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(Methodological Implications for Outpatient Drug Evaluation)

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Introduction

The last decade has witnessed the introduction and proliferation of psychotropic medications for the treatment of psychiatric patients. Coupled with this development, there has been a growing awareness of the many factors influencing patient response to medication and increasingly more attention has been given to the role of a variety of nonpharmacological factors which may affect the variable response of patients to psychotropic drugs.[1-6] These factors appear to be particularly important in the treatment of neurotic outpatients where drug effects are less apparent to the treating physician than to his counterpart treating psychotic patients in an inpatient setting. This situation stems in part from the lower efficacy of the medications administered and also from the far greater difficulty in obtaining procedural and life-situation controls in the outpatient sphere.

It now seems clear that in order to provide a reasonably precise evaluation of the efficacy of outpatient medication, it is necessary to introduce a number of specific and purposeful controls — both of an experimental and statistical nature — into the therapeutic trial.

The placebo, for example, has been introduced to keep patients "blind" to the medication they were receiving, thereby controlling for patient "suggestibility," i.e., for the patient's expectation that improvement typically follows the taking of medicine prescribed by a physician. In addition to being identical in appearance and taste to the "trial" medication it has also been suggested that the placebo should mimic the side effects of the drug under investigation[7] to control for the possible patient presumption that such effects and therapeutic effectiveness go hand in hand. It has also been suggested that the identification and elimination of "placebo responders" from the study will increase the sensitivity of the drug trial although, to date, this approach has not been very fruitful.[8]

As a further refinement upon the single-blind procedure, the double-blind technique has been introduced as a control for possible doctor bias — both in the manner in which he interacts with patients receiving different medication and in his role as observer and recorder of therapeutic improvement.[9]

Within the context of the double-blind placebo controlled study, the experimental manipulation of the patient's therapeutic expectations — via the training of doctors to play prescribed roles in order to convey specific levels of confidence toward the medication — represents a controlled attempt to test the critical hypothesis that drug effects may only become apparent under "appropriate" patient sets.[2] Some presumptive but naturalistic evidence along these lines is reported by Uhlenhuth *et al.*[10] Patients treated by an enthusiastic, drug-oriented doctor did reliably better on active drugs than on placebos, whereas similar patients treated by a less enthusiastic doctor did about as well on all medications.

Other studies have examined the hypothesis of "drug-personality" interaction in an attempt to provide a better understanding of the type of patient who may or may not derive benefit from a particular treatment or treatment combination.[11]

Still other attempts to increase the precision of the therapeutic trial have centered upon the identification of patients who deviate from the prescribed dosage regimen either by taking less than a "therapeutic" minimum of the prescribed drug or by taking psychotropic medication other than the study medication.[12,13] In unpublished data from an NIMH-PSC Collaborative Outpatient Project it was found that the magnitude of the drug effect was actually increased by including deviators of this type — a finding which probably reflects a basic difference in the motivation of deviation in drug and placebo treated patients.

Patients who voluntarily terminate treatment before completing the period of treatment specified in the research design represent another source of potential bias in outpatient trials.[14] The therapeutic improvement of patients who remain in treatment (and whose data, therefore, are available for statistical evaluation) may systemically differ, regardless of the treatment. If we assume, for example, that dropouts represent "treatment failures," then a 3:1 ratio of early termination of treatment on placebo to that on drug strongly suggests the drug's efficacy; however, if only improved patients continue in treatment, this leaves us in the statistical quandary of comparing improved drug with improved placebo patients. The situation may, however, be still more complex than this since the direction of bias may vary with the particular treatment condition. For example, drug patients may terminate because they feel themselves "cured" whereas placebo patients may drop out because they are not being helped, and it is conceivable that the relative proportion of drug "cures" and placebo "failures" may be identical. For these reasons, in the present series of NIMH-PSC Collaborative Outpatient Studies, a social worker is routinely employed to obtain follow-up criterion information on all patients who prematurely terminate treatment. Our experience over the last few years suggests the feasibility and desirability of this procedure.

