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THE INFLUENCE OF MEDICATION (IMIPRAMINE) AND DOCTOR IN RELIEVING DEPRESSED PSYCHONEUROTIC OUTPATIENTS*

E. H. UHLENHUTH† and LEE C. PARK†‡

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INTRODUCTION

THE critical role of nonpharmacologic factors in human responses to medication has become increasingly evident during recent years. HILL *et al.*[1] showed that the effects of morphine and pentobarbital on the reaction time of former morphine addicts can be reversed by providing different rewards for participating in the experiment. NOWLIS and NOWLIS[2] showed that a subject experiences different effects from dramamine and phenobarbital, according to the prevailing mood of the other members in his experimental group. FISHER[3] found that certain effects of amphetamine and placebo depend upon the information given to the subjects in advance. SCHACHTER and his co-workers[4,5] showed that emotional states depend jointly upon physiological arousal and cognitive cues. The outcome of such situations is determined not simply by adding the effects of the two variables, but rather by a complex interaction between the two variables.

Meanwhile, the same principle was emerging from studies in clinical settings. FELDMAN[6] in 1956 systematically examined the effects of a nonpharmacologic factor — the physician's attitude about medication — on the outcome of drug therapy in patients. He found that doctors with a more optimistic attitude about the medication tend to get better results than doctors with a less optimistic attitude. UHLENHUTH *et al.*[7] studied the relative effectiveness of meprobamate, phenobarbital and placebo in relieving anxiety symptoms in psychoneurotic patients treated by two different doctors. One doctor's patients responded better to the active medications than to placebo, whereas the other doctor's patients responded equally well to all the medications. DIMASCIO and KLERMAN[8] and SHERMAN[9] summarized many of the nonpharmacologic factors which are important in the clinical situation where patients are treated with drugs.

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†Assistant Professor of Psychiatry, The Johns Hopkins University Medical School, Baltimore 5, Maryland.

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The present comparison between imipramine and placebo was designed both to hold constant the effects of most nonpharmacologic factors, and also to permit us to study the possible effects of one such important variable, the doctor, and the possible interaction between the doctor and the drug variables. These aims are summarized in the following hypotheses to be tested in this study:

1. Imipramine is superior to placebo for relieving symptoms in depressed psychoneurotic outpatients.
2. These patients experience more relief with some doctors than with others.
3. The relative effectiveness of imipramine and placebo for relieving these patients depends upon the doctor administering the medications; that is, with some doctors imipramine is more effective than placebo, whereas with other doctors imipramine and placebo are equally effective (interaction).

METHOD

The general plan

This study was planned according to a 'double-blind', balanced, patient-own control (crossover) design with two medications, seven doctors and a total of 42 patients. The plan called for each patient to take imipramine for 4 wk and placebo for 4 wk. The patient was scheduled to see his doctor 5 times for assessment and instructions: at the beginning of treatment and at 2 wk intervals thereafter until the end of the 8 wk treatment period.

The setting

The study took place in the Outpatient Department of the Henry Phipps Psychiatric Clinic. This is an active outpatient service for patients over 14 yr who cannot afford private psychiatric consultation and treatment.

One of the clinic's treatment services offers 15 min supportive follow-up visits every 2–4 wk, often with medication. The present study was carried out in the rather bustling atmosphere of this service by the personnel regularly assigned there. The doctors saw their study patients during a portion of the afternoon especially set aside for that purpose.

Selecting the patients

The visiting psychiatrists referred to the study every suitable patient whom they saw for psychiatric consultation in the clinic. A research psychiatrist interviewed each candidate again to make sure he met the criteria for inclusion in the study:

1. Aged between 21–71.
2. Primary diagnosis of depressive reaction (neurotic).
3. No evidence of brain syndrome, mental deficiency, schizophrenic reaction or sociopathic personality disturbance.
4. No other treatment required during the course of the study. (Occasionally an otherwise suitable patient was excluded from the study because the consultant thought that prompt psychotherapy was strongly indicated.)

Assigning the patients to a treatment condition

As patients entered the study, they were assigned in rotation to the study doctors. We assigned each doctor's patients to the imipramine-placebo or placebo-imipramine sequence according to a schedule prepared in advance. The early part of the schedule was determined by a table of random numbers, but the last part was distorted, if necessary, to equalize the number of patients starting on each medication sequence. Drop-outs were replaced by assigning the doctor's next new patient to the same medication sequence as the drop-out. Patients entered the study as described above until it appeared that each doctor would complete a total of 6 patients.

The study doctors

The entire group of 7 first year residents* at the Phipps Clinic participated as study doctors.

The medications

Each patient took each medication for 4 wk. The medications consisted of coated tablets containing 25 mg of imipramine (Tofrānil) and placebos of identical appearance containing 0·1 mg atropine.† The prescribed dosage of each medication was two tablets three times a day.

The research psychiatrist coded and labeled each bottle so that the patient and his doctor would not know which of the two medications the patient received at any time. The patient received his assigned medication from a nurse who did not know which medication she was giving. Both the nurse and the doctor knew the names of the two medications being studied. The patient knew that he was trying two medications, but he did not know their names.

The patient received his medication in a bottle containing more than enough tablets for the current 2 wk treatment period. The doctor asked the patient to return the bottle with the remaining medication at the next visit.

The treatment interviews

We attempted to structure the study doctors' interviews with their patients to minimize uncontrolled nonpharmacologic factors. Before the study began, each doctor received a set of printed instructions to learn and to keep for future reference. The doctor was to limit each interview to about 20 min. He was to review the patient's symptoms briefly, fill out the necessary forms with the patient, prescribe the medication and explain the therapeutic regimen to the patient. He was to ask the patient to contact him if the patient had any questions or required any medical attention other than the prescribed treatment.

During the first interview, the doctor was to introduce the medication as follows: "The kind of trouble you have been telling me about often responds quite well to medicine. We now have 2 different medicines available that we know help many people with difficulties like yours. However, some people do better with one and other people do better with the

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†Geigy Pharmaceuticals kindly supplied generous quantities of both medications.

other medicine. The best way to find out which of the two medicines is best for you personally is to try them both. So we have set up a treatment program which will give you the opportunity to do just that. You will be able to take each medicine for 4 wk. At the end of the 8 wk, if necessary, you may continue to take whichever medicine works best for you. (Many people already feel well by then and need not continue with medicine.)" The doctor also had a list of standardized replies to questions patients commonly ask.

Assessing the patient's condition

At each treatment visit, that is, at 2 wk intervals throughout a patient's participation in the study, we assessed his clinical condition in several ways:

1. *The patient's overall estimate of his condition.* The doctor asked the patient to select the word — better, same or worse — which best described his progress since his last visit to the clinic. At the first treatment visit, the assessment referred to the interval since the initial clinic consultation.

2. *The doctor's overall estimate of the patient's condition.* On the basis of all the information about the patient at his disposal after each interview, the doctor rated the patient's progress since his last visit according to the same categories: better, same or worse. In general the doctor relied mainly on the symptomatic picture in making his judgement.

3. *The symptom check list.* This list was adapted for this particular study from lists developed and used for many years by FRANK *et al.*[10] Our list contained 62 symptoms. There were spaces opposite each symptom to indicate whether it bothered the patient not at all, just a little, pretty much, or very much.

During each interview, both the patient and the doctor had a copy of the symptom check list. They went over the list together, item by item. The patient told the doctor how much each symptom bothered him, and the doctor marked it accordingly on his own copy. The doctor attempted to have the patient rely on his own interpretation of what each symptom meant. Patients rarely were so deficient in their grasp of English that the doctor had to clarify the items on the list.

