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Predicting the Relief of Anxiety with Meprobamate

Nondrug factors in the response of psychoneurotic outpatients.

As THE minor tranquilizers gain increasing acceptance in the treatment of ambulatory psychiatric patients, a closer delineation of their clinical effects and the most favorable circumstances for their use become important considerations. This report is one of a series based on a multiclinic, placebo-controlled trial of meprobamate in anxious outpatients, directed toward these questions.

The study was designed originally to determine whether the doctor's expressed attitude toward the prescribed medication influences the effect of the drug (defined as the difference in response to drug and placebo). Psychoneurotic outpatients manifesting anxiety were treated for 6 weeks with medication and brief, supportive interviews every 2 weeks with a psychiatric resident. The patient reported his symptomatic condition before each interview by means of 5 ratings. These ratings included an overall 7-point judgment of change, a checklist of 64 common symptoms, a score based on the patient's presenting (target) complaints, and an adjective checklist for registering anxiety and depression.

The original analyses showed differential treatment effects mainly in the overall judgments of change and the patient's score for presenting complaints on the symptom checklist. The results at one clinic showed the expected interaction between medication and doctor's expressed attitude: with the enthusiastic doctors, patients taking meprobamate improved more than patients taking placebo, whereas with the skeptical doctors, patients taking placebo tended to improve more than patients taking meprobamate. At the other two clinics, however, this interaction was absent or possibly reversed.

In order to determine the more specific effects of the treatment conditions, further analyses were done in terms of the scores for 6 symptom clusters (anxiety, depression, anger-hostility, obsessive-compulsive, phobic, and unclassified) developed on the basis of clinical judgment and 5 factors (neurotic feelings, somatization, performance difficulty, depression, and fear-anxiety) derived empirically from the patients' symptom checklist reports. This procedure provided a much simpler and more direct picture suggesting that meprobamate administered for 6 weeks has an important, specific effect in reducing anxiety and somatic symptoms.

This paper reports more recent analyses of the change in anxiety level among the pa-

Condensation of "Predicting the Relief of Anxiety with Meprobamate" by E. H. Uhlenhuth, M.D., R. S. Lipman, Ph.D., K. Rickels, M.D., S. Fisher, Ph.D., L. Covi, M.D., and L. C. Park, M.D., from *Archives of General Psychiatry, 19:* 619, 1968. Requests for reprints should be addressed to Dr. Uhlenhuth, 950 E. 59th St., Chicago, Ill. 60637.

tients in the study described above, in relation to the medication they received and 29 other characteristics of the patient and the treatment situation, particularly the patient's treating doctor. The present analyses were performed by means of a multiple covariance procedure programmed for the IBM 7094.

The search procedure selected 2 types of variables related to change in anxiety. One type "predicted" relief without respect to medication (main effects). All the variables of this type represented characteristics of the patient. Another type "predicted" different degrees of relief for patients treated with meprobamate and for patients treated with placebo (interaction effects). Some variables of this type represented characteristics of the patient and some represented characteristics of the treating doctor.

Patients with higher initial levels of anxiety experienced more relief. Patients with higher initial scores on a cluster of unclassified symptoms from the checklist, however, experienced less relief. More than ⅓ of these symptoms represent somatic complaints, and the remainder represent mainly interpersonal problems and difficulties in performance. Negro patients experienced more relief than white patients. The patient's treatment goal as judged by the psychiatric consultant after the initial evaluation interview, was related to relief as follows. Patients seeking relief of psychologic symptoms experienced most relief, and patients seeking relief of physical symptoms experienced least relief. Patients seeking psychologic readjustment or other objectives had intermediate degrees of relief.

Married and widowed patients responded relatively more to meprobamate than did single, separated, or divorced patients. Heavier patients responded relatively more to meprobamate than did lighter patients. Patients who were liked less by their doctor responded relatively more to meprobamate than patients who were liked better. Patients treated by a doctor with a more favorable attitude toward drug therapy responded relatively more to meprobamate than did patients treated by a doctor with a less favorable attitude toward drug therapy.