It has also become clear that a very important source of variance determining the post-treatment distress level of the patient is how sick the patient was prior to treatment. This source of variance may be statistically removed by the use of covariance procedures.[6,15]

Still another nonpharmacological factor which would seem related to the variability of patient response associated with drug treatment — significant changes in the life situation of the patient during the course of the trial — has been largely neglected with but one exception known to these authors[3]. The potential relevance of this variable was, however, recognized earlier by Sargent and her colleagues at the Menninger Clinic. They developed a questionnaire to identify patients participating in their psychotherapy projects, for whom "critical" changes in the life situation had occurred, in order to test their hypothesis that "The group whose environment remained relatively stable provides, therefore, an opportunity to relate . . . change more directly to treatment as such."[16] (p. 163)

Thus, it would seem that any sharp increase or decrease in the stress level of the patient undergoing drug treatment could cloud the clinical response of the patient to the medication being evaluated, and, therefore, by eliminating patients (both drug and placebo) where these critical events had occurred, the drug-placebo comparison in the remaining patients should be made more sensitive. One might argue, however, that one function of the medicine being prescribed is, in part, to help the patient deal more effectively with the vicissitudes of the life situation and, therefore, given the presence of placebo controls, that the sensitivity of the trial might actually be decreased by eliminating these patients.

The present paper presents data on this question.

Method

Background, Setting and Patient Sample

The present data were obtained at one of three clinics (The Henry Phipps Psychiatric Clinic of The Johns Hopkins University) participating in a one-week, double-blind placebo controlled evaluation of chlordiazepoxide (Librium). The design of this NIMH-PSC Collaborative Outpatient Study (No. 2) consisted of the q.i.d. administration of Librium (10 mg.), Librium (10 mg.) in combination with atropine (0.5 mg.), atropine (0.5 mg.) and placebo by two doctors (at each clinic) who had been trained to convey a "positive-therapeutic" attitude toward dry mouth to half their patients and a "neutral" attitude to the other half. Results will be published in a separate paper.

Of the 71 patients on whom criterion data were available (80% female, 74% white, mean age 31, 46% and 47%, respectively, classified as Hollingshead and Redlich[17] Class V or Class IV, judged by an experienced intake psychiatrist to be anxious neurotics without marked depression, organic impairment, sociopathy or alcoholism), the treating psychiatrists obtained information on the possible occurrence of significant life situation events in 62 patients.

Procedure

This information was elicited from the patients toward the end of a semi-structured symptom-focused, interview. Briefly, the psychiatrist asked the patients if anything "significant" or "important" had occurred in their life situation during the previous week. With the very few patients who seemed confused by this request, the examples of a marriage or a death in the family were cited by the doctor to aid the patient in understanding the type of information that was being sought. The response of the patient (or lack of response) was then rated by the psychiatrist as falling into one of the following categories of life situation events: (a) No change, (b) Positive change, and (c) Negative change.

Results

We first sought to determine whether the type of life situation event reported was related to differential patient improvement. As shown in Table I, there is a very strong trend to support this hypothesis with patients who report positive events doing very well therapeutically as contrasted with the other patient categories.

In redistributing these cases as a function of whether or not the patient had received the "active" medication (chlordiazepoxide and chlordiazepoxide + atropine) or the "inactive" medication (atropine or placebo), a rather unexpected but important finding came to light; namely, the patient's report of life situation events was reliably related to whether he had received chlordiazepoxide medication during the previous week. In Table II it is clear that a disproportionately higher percentage of chlordiazepoxide-treated patients

TABLE I

*Patient Improvement (above or below the median for that particular treatment cell) as Related to Life Situation Events**

	Life Situation Events		
	None	Negative	Postive
Improvement			
Above Median	15	6	12
Below Median	18	8	3
	33	14	15

$X^2 = 5.95$; $.10 > p > .05$
(X^2 of 5.99 $= p = .05$)

* In this Table and in Table III Target Symptom change scores derived from the pre-post administration of the Johns Hopkins Distress Inventory[20] were used as the dependent criterion of patient improvement. Briefly, these complaints are considered to be among the most salient to the patient insofar as the patient has both indicated them as symptoms on his checklist and also verbally mentioned them to the treating psychiatrist during the initial treatment interview.

were judged as reporting positive changes and a lower proportion as reporting negative changes relative to the non-chlordiazepoxide-treated patients.

