Predicting the Relief of Anxiety With Meprobamate

An Attempt at Replication

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Nonpharmacologic factors affecting anxiety relief were compared in two independent samples of psychoneurotic patients treated four or six weeks with meprobamate or placebo. Patient reports of anxiety relief were analyzed with respect to medication, some 20 characteristics of patient and treatment, and the interaction of medication with each characteristic. The results indicate that anxious neurotic outpatients who are black and better educated are likely to respond best to the act of pill-taking in general, whereas the specific pharmacologic effect of meprobamate is likely to be most helpful with patients who are older and less enthusiastic about pill-taking. Patients taking meprobamate improved more in one sample, whereas patients taking placebo improved more in the second sample. The effect of more experienced therapists in the second sample probably washed out the effect of meprobamate in that sample.

ACCORDING to Hollister,[1] studies of drug effects in psychoneurotic anxiety states require greater methodologic elegance and refinement than similar studies in more serious illnesses. Research directed toward identifying the characteristics of responders to antianxiety drugs, particularly when supported by replication, is a promising refinement and one to which we have devoted our efforts for some years.

In a previous communication,[2] we reported an analysis of anxiety relief among anxious psychoneurotic outpatients designed to identify characteristics of the patient and

the treatment situation associated with a favorable response to meprobamate. The present report concerns parallel analyses of anxiety relief in the original sample and in an independent sample of psychoneurotic outpatients treated under comparable, though by no means identical, conditions.

Method

Study I.—In a large, collaborative study[3] conducted at three different outpatient clinics, 138 psychoneurotic outpatients manifesting anxiety were treated for six weeks with medication and brief, supportive interviews every two weeks with a psychiatric resident. The patients were assigned at random to four treatment conditions (2×2) composed of: (1) meprobamate 400 mg, four times a day, vs an identical placebo in a double-blind arrangement and (2) a doctor trained to express an enthusiastic attitude toward the medication vs a doctor trained to express a skeptical attitude toward the medication.

The patient reported his symptomatic condition before each interview by means of several ratings, including a checklist of 64 common symptoms. The patient rated each complaint on a 4-point scale of intensity. Five symptom clusters representing anxiety, depression, anger, compulsive symptoms, and phobic symptoms were selected from the 64 symptoms on the checklist by consensus of at least 14 of 20 psychiatrists. The remaining symptoms were grouped in an "unclassified" cluster. Scores for each cluster were computed by summing the ratings for the individual symptoms composing the cluster.[4]

The criterion in the analysis was the change in the patient's report of distress at the end of the six weeks of treatment on the cluster of anxiety symptoms, listed in Table 1. The independent variables in the analysis included drug, doctor's attitude, and 20 other characteristics of the patient and the treatment situation. All patients with complete data on all characteristics (N = 107) entered into the analysis.

The analysis was performed by means of a multiple covariance procedure programmed for the IBM 7094.[5]

This procedure estimates the simultaneous independent effects of several variables, including both quantitative data, such as age, and qualitative (classification) data, such as marital status. It also allows for a disproportionate distribution of subjects among categories in classification data. The procedure offers the option of searching set-wise a set or pool of independent variables for the subset which best describes the change in the dependent variable. This option selects only the most important of several highly correlated variables. The method combines, in effect, the functions of analysis of variance, analysis of covariance, and multiple regression analysis in a form sufficiently flexible to cope with many problems in the statistical evaluation of quantitative observations in real-life situations.

The analysis in this case consisted of two parts: (1) a nonsearch analysis of the change in the patient's anxiety score with respect to the complete pool of independent variables and (2) a search of the pool for the most important subset of independent variables.