After the study was completed, eight senior staff psychiatrists independently classified the 62 symptoms into the following subgroups*: depression (13 symptoms), anxiety (13 symptoms), secondary (10 symptoms such as phobias, obsessions, conversions), overlapping (12 symptoms which might belong in two or three of the first three subgroups) and miscellaneous (8 symptoms which did not belong in any of the first three subgroups). We included a symptom in the depression, anxiety, secondary or miscellaneous subgroups only if at least five psychiatrists classified it in the same subgroup. Six symptoms were segregated into a 'reject' subgroup, since we expected higher scores on these items to accompany *less* distress.

Each symptom was scored zero, one, two or three, according to the degree of distress reported by the patient. The total distress score and the scores for each subgroup were computed by adding the individual scores on the appropriate items.

4. *The Morale Loss (M-L) Scale.* CANTER[11] developed this scale by selecting from the D and Pt scales of the MMPI the 30 items which correlated best with clinically observed

*See Appendix for list of symptoms in each subgroup.

depression. In our study, the doctor administered this scale in the same fashion as the symptom check list. The scale was scored simply by counting the number of items which the patient marked in the depressive direction.

Analyzing the Data

The study yielded two basic types of information about the groups of patients in the different treatment conditions. For classification data, such as sex and overall estimate of the patient's condition, we tested the significance of differences in distribution between groups by the chi square method, with one exception noted below. For continuously variable data, such as age and the scores derived from the symptom checklist and the M-L Scale, we tested the significance of differences between group means by the analysis of variance. We modified the basic method where indicated, for example, by introducing a covariable. Such modifications are explained in connection with the corresponding results.

RESULTS—INDEPENDENT VARIABLES

The patient population

As it turned out, 50 patients entered the study and 42 completed the experimental treatment. Eight patients stopped coming for treatment visits before the end of the study.

Table 1 compares some characteristics of the drop-outs and the patients who completed the study. There are no significant differences. Six drop-outs failed to return while taking imipramine and two while taking placebo. Four of the 8 drop-outs were under the care of the same doctor. This doctor differs significantly ($p<0{\cdot}01$) in this respect from the other 6 doctors, according to the extreme value test.[12]

Since the drop-outs were unevenly distributed, the treatment groups finally were unequal, despite our efforts to replace the drop-outs. Twenty-two patients completed the imipramine-placebo sequence, and 20 completed the placebo-imipramine sequence. Table 1 compares the characteristics of these two groups. They did not differ significantly in regard to age, sex, race, marital status or final diagnosis. However, the group starting on imipramine had significantly higher initial mean total distress and M-L Scale scores than the group starting on placebo.

Seven patients completed treatment with one doctor, 5 with another doctor and 6 with each of the remaining doctors. These 7 groups did not differ significantly in regard to age, sex, race, marital status, final diagnosis or initial mean M-L Scale score. However, there were again significant differences between these groups in their initial mean total distress scores.

After a detailed and critical review of the way all the experimental procedures were carried out, we concluded that the discrepancies in initial status between the groups of patients assigned to different medications and doctors occurred completely by chance. However, we chose procedures for analyzing the results of treatment that take into consideration these discrepancies in initial status.

TABLE 1. THE PATIENT POPULATION

	Completed Study		Dropped Out	
First Medication	Imipramine	Placebo	Total	Total
Number of patients	22	20	42	8
Age:				
Average	44·5	39·7	42·2	40·3
Range	29–71	22–60	22–71	24–63
Sex:				
Male	7	4	11	1
Female	15	16	31	7
Race:				
White	12	13	25	7
Colored	10	7	17	1
Marital Status:				
Single	1	1	2	0
Married	10	16	26	7
Widowed	3	2	5	0
Separated	8	1	9	1
Divorced	0	0	0	0
Final Diagnosis:				
Depressive reaction	21	20	41	7
Psychotic depressive reaction	0	0	0	1
Paranoid state with depressive features	1	0	1	0
Initial Total Distress Score:				
Average	85·8	66·3	76·5	67·6
Range	34–127	13–140	13–140	29–122
Initial M-L Scale Score:				
Average	22·5	17·0	19·9	16·4
Range	12–30	3–27	3–30	5–20

The experimental treatment

Most patients took their medications essentially as prescribed. There were 168 treatment periods in the entire study (42 patients × 4 periods), 84 treatment periods for each medication. According to the patients' own reports, they averaged at least 4 tablets of imipramine per day during 79 periods (93%) and at least 4 tablets of placebo per day during 81 periods (96%).

Patients usually returned the bottle and remaining tablets at the end of each treatment period. Unfortunately we counted these only after all patients had completed the study. At that time 118 reliable tablet counts were available (70% of 168 treatment periods), 60 imipramine and 58 placebo. Fifty-one (85%) imipramine counts and 53 (91%) placebo counts showed that the patients took an average of at least 4 tablets of medication per day. Data from every patient who came for all 5 study visits were included in the analyses, whether or not the patient took the prescribed dosage of medication.

We checked the doctor's blindness by asking him after each treatment period to guess which medication his patient had received. The 7 doctors made only 112 guesses (67% of 168 periods). They felt they could not guess which medication their patients had received during the remaining 56 periods. They guessed correctly 61 times (55% of 112 guesses). Unfortunately we could not observe continuously the doctor's interview performance with his patients.

Patients usually received no treatment from an outside physician during the course of the study. In 34 treatment periods (20% of 168), the patient saw another doctor or took another medication. Patients often telephoned their study doctor, the research psychiatrist or another doctor.

RESULTS—DEPENDENT VARIABLES

The patients' overall estimates of their condition

Table 2 shows the number of patients on imipramine and placebo who rated themselves improved and unimproved at the end of each 2 wk treatment period. These ratings refer only to change during the 2 wk just past. Although more patients reported improvement on imipramine than on placebo during the first two treatment periods, these differences did not approach statistical significance.

TABLE 2. THE PATIENTS' OVERALL ESTIMATES OF THEIR CONDITION

Period		0–2 Wk		2–4 Wk		4–6.Wk		6–8 Wk	
Medication		Imip.	Plac.	Imip.	Plac.	Imip.	Plac.	Imip.	Plac.
No. of Patients	Imp.	11	8	14	11	12	13	12	13
	Unimp.	11	12	8	9	8	9	8	9

More patients reported improvement with some doctors than with others, but these differences between doctors also did not reach statistical significance.

The doctors' overall estimates of the patients' condition

Table 3 shows the number of patients on imipramine and placebo whom the doctors rated improved and unimproved at the end of each 2 wk treatment period. These ratings refer only to change during the 2 wk just past. The doctors rated more patients improved on imipramine than on placebo during the first 2 treatment periods, although these differences again were not statistically significant.

TABLE 3. THE DOCTORS' OVERALL ESTIMATES OF THE PATIENTS' CONDITION

Period		0–2 Wk		2–4 Wk		4–6 Wk		6–8 Wk	
Medication		Imip.	Plac.	Imip.	Plac.	Imip.	Plac.	Imip.	Plac.
No. of Patients	Imp.	9	6	12	6	11	11	8	8
	Unimp.	13	14	10	14	9	11	12	14

Some doctors rated more patients improved than did other doctors, but these differences between doctors also did not reach statistical significance.