A noteworthy gain in predictive power was achieved by including the additional characteristics of the patient and the treatment situation in the new analyses. The usefulness of the present sample is limited, for instance, by the fact that patients assigned to meprobamate had had shorter illnesses than patients assigned to placebo. Certain characteristics of the patient also are associated with certain characteristics of the doctor.

More detailed consideration of the findings of the search analysis reveals some familiar themes, as well as some that appear new or unexpected. The observed relationship between relief of anxiety and its initial level, as reported by the patient, is a well known feature of biologic and psychologic functions. The greater relief experienced by patients who, according to the psychiatric consultant, sought primarily relief of psychologic symptoms complements the 1st finding from another point of view.

The negative prognostic significance of marked somatic complaining appears from the same 2 viewpoints: the initial score on the cluster of unclassified symptoms on the checklist and the psychiatric consultant's judgment that the patient sought primarily relief of somatic symptoms. Previous controlled studies are in conflict about the significance of somatization. The results of the present analysis differ from all the previous studies, but agree with clinical experience, which suggests that somatic preoccupation ordinarily is a poor prognostic sign without respect to treatment.

Apparently, neither race nor marital status were investigated previously as predic-

tors of response to minor tranquilizers. Since race in this sample was not related to the usual indices of social class, its effect may depend upon more specific cultural or biologic characteristics of the races. The negative prognostic significance of marriage among patients treated with placebo is somewhat unexpected. Surveys indicate that both the incidence and the duration of psychiatric illness is greater among the unmarried. The tendency for married patients to be employed represented a favorable bias. Their low initial depression score represented an unfavorable bias. Although it is difficult to evaluate the net prognostic contribution of these associated variables to marriage in the patients of this sample, the possibility of an overall negative prognostic effect on this basis alone clearly is present.

The greater drug-placebo difference reported here for heavier patients also seems paradoxical in a study employing a fixed dose of medication. The effect of weight, however, was confounded with the effect of sex. Heavier patients more often were men. It has been found that men showed a greater drug-placebo difference in response than did women. In this study, the prognostic significance of weight was most noticeable in patients who received placebo: lighter patients improved more than heavier patients. The combination of heavy weight and placebo treatment was associated with less improvement than the 3 other possible combinations of weight and treatment.

The greater drug-placebo difference reported here for patients who were liked less by their doctor contradicts an earlier finding. This contradiction raises the question whether the doctor's attitude toward the patient in the earlier study may have been confounded, for example, with the doctor's attitude toward the medication. In this analysis, the effect of each of these 2 variables is adjusted for the effect of the other. This adjusted result is more in accord with the findings on the therapist's warmth by the client-centered therapists. The doctor's dislike presumably interferes with his ability to offer warmth and so constitutes a negative factor in treatment. It is not surprising that patients who receive lower levels of an important psychotherapeutic ingredient stand to gain more from medication.

The effectiveness of minor tranquilizers as compared to placebo seemed particularly apparent in the presence of poor prognostic indicators. This impression is supported by the present findings in regard to marital status, weight, and the doctor's attitude toward the patient. (The pharmacologic effect of the drug in the present study does not significantly modify the effects of some other negative prognostic factors, however, such as a high initial level of unclassified symptoms.) From another viewpoint, drug therapy apparently evokes no additional improvement if other prognostic factors are favorable.

The doctor's attitude toward drugs probably does not share the broad prognostic significance of the 3 variables discussed above. The importance of the doctor's attitude toward drug therapy in modifying the patient's observed response to medication has been subject to conflicting reports. These conflicts also may depend in part upon different degrees of confounding between the doctor's attitude toward medication and toward the patient. A methodologic feature of most controlled studies also bears on the interpretation of results on this area. The effect of the observer's attitude toward drugs on the rating process may be confused with the effect of the doctor's attitude toward drugs on the patient's actual response to medication.