Study II.—As part of another large collaborative study[6] in the same three outpatient clinics, 110 psychoneurotic outpatients manifesting anxiety were treated for four weeks with medication and brief, supportive interviews every two weeks with a trained, practicing psychiatrist. The patients were assigned at random to four treatment conditions (2×2) composed of: (1) meprobamate 400 mg, four times a day, vs an identical placebo in a double-blind arrangement and (2) a doctor selected for his enthusiastic attitude toward medication vs a doctor selected for his neutral attitude toward medication.[7] The patient's perception of the psychiatrist's warmth, however, was a stronger determinant of relief than the original classification of psychiatrist's attitude. Warmth was measured immediately after the first study interview by means of a questionnaire containing 27 words or phrases describing the psychiatrist, each rated by the patient on a 4-point scale. The warmth score was computed by summing the scores on 21 selected items from the questionnaire, such as "friendly, patient, encouraging, likes me as a person."[6]

The patient reported his symptomatic condition before each interview

as in study I. Symptom cluster scores also were computed in a similar way.

The analysis of the data followed the same pattern as in Study I, with nonsearch and search parts. The criterion was the change in anxiety symptom cluster score at the end of the four weeks of treatment. The independent variables in the analysis included drug, warmth, and 18 other characteristics of the patient and the treatment situation. All patients with complete data on all characteristics (N = 97) entered into the analysis.

Table 2 shows some demographic characteristics of the patients in both studies. They are remarkably similar. Although education, prognosis, and the doctor's liking of the patient were measured somewhat differently in the two studies and are not shown in the table, the two patient samples also appeared to be quite comparable in these respects.

Two substantial improvements were made in the computer program after the analysis of study I was published.[2] In addition, certain highly correlated variables in the published analysis, particularly the initial scores on symptom clusters other than anxiety, were omitted from the pool for the present analysis. For comparison, study I as well as study II were analyzed with the improved procedure, and both results are set out in full below.

Results

The nonsearch multiple covariance analysis in study I revealed a multiple correlation of $R = 0.82$ between the change in anxiety score and the complete pool of independent variables. The full set of variables, then, accounted for about 67% of the variation in the criterion. The overall F-ratio was 2.281, with $P < 0.005$. These results indicated that the variables in the pool made an important contribution to the change observed in the patient's anxiety level after treatment in study I.

The nonsearch multiple covariance analysis in study II revealed a multiple correlation of $R = 0.85$ between the change in anxiety score and the complete pool of indepen-

dent variables. In this case, then, the full set of variables accounted for about 72% of the variation in the criterion. The overall F-ratio was 3.481, with $P < 0.001$. These results indicated that the variables in the pool made an important contribution to the change observed in the patient's anxiety level after treatment in study II, as in study I.

The stepwise search of the pool of independent variables in study I and in study II is summarized in Table 3. On the left, the table lists all the characteristics of the patient and the treatment included in the pool of independent variables. Characteristics that were not available for analysis in one or the other study are designated by a dash in the appropriate column on the right of the table.

Characteristics selected as important by the search procedure are designated by M or I under the appropriate study heading, I or II, in the columns on the right. M (main effect) opposite a characteristic indicates that the characteristic had an effect on anxiety relief irrespective of the patient's medication. I (interaction effect) opposite a characteristic indicates that the characteristic had an effect on anxiety relief contingent on the patient's medication or, conversely, that the medication had an effect contingent on the characteristic in question. Neither the F-ratio nor the percent variation accounted for by each characteristic is given; since their interpretation is uncertain under these circumstances, these statistics would promote a misleading sense of precision about the results.

Nine characteristics in study I and 14 in study II, including study medication, were important in accounting for the relief of anxiety. Six characteristics were selected as important in *both* studies: (1) race, (2) education, (3) age, (4) patient's initial attitude toward treatment, as rated by the psychiatrist on a 5-point scale after the

first interview, (5) initial anxiety cluster score, and (6) medication.

Tables 4 and 5 show the adjusted mean relief of anxiety, as measured by the symptom checklist, associated with each of the independent variables selected as important by the search procedure in study I and in study II. In the case of a quantitative variable, such as age, the values given for anxiety relief are those associated with the highest and lowest observed values of the independent variable. Relief scores centered between the two medication columns indicate that there were no significant differences contingent upon medication.

