THE JOURNAL OF NERVOUS AND MENTAL DISEASE
Vol. 141, No. 1

Printed in U.S.A.

DOSAGE DEVIATION AND DRUG EFFECTS IN DRUG TRIALS[1]

EBERHARD H. UHLENHUTH, M.D.,[2] LEE C. PARK, M.D.,[3] RONALD S. LIPMAN, PH.D.,[4] KARL RICKELS, M.D.,[5] SEYMOUR FISHER, PH.D.[6] AND JOHN MOCK, M.D.[7]

People, unlike hybrid corn or even domesticated rats, lend themselves only to a relatively limited degree of experimental control when participating as subjects of a study. In clinical studies, for example, which depend upon the experimental manipulation of treatment variables, the question always arises, how are the results of the study affected by subjects who do not participate in the experimental treatments as prescribed? This can become a vexing problem, especially when the rate of nonparticipation differs among experimental treatments. Such an outcome suggests that the patients completing different treatments according to protocol select themselves on the basis of some unrecognized bias.

This problem emerges with special concreteness and clarity in outpatient psychopharmacologic studies when patients do not take the full dose of medication prescribed. Usually results are reported only from the group of patients who complete the study according to protocol (1, 12, 13, 15, 18, 22). Patients who take less than some predetermined minimum dosage are included among "dropouts." Often the investigator compares the characteristics of the dropouts and the completing group. Comparable outcome measures for the dropout group, however, usually are not reported.

Some investigators (3, 4, 7–10, 14, 20) have tried to deal more actively with data from patients who deviate from the prescribed experimental routines. Pointed discussions of this common problem, however, are surprisingly difficult to find (6, 8–10, 20). Presentations of examples that show how alternative treatments of data from dropouts affect the results of a study (8, 10, 20) are especially unusual.

This paper briefly reviews selected findings from two recent psychopharmacologic studies with the above considerations in mind. The data are drawn from placebo-controlled, double-blind drug trials with:

A. One hundred sixty-four anxious, adult psychoneurotic outpatients treated with 1600 mg of meprobamate daily and brief, supportive interviews biweekly for 6 weeks (4). Results are considered at the end of 6 weeks 1) for 138 patients who took at least ¾ of the medication prescribed and 2) for these patients plus 26 patients who deviated from protocol only during the last 2 weeks by taking less than ¾ of the prescribed medication.

B. One hundred ninety anxious, adult psychoneurotic outpatients treated with 30 mg of chlordiazepoxide daily during a single week (11). Results are considered at the end of the week 1) for 160 patients who took at least ¾ of the medication prescribed and 2) for these patients plus 30

[1] This study was supported by Grants MH-K3-18611, MH-06350, MH-04731 and MH-04732 from the National Institute of Mental Health.

[2] Assistant Professor of Psychiatry, the Johns Hopkins University School of Medicine, Baltimore, Maryland 21205.

[3] Assistant Professor of Psychiatry, the Johns Hopkins University School of Medicine, Baltimore, Maryland 21205.

[4] Program Head, Outpatient Studies, Psychopharmacology Service Center, National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland 20014.

[5] Associate Professor of Psychiatry, School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania 19104.

[6] Research Professor and Director, Psychopharmacology Laboratory, Division of Psychiatry, Boston University School of Medicine, Boston, Massachusetts 02108.

[7] Director of the Psychiatric Outpatient Clinic of the Pennsylvania General Hospital, Philadelphia, Pennsylvania 19104.

patients who took less than ¾ of the prescribed medication.

In these studies the amount of medication the patient took was assessed by both 1) asking the patient and 2) counting the capsules he returned. Patients were classified as taking insufficient medication on the basis of evidence from either source of information.

MEASURE OF RESPONSE

The results from a measure of symptomatic distress were chosen for this discussion. At each treatment visit the patient reported his discomfort on a list of 64 to 65 symptoms (5, 17). The patient indicated how much each symptom bothered him during the previous week on a four-point scale: 1) not at all; 2) a little; 3) quite a bit; or 4) extremely. The list was modified slightly to suit the needs of each study. A technician administered the form, and the patient filled it out independently before his interview with the doctor.

A group of "target symptoms" was identified at the patient's first treatment visit. A complaint reported by the patient on his symptom checklist and also by the doctor on a similar checklist that he filled out after his interview with the patient, was defined as a target symptom. The patient's target symptom score at each visit was obtained by summing his responses to this same group of symptoms and dividing the total by the number of target symptoms.

RESULTS

Table 1 presents results from drug trial A after six weeks of treatment. It shows the mean target symptom scores for patients taking meprobamate and for patients taking placebo. These scores are adjusted by covariance for differences between the initial means of the two groups. The entire sample of 164 patients shows a slight gain in the significance of the difference between the treatment means, as compared to the 138 patients who took at least ¾ of the medication prescribed. This gain depends mainly upon the larger number of patients.