TABLE 4. TOTAL DISTRESS SCORES AND MORALE LOSS SCALE SCORES DURING THE FIRST TWO TREATMENT PERIODS FOR THE 42 PATIENTS WHO COMPLETED THE STUDY

Patient Number	Doctor Number	Medication	Total Distress Score			Morale Loss Scale Score		
			Initial	2 wk	4 wk	Initial	2 wk	4 wk
1	1	Im	95	60	40	21	18	17
2	1	Im	122	83	94	26	27	25
3	1	Im	116	88	82	23	21	25
4	1	Im	127	81	45	27	24	16
5	1	Pl	106	78	22	25	28	21
6	1	Pl	37	18	14	7	6	3
7	1	Pl	25	27	16	3	8	3
8	2	Im	63	30	17	17	19	17
9	2	Im	83	51	78	24	15	22
10	2	Im	36	50	70	22	18	20
11	2	Pl	28	38	47	14	18	20
12	2	Pl	47	39	53	14	13	19
13	2	Pl	13	9	4	5	6	6
14	3	Im	123	65	62	26	26	17
15	3	Im	65	66	56	25	27	23
16	3	Im	58	16	30	17	16	13
17	3	Pl	93	116	96	23	26	27
18	3	Pl	100	101	107	26	25	27
19	3	Pl	96	95	72	27	26	20
20	4	Im	85	47	52	23	18	22
21	4	Im	56	45	40	15	14	9
22	4	Im	34	13	20	12	6	5
23	4	Pl	58	32	38	21	9	12
24	4	Pl	52	37	10	18	18	8
25	4	Pl	95	106	92	24	26	27
26	5	Im	103	68	27	30	19	15
27	5	Im	69	60	57	27	26	26
28	5	Im	112	111	100	23	27	25
29	5	Pl	59	69	58	10	11	11
30	5	Pl	69	43	41	19	16	16
31	6	Im	65	55	52	19	17	17
32	6	Im	73	70	52	26	26	24
33	6	Im	84	32	21	20	11	3
34	6	Pl	75	68	72	20	16	22
35	6	Pl	140	103	109	22	22	20
36	6	Pl	44	24	36	5	2	3
37	7	Im	116	128	118	26	23	22
38	7	Im	86	89	94	24	26	26
39	7	Im	116	86	56	22	15	17
40	7	Pl	80	83	66	16	19	19
41	7	Pl	64	54	77	23	25	25
42	7	Pl	44	88	48	18	24	19

The total distress scores

For each of the 42 patients who completed the study, 5 total distress scores were available, one at the beginning of the study and one at the end of each 2 wk treatment period. Table 4 shows these scores for the first half of the study. We analyzed these scores for

TABLE 5. ANALYSIS OF VARIANCE OF TOTAL DISTRESS SCORES

Source of Variation	Sum of Squares	df	Mean Square	F	*p*
Among regimen groups	84763·76	13	6520·29		
Between regimens	3778·14	1	3778·14		
Among doctors	30881·60	6	5146·93		
Doctors × regimens	50104·02	6	8350·67		
Error 1 (among patients)	71236·57	28	2544·16		
Among periods	17387·79	4	4346·95	13·31	<0·005
Regimen groups × periods	17656·35	52	339·55	1·04	n.s.
Regimens × periods	1802·65	4	450·66	1·38	n.s.
Doctors × periods	7820·82	24	325·87	1·00	n.s.
Doctors × regimens × periods	8032·88	24	334·70	1·03	n.s.
Error 2 (within patients)	36573·06	112	326·55		

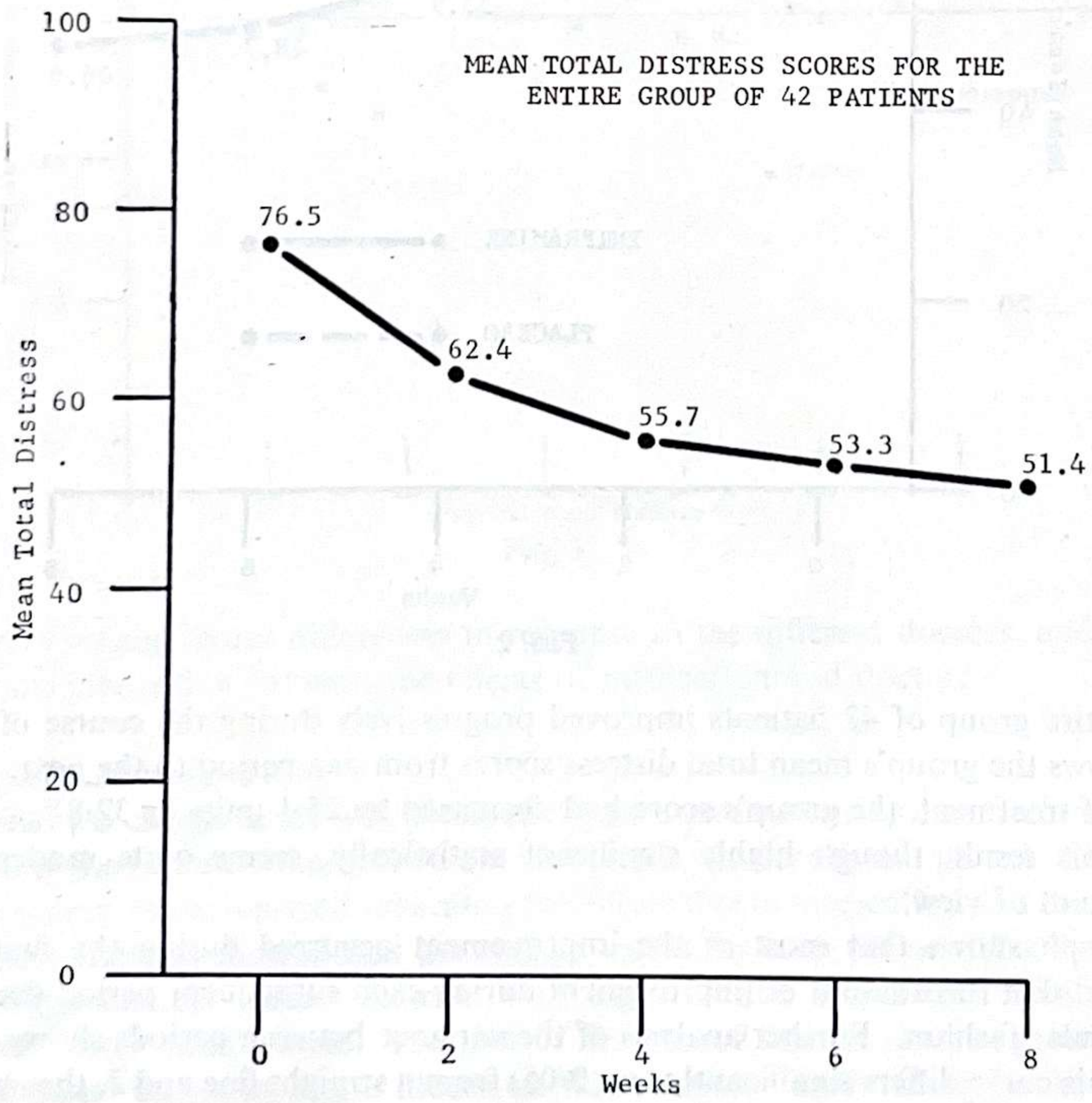

FIG. 1.

effects due to the following independent variables: medication regimen (imipramine-placebo or placebo-imipramine), doctor and treatment period (time).

A preliminary analysis showed that patients maintained the same rank order of total distress throughout their course in the study: patients with higher initial scores did not reach the same level as patients with lower initial scores. Consequently we treated these data further by an analysis of variance separating out differences in initial distress levels between and within patients. The results of this analysis of variance appear in Table 5.