The results for the first five replicated characteristics corresponded closely in the two studies. One group of characteristics was associated with relief of anxiety, irrespective of medication. Black patients, for example, experienced more relief than white patients. More educated patients experienced more relief than less educated patients.

Another group of characteristics was associated with different amounts of relief with the two medications. Older patients, for example, experienced more relief with meprobamate than with placebo, whereas the reverse was true of younger people. Patients who accepted the treatment regimen reluctantly, as perceived by the psychiatrist, experienced more relief with meprobamate than with placebo, whereas patients who accepted the treatment eagerly experienced more relief with placebo.

Finally, in study II, patients with higher initial levels of anxiety experienced more relief with placebo than with meprobamate, whereas patients with low initial levels experienced more relief with meprobamate. This result differed somewhat from the result in study I, where patients experienced more relief with meprobamate irrespective of their initial level of anxiety. In both studies, the plots of relief against initial level of anxiety yielded lines

Table 1.—Anxiety Symptoms

Nervousness or shakiness inside
Faintness or dizziness
Sweating
Trembling
Suddenly scared for no reason
Feeling fearful
Heart pounding or racing
Trouble getting your breath
Hot or cold spells
A lump in your throat
Feeling tense or keyed up

Table 2.—Characteristics of Patients in Two Studies

		Study	
Characteristic		I(N=107)	II(N=97)
Mean age		32.98	32.08
Sex			
Male		38	33
Female		69	64
Race			
White		44	41
Negro		63	56
Marital status			
Single		31	17
Married & widowed		56	59
Separated & divorced		20	21
Previous outpatient admission			
Yes		73	64
No		34	33
Duration of illness			
6 months or less		28	26
Over 6 months		79	71
Previously Treated with Psychotropic Drugs			
Yes		83	79
No		24	18
Patient's treatment goal			
Psychological readjustment		23	23
Relief of psychological symptoms		41	53
Relief of somatic symptoms		29	19
Other		14	2
Off drugs during past week (4 days in Study II)			
Yes		75	83
No		32	14
Patient's mean initial attitude toward treatment (very eager = 1, very reluctant = 5)		2.65	2.52
Mean weight		143.61	147.85
Initial mean symptom distress score, anxiety (range 0-33)		11.78	12.00
Study medication:			
Meprobamate		53	48
Placebo		54	49
Previous OPD admission X previous drug treatment:			
Yes	Yes	54	52
Yes	No	19	12
No	Yes	29	27
No	No	5	6

with positive slopes in both medication conditions. In study II, the placebo line had a steeper slope than the meprobamate line, whereas the slopes of both lines in study I were the same and intermediate between the slopes in study II. The Figure shows these relations.

The overall effect of meprobamate in the two studies clearly differed, unlike the effects of the other variables. In study I, patients experienced more relief with meprobamate than with placebo, whereas in study II, the reverse was true.

Comment

In a general way, the results of study II confirm the results of study I: The complete pool of characteristics of the patient and the treatment situation accounted for a large and significant proportion of the change observed in the patient's anxiety level.

The replication of the most important individual characteristics of the patient and the treatment situation, as selected from the complete pool by the search procedure, is not as satisfactory as the overall result. Fundamental to a consideration of the specific discrepancies in the two analyses is the notorious instability of the detailed results of analyses based on the multiple regression model using a set of independent variables with moderate correlations that are subject to change

from one sample to another. In the present case, for example, marital status was selected as a variable important in relation to relief in study I, but not in study II. In study II, however, marital status was related to age, previous outpatient admission, patient's attitude toward treatment, and prognosis—all selected as variables important

in relation to relief.

