opposed finding of the present study with that of Kast and Loesch may have arisen from the many procedural differences which obtained in these studies. To highlight some of these differences the following should be noted. (1) The Kast and Loesch studies introduced atropine only after patients had a rather extended period of doctor contact. (2) Their nontherapeutic set was more "negative" than "neutral" insofar as they "cautioned" or "warned" patients about dry mouth which seems to have been given a toxic interpretation. (3) Doctors in their studies were not blind to medications and only doctor and not patient ratings were employed.

Our results lead us to question the advisability of using an "active" placebo (at least atropine) as opposed to an "inactive" placebo as a reference medication for evaluating the efficacy of the minor tranquilizers. A close inspection of these data reveals that atropine, even under the neutral set, produced a markedly poorer therapeutic response at one of the clinics while producing only a marginally better response than placebo at the other clinics. The clinic (PGH) where the atropine response was markedly poor is characterized by a larger percentage of lower class patients whom Rickels [12] describes as hypochondriacal, somatically focused, and particularly disturbed by autonomic side effects.

Finally, these data have relevance for the tenability of the interactive as opposed to additive model for conceptualizing drug effects. The relative efficacy of both the psychotropic (chlordiazepoxide hydrochloride vs nonchlordiazepoxide hydrochloride) and atropine medications was found to interact with other variables included in the study design. These interactions indicate that drug effects do not remain constant regardless of the treatment context as specified by the additive model. The interactive model, on the other hand, assumes that the magnitude of the drug effect may vary reliably as a function of "nonspecific" factors in the treatment situation. The interactive model, supported by the findings of the present study, indicates that it is entirely possible to have scientifically valid studies reporting highly discrepant findings with regard to the efficacy of the minor tranquilizers. It suggests, further, that future research should concentrate on identifying and quantifying those "nonspecific" factors that influence treatment outcome.

Summary

In a one-week methodologically focused study, anxious neurotic outpatients ($N = 204$) were administered chlordiazepoxide hydrochloride (Librium), chlordiazepoxide hydrochloride + atropine, atropine, and placebo by doctors trained to convey a "positive" therapeutic interpretation of dry mouth to one half their patients and a "neutral" attitude to their remaining patients.

Results indicate a general therapeutic superiority of the chlordiazepoxide hydrochloride medications which varied reliably, however, as a function of the doctors' roles at the different clinics. The atropine medications were found less effective than the nonatropine medications, and this therapeutic disadvantage was most pronounced under the "positive" dry mouth treatment.

These findings were discussed in relation to the relevant literature and implications were drawn for the "additive" vs "interactive" model for conceptualizing drug effects.

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Generic and Trade Names of Drugs

Chlordiazepoxide Hydrochloride—*Librium.*

Imipramine—*Tofranil.*

Meprobamate—*Equanil, Miltown.*

Benactyzine—*Suavitil.*

Phenobarbital—*Luminal.*

Reserpine—*Rauloydin, Raurine, Rau-Sed, Reserpoid, Sandril.*

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