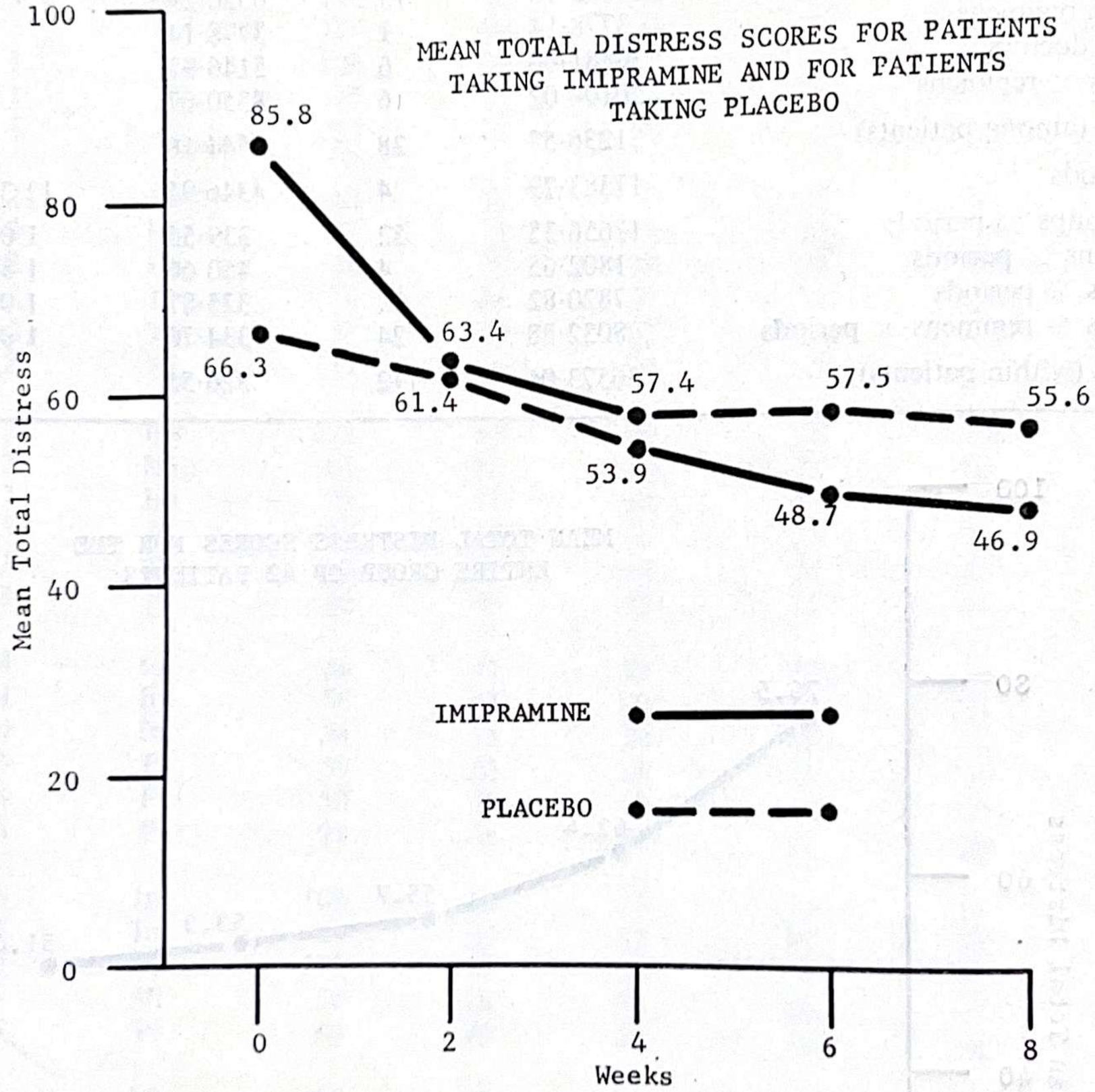

FIG. 2.

The entire group of 42 patients improved progressively during the course of treatment. Fig. 1 shows the group's mean total distress scores from one period to the next. At the end of 8 wk of treatment, the group's score had decreased by 25·1 units or 32·8% of the initial score. This result, though highly significant statistically, seems quite modest from the clinical point of view.

The graph shows that most of the improvement occurred during the first treatment period and that the amount of improvement during each subsequent period decreased in a rather regular fashion. Further analysis of the variance between periods shows that: 1. the form of this curve differs significantly ($p<0·05$) from a straight line and 2. the improvement in the first two treatment periods is significant ($p<0·01$).

Since most of the improvement occurred during the first 2 wk, we extracted from the overall analysis the variance due to only this treatment period. The group of patients taking imipramine responded significantly ($p<0{\cdot}05$) better than the group taking placebo. After the first treatment period there were no significant differences in response to the two medications. Fig. 2 shows the mean total distress scores of the patient groups on the two different medication regimens.

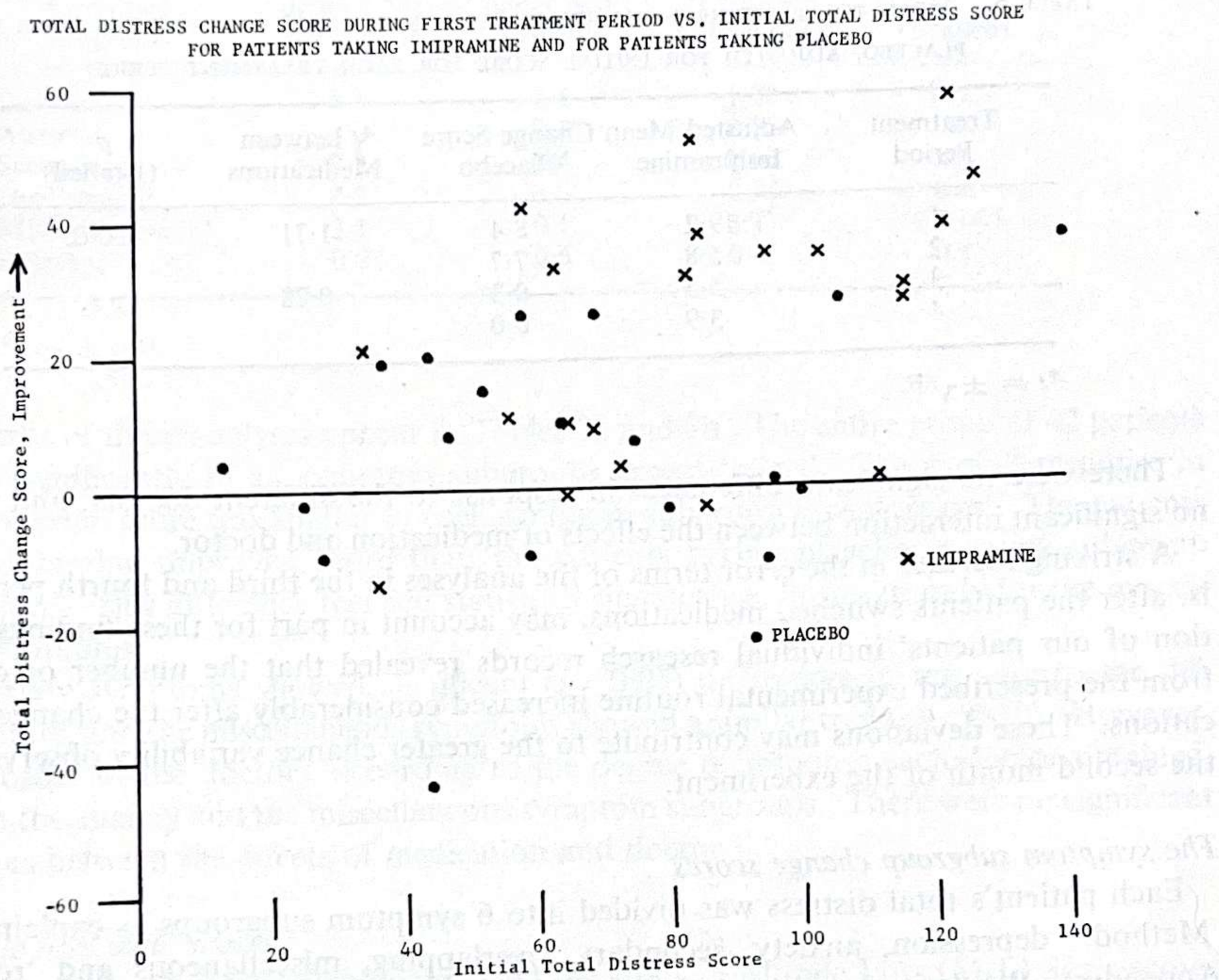

FIG. 3.