The instability of the results obtained by this analytic method is likely to become most apparent under some of the conditions that obtain in the present comparison between study I and study II: (1) small sample size, ranging around 100 in each study, especially in the face of rather broad criteria for

Table 3.—Predictors of Anxiety Relief in Two Studies

Characteristic	Study I	Study II
Age	I	I
Sex		M
Race	M	M
Marital status	I	
Education	M	M
Previous outpatient admission		I
Duration of illness		I
Previously treated with psychotropic drugs		
Patient's treatment goal	M	
Off drugs during past week		
Patient's initial attitude toward treatment	I	I
Prognosis		I
Weight in pounds	I	
Initial symptom distress score: anxiety	M	MI
Study medication	M	M
Doctor's role ("therapeutic" vs "experimental")		—
Doctor's warmth as perceived by patient	—	I
Doctor's comfort with patient		—
Doctor likes patient		M
Doctor's attitude toward drug therapy (Mason-Sachs)		—
Doctor's attitude toward drug therapy (MacAndrew-Rosen)	—	
Doctor's F Scale score		
Doctor's experience (senior faculty)	—	I
Doctor's social class index (family of origin)		—
6 × 8		M

* M, main effect; I, interaction effect (see text).

selecting patients, coupled with other competing needs for similar patients in the participating clinics. (2) differences in the assortment of characteristics included in the pool of independent variables in the two studies, and (3) gross differences in the drug effect in the two studies. In study I, meprobamate clearly was an effective drug on the whole; whereas in study II, meprobamate on the whole was ineffective.

A review of the features affecting the analysis in similar studies predicting the response of schizophrenic patients to pharmacotherapies,[8,9] where the replication of individual predictors has been somewhat more successful, is informative: (1) Sample sizes often were two to four times as large. (2) Independent variables in the pool were identical across the studies compared. In most cases, the predictors were relatively few in number and were limited to relatively independent (factored) dimensions of symptomatology. (3) The medications were clearly and consistently effective major tranquilizers. Even so, replication of pre-

dictors was limited.[10]

Considering the circumstances of the present comparison between study I and study II, the repeated identification of five patient characteristics is of interest. These results indicate that race, education, age, initial attitude toward treatment, and initial level of anxiety should be taken into account in treating psychoneurotic outpatients for the relief of anxiety with minor tranquilizers and supportive interviews.

In these studies, black patients improved more than white patients, irrespective of medication. Race was not related to the usual indices of social class in study I and was related only moderately in study II. This finding strengthens the earlier suggestion[2] that the observed effect of race depends partly upon more specific subcultural characteristics of the races, rather than upon social class differences alone.

Education, a prime indicator of socioeconomic level, related to improvement independently of race: more educated patients improved more. This result is in accord with the findings of Rickels et al,[11] showing that patients of higher socioeconomic levels improve more. Their group also found that differential drug-placebo responses with sedative drugs were more striking in patients of higher social class, whereas the present work indicates a consistent effect of education without respect to medication.

More interesting, perhaps, are those characteristics which affect the differential response to active drug and placebo. In the present studies, for example, older patients improved more with meprobamate, whereas younger patients improved more with placebo. The work of Rickels and Cattell[12] suggests a similar age effect. In their study of two groups of patients, they found a greater meprobamate-placebo contrast in the older group. However, their two groups also differed in a number of other respects.

The patient's initial attitude to-

ward the treatment offered, ie, a medication, also influenced the differential response to meprobamate and placebo in the present two studies. Patients who reluctantly accepted the treatment improved more with meprobamate, whereas patients who eagerly accepted the treatment improved more with placebo. These results again amplify the work of Rickels et al,[11] whose higher social class patients less often expected drug treatment, but showed a greater differential response to meprobamate and placebo.

The present results suggest that a number of specific characteristics usually associated with socioeconomic status may make relatively independent contributions to differential responses to medication. These specific characteristics may be especially worth considering in mobile subcultures, such as the emerging black middle class, where the commonly accepted indices of social class may not reflect the social structure in all its dimensions.