Finally, we sought to determine, as originally planned, whether or not the differential therapeutic effectiveness of the chlordiazepoxide medications was sharpened as a function of including or excluding patients reporting positive or negative life situation changes.

As would be anticipated from Table I and Table II, it can be seen in Table III that the magnitude of the mean drug-placebo improvement difference is increased by including all subjects regardless of reported life situation changes.

Discussion

The most interesting finding of the present study was that the patient's report of "significant" life situation events, as classified by the treating psychiatrists, acted as a sensitive criterion of the drugs' effectiveness. Of the several doctor improvement measures employed in the present study (e.g., Global Improvement, Anxiety, Depression, Target Symptoms) life situation events proved the single most sensitive criterion of drug efficacy. The presence of a drug effect as suggested by this criterion is congruent with other patient criterion information obtained in the present study and agrees with previous VA findings of chlordiazepoxide's effectiveness over a one-week period.[18,19]

It seems clear that life situation reports are projective in nature insofar as patients self-select environmental changes that they consider "significant" and, further, that they provide their own individual interpretation of the evaluative sign of these changes. Thus, for example, an argument with the patient's employer might be positively or negatively interpreted by the patient as either "clearing the air" or "further worsening an already bad situation."

By far the largest category of events reported by these patients related to their interactions with other people. In effect, then, these "significant" events reported by the patient probably reflect important aspects of how they perceive and relate to significant people in their environment. This raises the intriguing possibility that life situation reports may serve both as a sensitive criterion of drug efficacy and, perhaps of greater importance, as a *non-symptom-focused* criterion which comes much closer to the kind of dimension that many clinicians would really like to employ as a yard-stick of meaningful therapeutic change. It might be possible to find a more "objective" procedure for obtaining this kind of information by developing a patient self-rating scale incorporating the type of events reported by the present patient sample. This procedure, however, might destroy the more projective aspect of this measure and it would seem desirable, therefore, in any related future research,

TABLE II

Distribution of Life Situation Events as a Function of Medication Received by the Patient

	None	Negative	Positive	
Librium	19	3	10	32
Placebo	14	11	5	30
	33	14	15	62

$X^2 = 6.94$ $p < .05$

TABLE III

Mean Patient Improvement as Related to Medication and Life Situation Events

	None	Negative	Positive	Combined
Librium	.48 (19)*	.18 (3)	.85 (10)	.57 (32)
Placebo	.43 (14)	.46 (11)	.48 (5)	.45 (30)

* The number of patients in each category is shown in parentheses.

to obtain the doctor-elicited information prior to the administration of any more "objective" procedures.

While the finding of the present study should be replicated in other settings with different patient samples, the present data strongly argue against the exclusion of criterion information obtained from patients reporting positive or negative life situation events in comparing the relative improvement of drug with placebo-treated patients. By excluding these patients a serious source of bias would have been introduced into the present therapeutic trial. The study, in fact, suggests that such reports may well provide relevant and sensitive criteria in and of themselves.

Summary

Within the context of a one-week, methodologically focused double-blind placebo-controlled evaluation of chlordiazepoxide, it was found that the *evaluative component* of "significant" life situation events reported by anxious neurotic outpatients ($N = 62$) differed reliably as a function of the administered medication. Patients receiving chlordiazepoxide and chlordiazepoxide combined with atropine were more likely to report positive events and less likely to report negative events than patients receiving active (atropine) or inactive placebo.

These data indicate:

(a) Life situation events may serve as a fairly sensitive and *nonsymptom-focused* criterion of drug efficacy.

(b) The kinds of events reported are particularly intriguing clinically insofar as their projective nature provides insight into the patient's mode of perceiving and relating to "significant others" in his environment.