There were no significant differences in response to the different doctors, and there was no significant interaction between the effects of medication and doctor.

The total distress change scores

A total distress change score was obtained for each patient during each treatment period by subtracting the patient's final score from his initial score during that period. We analyzed the change scores for each period separately for effects due to medication and doctor.

Preliminary analyses showed that the change scores for each period depended upon the patients' initial distress scores: patients with higher initial scores improved more than patients with lower initial scores. The plot of first period change scores against their corresponding initial scores in Fig. 3 illustrates this relation. This finding led us to use the initial distress scores as a co-variable in analyzing the change scores.

The analyses of the change scores showed that the entire group of 42 patients improved significantly ($p<0{\cdot}025$) during each of the first two treatment periods.

The analysis for the first treatment period showed that the group of patients taking imipramine responded significantly better than the group taking placebo, even after we allowed for differences in initial distress. After the first treatment period there were no significant differences in response to the two medications. Table 6 shows these results.

TABLE 6. MEAN TOTAL DISTRESS CHANGE SCORES FOR PATIENTS TAKING IMIPRAMINE AND PLACEBO, ADJUSTED FOR INITIAL SCORE FOR EACH TREATMENT PERIOD

Treatment Period	Adjusted Mean Change Score Imipramine	Placebo	*t between Medications	p (1-tailed)
1	19·2	8·4	1·71	$<0{\cdot}05$
2	5·8	7·7		
3	5·5	−0·3	0·78	n.s.
4	3·9	0·0		

*$t = \pm\sqrt{F}$

There were no significant differences in response to the different doctors, and there was no significant interaction between the effects of medication and doctor.

A striking increase in the error terms of the analyses in the third and fourth periods, that is, after the patients switched medications, may account in part for these findings. Inspection of our patients' individual research records revealed that the number of deviations from the prescribed experimental routine increased considerably after the change of medications. These deviations may contribute to the greater chance variability observed during the second month of the experiment.

The symptom subgroup change scores

Each patient's total distress was divided into 6 symptom subgroups as explained under 'Method': depression, anxiety, secondary, overlapping, miscellaneous and 'reject' (see Appendix). We derived and analyzed the subgroup change scores for the first period for effects due to medication and doctor.

TABLE 7A. MEAN SYMPTOM SUBGROUP SCORES FOR 42 PATIENTS, FIRST TREATMENT PERIOD

Symptom Subgroup	Mean Initial Score	Mean Change Score	*t for Change	p (1-tailed)
Depression	18·1	3·9	4·26	$<0{\cdot}005$
Anxiety	16·5	2·6	4·14	$<0{\cdot}005$
Secondary	10·2	1·9	3·12	$<0{\cdot}005$
Overlapping	17·0	3·7	4·39	$<0{\cdot}005$
Miscellaneous	10·5	1·7	3·70	$<0{\cdot}005$
Reject	4·2	0·4	1·41	$<0{\cdot}10$

*$t = \pm\sqrt{F}$

In all symptom subgroups patients with higher initial scores improved more than patients with lower initial scores. We therefore used the initial subgroup scores as a co-variable in analyzing the subgroup change scores.

TABLE 7B. MEAN SYMPTOM SUBGROUP CHANGE SCORES FOR PATIENTS TAKING IMIPRAMINE AND PLACEBO, ADJUSTED FOR INITIAL SCORE, FIRST TREATMENT PERIOD

Symptom Subgroup	Adjusted Mean Change Score Imipramine	Placebo	*t between Medications	p (1-tailed)
Depression	5·1	2·5	1·22	n.s.
Anxiety	3·0	2·1	0·78	n.s.
Secondary	2·2	1·4	0·66	n.s.
Overlapping	4·3	3·0	0·75	n.s.
Miscellaneous	3·1	0·1	3·11	<0·005
Reject	0·2	0·6	0·61	n.s.

*$t = \pm\sqrt{F}$

The results of these analyses appear in Tables 7a and 7b. The entire group of 42 patients improved significantly in all symptom subgroups except 'reject'. The overall response in relation to initial score was similar in each symptom subgroup except 'reject'. The patients taking imipramine improved more than the patients taking placebo in every subgroup except 'reject'. This difference reached statistical significance, however, only for the miscellaneous symptoms.

The anxiety symptoms showed significant ($p<0·05$) differences in response to the different doctors, and the miscellaneous symptoms showed a similar trend ($p<0·10$). However, the rank order of the doctors, according to the degree of response each doctor obtained, differed in the anxiety and the miscellaneous symptom subgroups. There were no significant interactions between the effects of medication and doctor.

The morale loss scale scores

For each of the 42 patients who completed the study, 5 Morale Loss (M-L) Scale scores at 2 wk intervals were available, as in the case of the total distress scores. Table 5 shows these scores for the first half of the study. A preliminary analysis showed that patients maintained the same rank order of M-L scores throughout their course in the study, so that the M-L scores could be treated by an analysis of variance due to medication regimen, doctor and treatment period (time), like the total distress scores.

According to this analysis, the entire group of 42 patients improved progressively during the course of treatment. Fig. 4 shows the group's mean M-L scores from one period to the next. At the end of eight weeks of treatment, the group's score had decreased by 4·6 units or 23·3% of the initial score. This result, though highly significant statistically, is even more modest than the result with the mean total distress score.

The graph shows that improvement in the M-L score was about the same during every treatment period. Further analysis of the variance between periods shows that: 1. the form of this curve does not differ significantly from a straight line and 2. the improvement is