An interesting question is whether these patient characteristics affect the meprobamate-placebo differential primarily through shifts in the drug response or in the placebo response. One might speculate, for example, that a patient who eagerly accepts treatment with a medication would experience a strong placebo effect. The present studies, however, suggest that age and initial attitude affect drug and placebo responses about equally and in opposite directions, although the two studies differ in details of the responses. Other studies[13] have yielded still different results. The methodologic precision needed to achieve stable estimates of absolute treatment responses in independent samples apparently is not currently available.

The observed effect of the initial level of anxiety upon change is well known as the "law of initial value."[14] The results in study II are interesting in this respect, since they suggest that initial level had

less effect in patients taking meprobamate than in patients taking placebo. The fact that highly anxious patients improved more with placebo than with meprobamate is particularly remarkable. These results, however, correspond closely to those of McNair et al.[15] They found further that (1) the effects of initial level with chlordiazepoxide and with placebo were parallel and (2) meprobamate was a relatively ineffective medication and chlordiazepoxide was a relatively effective medication. These findings were confirmed

in another part of study II reported in detail elsewhere.[6]

The differing effects of initial level revealed by these data could be related to (1) qualitative differences between meprobamate and chlordiazepoxide or (2) quantitative differences in their common tranquilizing effect. The parallel effects of initial level with meprobamate and with placebo in study I, where meprobamate was an effective tranquilizer, supports the second interpretation. This constellation of findings supports a general proposi-

Table 4.—Adjusted Mean SCI Anxiety Relief in Relation to Medication and Patient Characteristics in Study I

Patient Characteristic	Medication	
	Meprobamate	Placebo
Age		
Old (59 years)	6.60	—0.36
Young (19 years)	2.80	2.86
Race		
White	1.55	
Negro	3.88	
Marital status		
Single	2.72	2.52
Married & widowed	5.49	1.09
Separated & divorced	2.51	2.31
Education		
Less than 5 years (scale 1)	0.08	
Beyond highschool (scale 6)	4.64	
Patient's treatment goal		
Psychological readjustment	1.49	
Relief of psychological symptoms	4.37	
Relief of somatic symptoms	1.59	
Other	3.76	
Patient's initial attitude toward treatment		
Very reluctant (scale 5)	5.17	0.49
Very eager (scale 1)	2.87	3.24
Weight		
Heavy (256 lb)	6.28	—2.86
Light (100 lb)	3.30	3.51
Initial symptom distress score, anxiety		
High (scale 28)	8.32	
Low (scale 1)	—0.66	
Study medication	4.13	1.73

Patient Characteristic		Medication	
		Meprobamate	Placebo
Age			
Old (59 years)		4.41	0.01
Young (18 years)		1.53	5.71
Sex			
Male		2.09	
Female		3.69	
Race			
White		2.41	
Negro		3.68	
Education			
Less than 7 years (scale 7)		0.53	
Graduate or professional training (scale 1)		7.27	
Previous outpatient admission			
Yes		4.43	1.93
No		1.54	4.70
Duration of illness			
6 months or less		4.48	3.55
Over 6 months		1.81	3.83
Patient's initial attitude toward treatment			
Very reluctant (scale 5)		3.94	0.34
Very eager (scale 1)		1.66	5.84
Prognosis			
Marked improvement (scale 4)		5.27	—0.21
No improvement (scale 1)		0.73	6.35
Initial symptom distress score, anxiety			
High (scale 33)		4.80	15.68
Low (scale 0)		1.22	—3.06
Study medication		2.52	3.76
Doctor's warmth as perceived by patient			
High (scale 3.91)		0.86	7.34
Low (scale 1.48)		4.39	—0.26
Doctor likes patient			
Much less than most (scale 5)		0.39	
Much more than most (scale 1)		5.55	
Doctor's experience			
Long (18 years)		1.19	4.37
Short (2 years)		4.84	2.69
Previous OPD admission × previous drug treatment:			
Yes	Yes	4.01	
Yes	No	—0.54	
No	Yes	2.81	
No	No	4.58	

tion suggested by Fisher[16]: interaction between drug and non-drug effects is more likely to occur with a less potent drug. This concept may extend to other forms of treatment as well.