(c) Drug-placebo comparisons would be made less sensitive rather than more sensitive by excluding patients who report "significant" positive or negative life situation changes during the treatment-evaluation period.

REFERENCES

1. DiMascio, A. and Klerman, G. L.: Experimental human psychopharmacology — the role of non-drug factors. "The Dynamics of Psychiatric Drug Therapy," Sarwer-Foner, G. J. (Editor), p. 56, *Charles C. Thomas,* Springfield, Illinois, 1961.
2. Fisher, S., Cole, J. O., Rickels, K. and Uhlenhuth, E. H.: Drug-set interaction: The effect of expectations on drug response in outpatients *in* Bradley, P.B.B et al., eds. "Neuropsychopharmacology." Amsterdam. *Elsevier,* 1964, pp. 149-156.
3. Kast, E. C. and Loesch, J. A.: Contribution to the methodology of clinical appraisal of drug action. *Psychosomat. Med.*, 11, 228, 1959.
4. Rinkle, M. (Editor): "Specific and Non-Specific Factor in Psychopharmacology" (See chapters by Lasagna, Di Mascio and Rinkel, and Feldman), *Philosophical Library, New* York, 1963.
5. Schachter, S. and Singer, J.: Cognitive, social and physiological determinants of emotional states. *Psychol. Rev.* 69, 379, 1962.
6. Uhlenhuth, E. H. and Park, L. C.: The influence of medication (imipramine) and doctor in relieving depressed psychoneurotic outpatients. *J. Psychiat. Res.*, 2, 101, 1964.
7. Lasagna, L. and Meier P.: Experimental design and statistical problems. "Clinical Evaluation of New Drugs," Waife & Shapiro (Editors), 37, *Hoeber, Inc.*, New York, 1959.
8. Beecher, H. K., Keats, A. S., Mosteller, F. and Lasagna, L.: The effectiveness of oral analgesics and the problem of the placebo "reactors" and "non-reactors." *J. Pharmacol. Expert. Therap.*, 109, 339, 1953.
9. Nash, H.: The double-blind procedure: Rationale and empirical evaluation. *J. Nerv. Ment. Dis.*, 134, 34, 1962.
10. Uhlenhuth, E. H., Canter, A., Neustadt, J. O. and Payson, H. E.: The symptomatic relief of anxiety with meprobamate, phenobarbital and placebo. *Amer. J. Psychiat.*, 115, 905, 1959.
11. Kast. E. C.: Alpha-ethyltryptamine acetate in the treatment of depression, a study of the methodology of drug evaluation. *J. Neuropsychiat.* Suppl. 1, 114, 1961.
12. Joyce, C. R. B.: Patient cooperation and the sensitivity of clinical trials. *J. Chronic Dis.*, 15, 1025, 1962.
13. Park, L. C. and Lipman, R. S.: A comparison of patient dosage deviation reports with pill counts. Submitted for publication.
14. Rickels, K., Boren, R. and Stuart, H. M.: Controlled psychopharmacological research in general practice: A contribution to the methodology of clinical drug evaluation, *J. New Drugs, in press.*

15. Snedecor, G. W.: "Statistical Methods," *Iowa State College Press*, 394-400, 1957.
16. Sargent, Helen D., Modlin, H. C., Faris, M. T. and Voth, H. M. III: Situational variables. *Bull. Menninger Clin.*, 22, 148, 1958.
17. Hollingshead, A. B.: Two factor index of social position. New Haven, 1957.
18. Lorr, M., McNair, D. M. and Weinstein, G. J.: Early effects of chlordiazepoxide (Librium) used with psychotherapy. *J. Psychiat. Res.*, 1, 2577, 1963.
19. McNair, D. M., Goldstein, A. P., Lorr, M., Cibelli, L. A. and Roth, I.: Some effects of chlordiazepoxide and meprobamate with psychiatric outpatients. *Psychopharmacologia*, in press.
20. Frank, J. D., Gliedman, L. H., Imber, S. D. and Nash, E. H.: Why patients leave psychotherapy. *Arch. Neurol & Psychiat.*, 77, 283, 1957.

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