Several strategies for coping with interpretation problems suggest themselves. Meanwhile, how can the tentative results currently available help the clinician with his daily problems in selecting "the right drug for the right patient"?

Given the appropriate measures of the characteristics of the patient and the treatment situation presented above (and their availability presents a large "if"), a new patient's responses both to meprobamate and to placebo could be estimated. This method is not yet ready for general clinical application, however, nor would most clinicians find such a mechanical approach attractive.

Only 4 of the predictor variables presented bear on the choice between meprobamate and placebo treatment. In summary the heavier male married patient who is less well liked by his doctor benefits most from the active drug. Conversely, the slim, single woman who is well liked by her doctor benefits least from the active drug, partly because of her strong positive response to placebo. These criteria the clinician can apply readily. Furthermore, the doctor who favors drug therapy is more likely to realize the potential benefit of the medication. Finally, even when all 4 differential predictors are unfavorable to meprobamate, the patient's predicted response to the drug is *no worse* than to placebo. It would be unwise, of course, to generalize these reassuring conclusions beyond the conditions of this study, which deals specifically with psychoneurotic patients, anxiety symptoms, and meprobamate.

950 East 59th Street
Chicago, Illinois

CONSULTANT'S COMMENT

Albert A. Kurland, M.D., *Director of Research, State of Maryland Department of Mental Hygiene, Baltimore.*

This study carried out by a group of highly experienced clinical psychopharmacologists with a good knowledge of statistical methods and computer technology underscores the accomplishments and limitations of utilizing these procedures. A study of this nature also emphasizes the necessity of a careful reading for its implications, as well as for the avoidance of misinterpretations. For the most part, this still depends upon the clinical experience of the reader.

This study focused on the nondrug factors in the response of psychoneurotic patients who had been subjects in a study predicting the relief of anxiety with meprobamate. A difference in the results obtained by research groups utilizing the same research design led to an attempt to clarify the different results obtained by the participating investigators.

The net result of this exhaustive statistical analysis was a series of statements and criteria which may be not unfamiliar to the sensitive clinician. For example, patients seeking relief of psychologic symptoms experienced most relief, and patients seeking relief of physical symptoms experienced least relief. A statement such as, "Patients seeking psychological re-adjustment or other objectives experienced intermediate degrees of relief," raises problems of interpretation, leaving the clinician with little problem as to the extremes on the continuum but uncertainty as to where the boundary lines are for the intermediate states.

Uhlenhuth and his associates emphasized that previous controlled studies are in conflict about the significance of somatization and that the results of the present analysis differ from all the previous studies, but they agree with clinical experiences. This is a rather sweeping statement. Does it infer that somatization preoccupation is ordinarily a poor prognostic sign without respect to treatment? The authors also raise the question as to whether the differences reported between the studies in their different investigative teams may have been caused by the fact that the doctor's attitude toward the patient may have been confounded, for example, with the doctor's attitude toward the medication. Resolution of this difference is brought about through an adjustment of each variable relative to the effect of the other, and the adjusted result is more in accord with the findings on the therapist's warmth by the client-oriented therapist. This is a rather interesting state, and

it would have been helpful to elucidate the means by which this was done.

Formulations emanating from the computer print-out also give rise to uncertainties. "The heavier, male, married patient who is less well liked by his doctor benefits most from the active drug. Conversely, the slim, single woman who is well liked by her doctor benefits least from the active drug, partly because of her strong positive response to placebo," which, the investigators state, can be readily applied by the clinician. In assembling the statistical considerations, the reader is confronted with the statement, "Even when all four differential predictors are unfavorable to meprobamate, the patient's predicted response to the drug is *no worse* than to placebo." How does one interpret this? Does it indicate a lack of sensitivity in the measuring devices which the statistical maneuvers may be compounding? Considering the challenging problems the behavioral scientist is faced with in delineating the end points, the presentation has much to offer for reflection in terms of its methodology.