The failure of any doctor characteristic to appear on the list of replicated variables affecting improvement is most unexpected. Such effects are well known[12,17,18] and powerful. Those doctor characteristics selected as important in study II (warmth, experience, and liking the patient) are entirely consonant with earlier work.[18] In study I, however, no doctor characteristic was selected as important. Quite probably this is related to the methodologic problems discussed earlier. In addition, the measurement of doctor characteristics may have been less satisfactory in study I. The learned, verbally conveyed doctor attitudes of study I also may have been less pertinent than the doctor's native attitudes as assessed by the patient in study II.

Finally, these findings may reflect real group differences between the doctors in study I and study II. In study I, the treating doctors were psychiatric residents of roughly similar age and professional inexperience. All were trained to adopt a similar approach to their study patients, except for conveying different attitudes toward the medication. In study II, the treating doctors received no preparatory training and were less homogeneous in background, although much more experienced on the average. Therefore, variation among treating doctors may indeed have been a more important source of variation in relief in study II than in study I.

These observations also may hold a clue to the relative effectiveness of placebo among the more anxious patients of study II. Here, as in the study by McNair et al,[15] the psychotherapeutic effectiveness of highly experienced therapists may have been a more potent factor in relief than the effect of a mild tranquilizer. Under these conditions, the action of a mild tranquilizer may manifest itself primarily through its relatively undesirable side effects.

This view gains support from the data within study II itself. The patients of more experienced therapists improved more with placebo, whereas the patients of less experienced therapists improved more with meprobamate. Patients who perceived their doctor as warm improved more with placebo, whereas patients who perceived their doctor as less warm improved more with
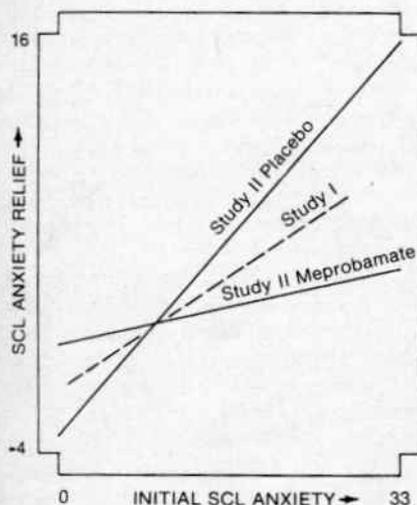
Anxiety relief in relation to initial anxiety level in two studies. Positive relief scores indicate improvement. In study 1, the slopes with meprobamate and placebo were similar. Mean differences between meprobamate and placebo have been statistically removed.

meprobamate. Still more detailed analysis revealed that the strong placebo response was confined specifically to the more anxious patients who perceived their doctor as warm.[6]

The clear identification of other important nonpharmacologic factors in this type of treatment and their relationship to the drug effect can be approached in a number of ways.[2] One strategy is to accumulate data through serial studies, albeit small, employing similar criteria of change and descriptors of the patient and the treatment situation. This strategy is most effective if the serial studies are designed for maximum uniformity in measuring the variables of greatest interest. The characteristics tentatively identified as important in these two studies, but not yet replicated, can serve as a guide to the selection of variables in such a strategy.

For the clinician, these results indicate that anxious neurotic outpatients who are black and better educated are likely to respond best to the act of pill-taking in general, whereas the specific pharmacologic effect of meprobamate is likely to be most helpful with patients who are older and less enthusiastic about pill-taking. The results also suggest strongly that a minor tranquilizer and a relationship with a warm, experienced therapist may be alternate means to the same end, relief of symptoms in the anxious psychoneurotic patient.

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