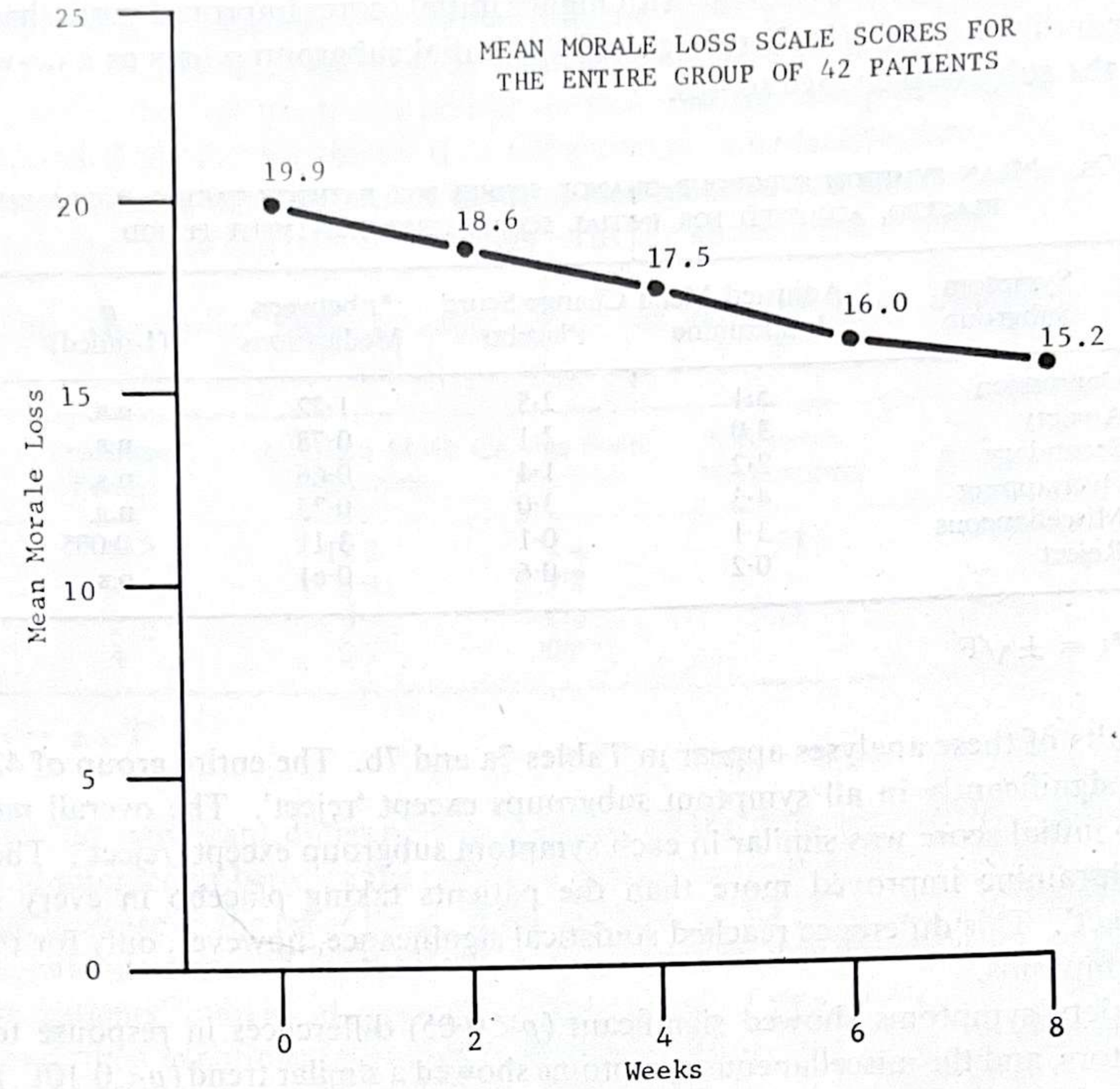

FIG. 4.

significant ($p<0{\cdot}025$) in each of the first three treatment periods. These results stand in contrast to the results with the total distress scores.

We extracted from the overall analysis the variance due to only the first treatment period. The group of patients taking imipramine responded significantly ($p<0{\cdot}05$) better than the group taking placebo. After the first treatment period, there were no significant differences in response to the 2 medications. Fig. 5 shows the mean M-L scores of the patient groups on the two different medication regimens.

There were no significant differences in response to the different doctors, and there was no significant interaction between the effects of medication and doctor. These results correspond to those found with the total distress scores.

The morale loss scale change scores

An M-L Scale change score was obtained for each patient during each treatment period in the same way as the total distress change score. We analyzed the M-L change scores for each period separately for effects due to medication and doctor.

In every period patients with higher initial M-L scores improved more than patients with lower initial scores. We therefore used the initial M-L scores as a co-variable in analyzing

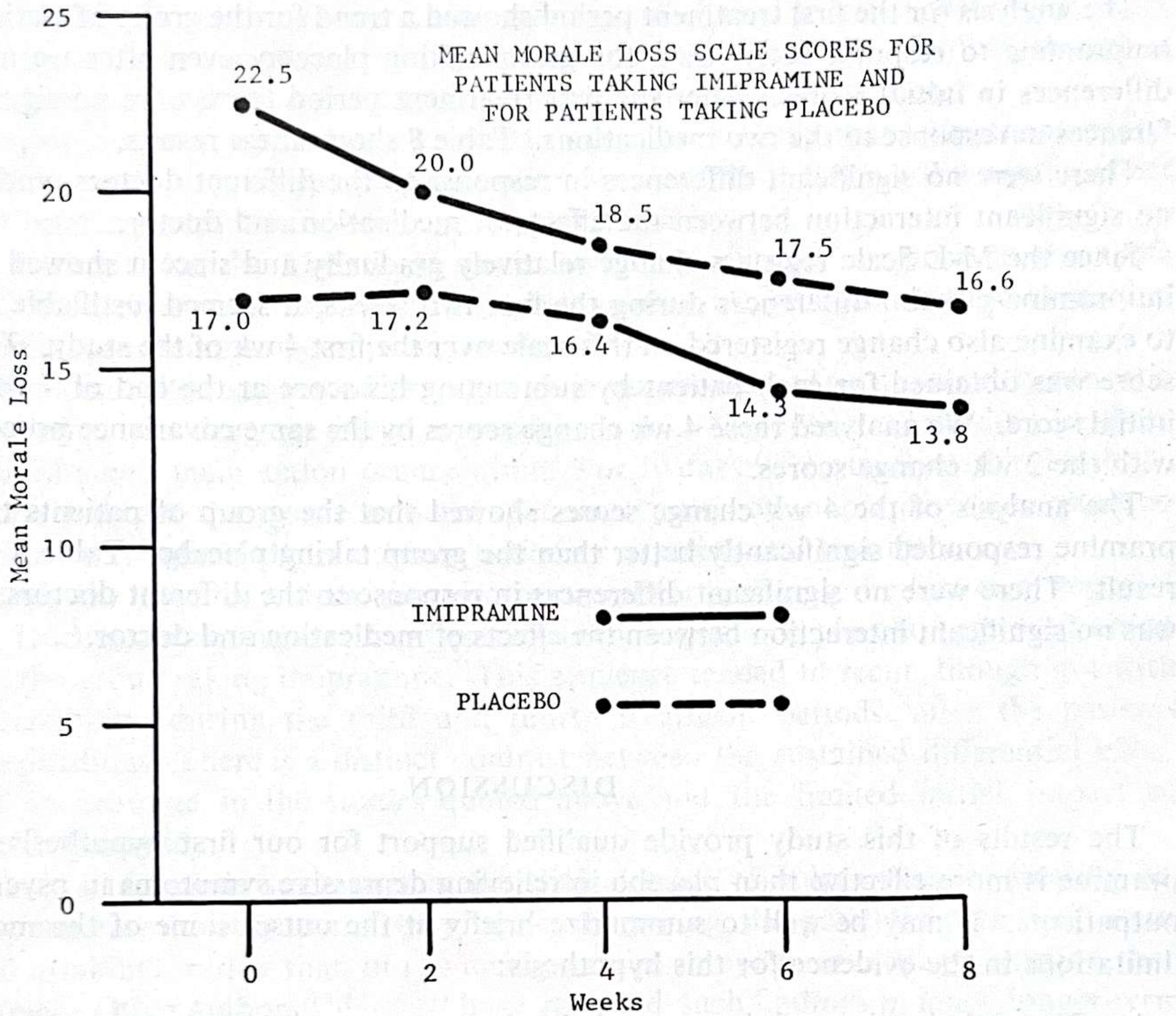

FIG. 5.

the M-L change scores. It is worth emphasizing that the relationship between M-L change scores and initial scores, though consistently present, was much weaker (the regression was less) than in the case of the distress change scores.

The analyses of the M-L change scores showed that the entire group of 42 patients improved significantly ($p<0{\cdot}05$) during the first 3 treatment periods and near-significantly ($p<0{\cdot}10$) during the fourth treatment period.

TABLE 8. MEAN MORALE LOSS SCALE CHANGE SCORES FOR PATIENTS TAKING IMIPRAMINE AND PLACEBO, ADJUSTED FOR INITIAL SCORE FOR EACH TREATMENT PERIOD

Treatment Period	Adjusted Mean Change Score Imipramine	Placebo	*t between Medications	p (1-tailed)
1	2·4	0·0	1·58	<0·10
2	1·4	0·9		
3	2·1	0·7	0·98	n.s.
4	1·2	0·7		
1 + 2	4·0	0·7	1·73	<0·05

*$t = \pm\sqrt{F}$

The analysis for the first treatment period showed a trend for the group of patients taking imipramine to respond better than the group taking placebo, even after we allowed for differences in initial scores. After the first treatment period there were no significant differences in response to the two medications. Table 8 shows these results.