Table 2 presents results from drug trial B after one week of treatment. It shows the mean target symptom scores for patients taking chlordiazepoxide and for patients taking placebo. These scores are adjusted by covariance for differences between the initial means of the two groups. The entire sample of 190 patients in this case again shows a slight gain in the significance of the difference between the treatment means, as compared to the 160 patients who took at least ¾ of the medication prescribed.

DISCUSSION

The results presented here indicate that patients taking substantially less than the prescribed amount of medication in a drug trial can show a differential response in symptomatic distress to drug and to placebo like that of patients taking the amount of medication specified in the protocol. Including data from patients who took insufficient medication does not alter the conclusion about the drug's effectiveness drawn from these studies.

Lasky (9) and Rickels (20) provide examples of a very different result. Including patients who terminated treatment early increases the drug-placebo contrast enough to alter the interpretation of the drug's effectiveness.

Joyce reports a more complex outcome in a placebo-controlled trial of two antirheumatic agents (8). In this study, the drug-placebo contrast varies as a complex function of the amount of medication taken, the particular drug, the type of statistical analysis and the criterion measure.

All these findings taken together throw considerable doubt on the assumption that patients who deviate from protocol are simply treatment failures. It seems more likely that patients actively manipulate their treatment for a variety of reasons, in-

TABLE 1

Study A: Patients' Mean Target Symptom Scores after Six Weeks of Treatment

	Meprobamate		Placebo		F	p
	N	Mean*	N	Mean*		
138 patients who took at least ¾ of medication prescribed	72	2.04	66	2.23	4.28	< .05
138 patients above plus 26 patients who took less than ¾ of medication prescribed during weeks 5 and 6	83	2.01	81	2.21	6.26	< .025

* Adjusted by covariance for differences between the initial means of the 2 treatment groups.

TABLE 2

Study B: Patients' Mean Target Symptom Scores after One Week of Treatment

	Chlordiazepoxide		Placebo		F	p
	N	Mean*	N	Mean*		
160 patients who took at least ¾ of medication prescribed	83	2.29	77	2.42	3.18	< .10
160 patients above plus 30 patients who took less than ¾ of medication prescribed	92	2.31	98	2.46	4.68	< .05

* Adjusted by covariance for differences between the initial means of the 2 treatment groups.

cluding both the failure of a less effective treatment and the success of a more effective one (20).

Some workers have attempted to "equalize" statistically (by covariance) the amount of treatment received by all patients in the sample (8, 9). Patients, of course, show great individual differences in their response to the same amount of treatment, for example, drug dose. These idiosyncrasies are determined by impressive variations in crucial individual characteristics such as the biotransformation rates of drugs (2). Patients' deviations from a prescribed treatment probably represent in part their own efforts to select an intensity of treatment according to their individual responsiveness (19). There is some question whether a superimposed statistical adjustment may distort rather than clarify this situation.

The assembled data from the present and from previous (8, 9, 20) studies, when considered together, indicate that conclusions drawn only from patients who complete the prescribed experimental routines may differ unpredictably from conclusions based on the entire sample. These observations underscore the need to consider anew for each study whether the data from completers alone or from the entire sample can answer the questions under investigation more appropriately. This concern arises especially in studies seeking information useful to the clinician in planning treatment with a patient who may or may not complete treatment. Evaluations of treatments usually are more pertinent in terms of the sample selected, rather than in terms of the sample completing.

What practical means can be employed to identify patients who do not follow the

prescribed experimental routines and to obtain complete data, including criterion measures, from them? Methods are being developed for identifying patients who deviate from the prescribed drug dosage (8, 16, 22). Patients may be given a known excess of medication and asked to return any remaining capsules at the next visit for counting. The treating doctor also may inquire routinely about dosage deviation and the use of other medication. Chemical methods of detection, though presently beset by many problems (8), offer possibilities of development in the future.

Complete data are readily available from the patient who deviates from the prescribed treatment routines, as long as he at least continues to come for visits. But what if he also breaks contact with the study? In some studies it is reasonable and feasible to obtain criterion measures when the patient discontinues and to equate these with the final measures of patients completing the study (3, 10, 20). In other situations it may be more appropriate to measure outcome after a specified time interval. It is surprising how often the patient who discontinues treatment visits responds to persistent efforts to obtain criterion measures. A home visit by a skillful social worker often is especially successful in eliciting the patient's cooperation.

More extensive observation of patients who deviate from the prescribed treatment offers opportunities not only for evaluating the results of a treatment more adequately, but also for exploring the factors entering into the deviation. This approach opens another possible avenue toward understanding the process of recovery in connection with the treatment under study.

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