There were no significant differences in response to the different doctors, and there was no significant interaction between the effects of medication and doctor.

Since the M-L Scale registers change relatively gradually and since it showed borderline imipramine-placebo differences during the first two weeks, it seemed justifiable and useful to examine also change registered on this scale over the first 4 wk of the study. This change score was obtained for each patient by subtracting his score at the end of 4 wk from his initial score. We analyzed these 4 wk change scores by the same covariance procedure used with the 2 wk change scores.

The analysis of the 4 wk change scores showed that the group of patients taking imipramine responded significantly better than the group taking placebo. Table 8 shows this result. There were no significant differences in response to the different doctors, and there was no significant interaction between the effects of medication and doctor.

DISCUSSION

The results of this study provide qualified support for our first hypothesis: that imipramine is more effective than placebo in relieving depressive symptoms in psychoneurotic outpatients. It may be well to summarize briefly at the outset some of the more serious limitations in the evidence for this hypothesis:

1. The global ratings of change made by the patients and their doctors at no time show statistically reliable differences between imipramine and placebo. The reliability of these global ratings is subject to further doubt since they do not take account of the patients' initial status.

2. The total distress scores and their changes show a statistically significant difference between medications only during the first treatment period and then only in moderate degree ($p<0{\cdot}05$). Since the imipramine group began with a higher initial level of distress than the placebo group and since more distressed patients improved more, the differential response between the imipramine and the placebo groups might have been expected on the basis of their initial scores alone. The validity of the method to 'adjust' for the difference in initial distress between the imipramine and the placebo groups therefore becomes crucial.

The covariance method used in this study assumes that the relationship between change and initial score is linear over the entire range of the data. Although this assumption is tenable, the data of the present study are too limited to put it to a definitive test. The data for the first treatment period (see Fig. 3) might lend themselves to an alternative assumption, for example, that the regression of change on initial score takes a quadratic form. In that case, the adjustment for initial score which we applied would be inadequate, and the significance of the differential response between the imipramine and placebo groups would be still more questionable.

In another study, as yet unpublished, the regression of change on initial distress appears to be linear for a larger sample of 198 psychoneurotic outpatients. This finding, though it cannot definitively answer the question raised above, is somewhat reassuring.

3. The symptom subgroup change scores do not show reliably that imipramine exerts a greater effect upon depressive symptoms than upon others. Such a differential effect would have been expected on the basis of our hypothesis.

4. The findings with the M-L Scale scores and their changes are open to the same questions of borderline statistical significance and validity of statistical method in dealing with the unmatched treatment groups as noted in 2.

Five earlier controlled studies of imipramine in outpatients or predominantly neurotic inpatients all find the drug an effective antidepressant.[13,14,15,16,17] According to these reports, imipramine's main action occurs within 9 or 10 days,[13] certainly within 1 mth.[15] These reports indicate that, once initiated, the superiority of imipramine over placebo persists at least throughout the remaining period of experimental treatment.

In this study the effect of imipramine also occurred early, during the first two weeks of treatment. During the second treatment period, the group taking placebo improved about as much as the group taking imipramine. This sequence tended to recur, though not with statistical reliability, during the third and fourth treatment periods, after the patients changed medications. There is a distinct contrast between the sustained differential effectiveness of imipramine in the studies quoted above and the limited initial impact of imipramine in our study.

The picture in this study suggests that the clinical value of imipramine for treating depressed psychoneurotic outpatients may lie in shortening the patient's period of acute distress and disability, rather than in producing a more complete or lasting remission than other therapies. Other authors[18,19,20,21] have reported such findings in much longer-term studies with other methods of treatment. Our data are consistent with the concept advanced by WHITEHORN[20] and STONE *et al.*[18] that treatment accelerates the patient's own processes of recovery.

Although the view just expressed is an attractive one, it may be well to summarize briefly at this point some of the more serious limitations in this study itself for picking up more marked and prolonged imipramine-placebo differences:

1. Each patient received the same medication for only 4 wk.

2. Our global improvement ratings may have been insensitive. Such ratings provide the major evidence of imipramine's effectiveness in the British studies,[13,14] although the other American studies[15,16,17] also rely heavily upon itemized or scalar devices for evaluation. Perhaps the greater emphasis upon phenomenology in Britain leads to more precise, consistent and symptom oriented global ratings. We did not attempt to standardize our doctors' criteria for global ratings or to train them in the global rating procedure. The fact that our global ratings were limited to the preceding 2 wk period and so did not register cumulative change may have been a further handicap. Finally, our subsequent experience indicates that more refined global rating scales, with 7 steps instead of a simple 'improved-unimproved' dichotomy, can discriminate differences between various treatment conditions.

3. The maximum dose of imipramine in this study was 150 mg per day, whereas dosages up to 200 or 250 mg per day were used in 4 of the 5 earlier studies. RICKELS,[16] who also

used 150 mg daily, found less definite differences between the effects of imipramine and placebo than the other 4 authors.

In addition, in about 15% of all treatment periods, our patients took less than 100 mg of imipramine daily, including occasional periods when they took none. Our analyses include all data from the patients who completed the study. Consequently the mean differences in response between the imipramine and placebo groups are diluted by data from patients who did not take the prescribed dosage of imipramine.

4. There remains still some doubt that our sample was comparable in diagnostic composition to the samples used in the previously mentioned studies. This is true especially of the study by WITTENBORN *et al.*,[17] in which all patients were hospitalized, even though diagnosed mainly as neurotic depressive reactions. Diagnostic inconsistency may be relevant in two respects. First, more severely depressed patients, even within the neurotic group, show greater improvement. Under these circumstances, differences between treatments may come into sharper focus.

Secondly, qualitative differences in depressive conditions also may play a role in their response to treatment. BALL and KILOH,[13] in agreement with most of the published work on imipramine from the beginning,[22] find that 'endogenous' depressions respond to the drug more regularly than 'exogenous' depressions. Quantitative differences in depth of depression may not entirely explain these findings.

This impression finds support in observations regarding relapse rates upon withdrawal of imipramine. Our (neurotic) patients generally did not relapse when they switched from imipramine to placebo during the second month of the study. FRIEDMAN *et al.*,[23] whose sample contained 26% reactive depressions, often had the same experience. In contrast, studies of patients hospitalized with endogenous depressions usually show a high relapse rate upon withdrawal of active medication.[24]

Side reactions did not constitute an important issue in our study. One patient was dropped on account of uncomfortable, though not dangerous, side reactions of nausea, dry mouth, and headache. Among the 42 patients who completed the study, 12 complained of side reactions while taking imipramine and 8 complained of side reactions while taking placebo. These side reactions included a large number of annoying but harmless complaints. The only ones showing a definite preponderance among patients taking imipramine were dry mouth (7–2) perspiration (4–1) and dizziness (4–0). Our experience in this study and others agrees thoroughly with the report of BUSFIELD *et al.*[25] upon the problems of distinguishing symptoms from side reactions.

The results of this study lend little or no support to the remaining two hypotheses tested: 1. that our patients would experience more relief with some doctors than with others and 2. that imipramine would be more effective than placebo with some doctors but not with others (interaction between medication and doctor effects). The one doctor's strikingly high drop-out rate and the differential responses of the anxiety and miscellaneous symptoms are the only significant indications of differences among doctors, and interaction effects nowhere even approach significance. Since these hypotheses derive from common clinical observation, the study's failure to confirm them is especially surprising and requires further consideration.

Indeed we were so concerned that the doctors' effects would be overwhelming that we deliberately took every precaution to minimize their influence. Patients were exposed very sparingly to their doctors by keeping the interviews brief and infrequent. Furthermore, the doctors learned to structure their contacts with patients: they spent the interviews mostly in a rather impersonal filling out of forms, and all the doctors introduced the medication to their patients consistently in the same positive terms. In the light of subsequent experience, it seems very likely that the doctors' training toward uniformity in certain critical procedures was more effective than we had anticipated in overriding individual differences among doctors.

In retrospect, other deficiencies also appeared in the experimental design for revealing differences among doctors. Six patients per doctor were too few in relation to the high variability among individual patients observed in the study. Furthermore the crossover design introduced more problems than it solved. The data gathered after crossover were nearly useless because prior treatment complicated their interpretation and error terms increased. HÖHN *et al.*[26] had a similar experience. If the influence of the doctor's distinctive personality increases with repeated contacts, as seems likely, then the absence of reliable data during the second month of the study becomes a critical issue.

We conclude that differences among doctors in the extreme degree hypothesized did not emerge. On the other hand, the test was far too stringent to justify concluding that differences among doctors play no important role in the usual psychopharmacologic treatment situations.

Surely the most striking finding in this study is one quite apart from the formal hypotheses. It is the quantitative relationship between change in subjectively experienced distress and its initial level: patients with greater initial levels of distress obtain greater relief (although they do not reach the level of patients starting with less distress). This dependence of change on initial level emerges in both the distress scores and the M-L Scale scores during all 4 treatment periods, though in differing degrees.

Furthermore, this finding in the present study of depressed psychoneurotic outpatients replicates our earlier experience[27] with a group of anxious psychoneurotic outpatients who received medication and brief supportive interviews every 2 wk over a period of 6 wk. STONE *et al.*[18] reported similar results from a long-term, follow-up study of psychoneurotic outpatients in the psychotherapy project at the Phipps Clinic. LUBORSKY[28] also reported related findings from the psychotherapy project of the Menninger Clinic. All of these examples furnish evidence that WILDER'S 'law of initial value'[29] applies to measures of patients' clinical states in psychiatry and specifically to patients' reports of their subjectively experienced distress.

It may seem easy to dismiss the significance of this finding as an example of 'regression toward the mean'. Such a regression results from a different distribution of measurement errors on the first and second occasions of measurement. Thus patients whose observed initial distress is inflated by large positive errors in measurement appear to improve simply because the errors at the second measurement tend toward a random distribution, some still positive, but others now negative. The reverse applies to patients whose observed initial distress is deflated by large negative errors in measurement.

The relatively low error term within patients shown in Table 5 indicates that the errors in measuring symptomatic distress are relatively small in this study. Under these conditions, the regression observed in comparing patients with one another may reflect a clinically valid relationship between change in subjectively experienced distress and its initial level.

In short, subjective distress may itself exhibit a central tendency, quite apart from errors in its measurement, like some physiologic functions, notably those regulated by the autonomic nervous system. This line of thought leads to the interesting speculation that subjective distress may exemplify a psychologic function maintained in homeostatic equilibrium, presumably by the coordinated activity of the total person. By implication, then, the person may act to bring his level of subjective distress within bounds from either a high or a low extreme. This view would differ from the usual one, which assumes that the person always strives to maintain his subjective distress at zero or the lowest possible level.

The observed relation between change in subjective distress and its initial level also raises many other questions with interesting clinical implications. For example, does distress in psychotic patients respond in the same way, or does the psychotic disorganization fracture this response pattern along with others? Preliminary results from the Menninger Clinic project[28] speak in favor of the latter alternative.

How much does change in other psychologic functions, especially character traits, depend upon their own initial status? How much does change in such functions depend upon the patient's initial distress level? These questions imply a quantitative approach to the usual clinical impressions that 1. patients with greater initial resources are better therapeutic risks and 2. distress is a motivating force toward change in many aspects of personal function. The first proposition might lead toward clearer characterization and measurement of personal resources. The second proposition might lead toward defining more precisely the roles of anxiety, depression and other forms of distressing affect. These problems offer significant areas for further investigation.

SUMMARY

The purpose of this study was to test whether: 1. imipramine is superior to placebo for relieving symptoms in depressed psychoneurotic outpatients, 2. these patients experience more relief with some doctors than with others and 3. the relative effectiveness of imipramine and placebo depends upon the doctor administering the medications (interaction).

A double-blind, crossover design with two medications, 7 doctors and 42 psychoneurotic patients was employed. The distribution of patients who completed the study was slightly unbalanced among treatment condtions. The patients took each medication for 4 wk. Each patient's condition was assessed every 2 wk by means of 1. the patient's global rating of his condition, 2. the doctor's global rating of the patient's condition, 3. a checklist of 62 symptoms and 4. the Morale Loss Scale.

The results showed that patients who were more distressed initially improved more, but did not reach the level of patients who were less distressed initially. The patients' initial distress was the most consistent single factor determining their improvement. Apparently subjective distress exemplifies a psychological function which, in psychoneurotic patients,

behaves in accord with the 'law of initial value'. Some possible implications of this finding are discussed.

The first hypothesis noted above found qualified support in that the group of patients taking imipramine initially improved more than the group taking placebo. After the first 2 wk of treatment, the improvement rate of the two groups was similar. Because of limitations in the evidence, however, the study does not definitely establish the role of the medications in the results.

Little evidence appeared in this study to support the second hypothesis and none to support the third. However, the conditions were so stringent that only extreme differences in doctor effects could have been detected. The study does not rule out differences among doctors as important factors in the usual psychopharmacologic treatment situation.

APPENDIX

A. Depressive symptoms

1. Poor sleep. 2. Poor appetite. 3. Constipation. 4. Feeling blue. 5. Crying. 6. Blaming yourself for things. 7. Feeling low in energy or slowed down. 8. Feeling hopeless about the future. 9. Feeling no interest in things. 10. Feeling worthless. 11. Loss of sexual desire. 12. Thoughts of ending your life. 13. Weight loss.

B. Anxiety symptoms

1. Faintness or dizziness. 2. Shyness and uneasiness with the opposite sex. 3. Heart pounding or racing. 4. Trouble getting your breath. 5. Sweating. 6. Loose bowel movements. 7. Hot or cold spells. 8. Frequent urination. 9. Nervousness or shakiness inside. 10. Sudden fright for no apparent reason. 11. Bad dreams. 12. Feeling tense and keyed up. 13. Trembling.

C. Secondary symptoms

1. Having to ask others what you should do. 2. Bad thoughts that stay on your mind. 3. Having to repeat the same actions — such as touching, counting, hand washing. 4. Having to check and double check what you do. 5. Having to avoid certain things or places or activities because they frighten you. 6. Your mind going blank. 7. Weakness in one part of your body. 8. Numbness or tingling in certain parts of your body. 9. Feeling that people were watching or talking about you. 10. Feeling others are too critical of you.

D. Overlapping symptoms

1. Worrying or stewing about things. 2. Trouble concentrating. 3. Difficulty in making decisions. 4. Trouble remembering things. 5. Feeling bothered by the presence of other people. 6. A lump in your throat. 7. Loneliness. 8. Feeling others don't understand or are unsympathetic. 9. Headaches. 10. Pains in the heart or chest. 11. Sleepiness during the day. 12. Twitching of the face or body.

E. Miscellaneous symptoms

1. Feeling annoyed or irritated. 2. Your 'feelings' being easily hurt. 3. Nausea or upset stomach. 4. Feeling confused. 5. Strange thoughts or fears. 6. Soreness of your muscles. 7. Poor coordination. 8. Ringing in the ears.

F. Reject symptoms

1. Dryness of the mouth. 2. Blurred or double vision. 3. Gain in weight. 4. Skin rashes or hives. 5. Itching. 6. Painful urination.

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