mental health 

Recommendations for Reporting Studies of Psychiatric Drugs

LEADING clinical investigators and editors of scientific journals conferred in Washington, D. C., January 14–15, 1957, on questions in the reporting of psychiatric drug studies. The conference was arranged by the recently established Psychopharmacology Service Center of the National Institute of Mental Health, Public Health Service, in collaboration with the American Psychiatric Association.

Several specific conditions in the field of psychopharmacology prompted the calling of this conference. Among these were (*a*) the great and expanding mass of literature dealing with clinical evaluation of drugs, (*b*) inadequacies of published papers, particularly with reference to details of pertinent information, (*c*) present pressures and anticipated pressures for space in existing journals, and (*d*) need for rapid presentation and exchange of information in order to provide for optimal development of techniques and utilization of research findings.

The major purpose of the conference was to consider ways in which reports of clinical evaluation studies of psychiatric drugs might be made more informative and more useful. The objective was not merely to develop recommendations on how more information might be provided, but rather to consider what kinds of information might help make reports more relevant, more meaningful, and more conducive to improved research efforts. It was not within the scope of the conference to set down details of methodological standardization. The mission was to improve communication in the published literature.

A number of clinical psychiatrists, together with representatives of other pertinent areas (psychology, pharmacology, and internal medicine), were invited to participate. A group of scientific journal editors were also invited to examine the impact of research in psychopharmacology on their publications and consider the implications for the scientific and medical literature of the major effort now under way. Nathan S. Kline represented the American Psychiatric Association.

Each participant served as a member of 1 of 5 committees: Patient Selection and Description, Evaluation of Change, Description of the Treatment Setting, Drug Therapy and Toxicity Reactions, and Editors. The work of these committees constitutes an unusually detailed analysis and delineation of the problems of adequate reporting of clinical drug evaluation studies. Proper focusing and selection in relation to the particular problem under study must remain the decision of the individual investigator.

The reports of four of the committees, with only slight editorial changes, are presented below. The report of the fifth, the Committee of Editors, dealt with a wide variety of problems related to psychopharmacology. Specifically, this committee was concerned with the quality of many papers submitted for publication, the peak point that will be reached in the number of articles dealing with psychopharmacological research, the need for immediate publication of many papers, the usefulness of a new publication, and the role of the Psycho-

pharmacology Service Center as a focus of information and communication. Roy R. Grinker was chairman of the Committee of Editors.

The productive efforts of the committees deserve the commendation of the workers in this field. The committees have attempted to analyze a host of significant variables that are related differentially to any single study on any specific drug on any sample population. They have developed an outline of the factors that any research worker must consider when reporting drug evaluation studies. Clearly, however, the committees have set forth guidelines, not standards of excellence, in their recommendations.

It is our hope that the committees' recommendations will prove useful and meaningful to the wide variety of technical personnel interested in drug evaluation studies and their outcome. In many instances there are direct implications to the nature of experimental designs employed. It is not intended, however, that the nature of such studies be prescribed or standardized. The purpose of the conference was to consider the reports of investigations. In this purpose we hope the conference has been successful.

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Committee on Patient Selection and Description

Harry Freeman, chairman

The committee focused its discussion and recommendations along the lines that seemed most likely to achieve the following two purposes: (*a*) that the reader of a report be adequately informed concerning patient selection and description in a given study and (*b*) that the results of smaller studies might conceivably be pooled for statistical analysis. The first purpose is probably an obvious one, but at this stage of research in drug evaluation it may be useful to spell out in some detail the kinds of information that should be included, or at least considered for inclusion, in all reports.

Factual Information

In order to achieve some comparability in research reporting, the following might be given in descriptions of patients:

Age. It appears that there may be some relation between age and responsivity to drugs.

Sex. Response to drug therapy might vary with sex, and it is therefore desirable to record it.

Ethnic origins. Cultural or genetic patterns might show differences in type or severity of psychosis and in response to drugs.

Religion. This factor should be recorded as an ethnic element because of its possible influence.

Intelligence. This factor should be noted, ideally by a precise psychological evaluation, but at least by clinical impression of the investigator.

Education. The last year of schooling is the most practical measure that can be used.

Socioeconomic factors. The last usual occupation and the average yearly income of the patient or of the household should be listed.

Community from which patient is drawn. Information on the type of community (urban or rural) and its general economic level might be included.

Marital status. A simple statement of marital status is suggested.

Premorbid personality. Information can usually be obtained only from the family and is often inadequate, but, if possible, it might be recorded. The type of personality (inadequate or schizoid, for example) and the degree of stability of the personality and any antisocial trends should be noted.

Family history. Information is ordinarily

limited, but incidence of mental illness in the immediate family could be determined.

Duration of illness. Data are usually inadequate, but some differentiation can be made on the basis of whether the illness is relatively recent or long standing.

Onset of illness. The onset characteristics (sudden or gradual) should be given.

Duration of hospitalization or treatment. A statement of the history of previous hospitalization or of psychiatric treatment should be made.

Description of present mental illness. The following items should be included: psychiatric diagnosis, description of motor activity, degree of socialization, mood disturbances, disturbances in ideational content.

Complications of preexisting organic disease. Although the committee feels that usually these conditions do not affect the therapeutic result, it is suggested that they be noted in view of the possible side effects of the drugs.

Previous treatment. The type of treatment, its intensity, its therapeutic result, and the interval since its discontinuance should be reported.

Physiological data. Where relevant, estimates of physiological functioning should be made prior to therapy. Simple evaluations of body type, height, weight, electroencephalograms, biochemical data, and autonomic responsivity as measured, for example, by the Funkenstein test might be included.

Diagnostic Categories

The committee believes that the tranquilizing drugs will probably be tried in all the diagnostic categories of psychiatric disturbance. Although the American Psychiatric Association system of diagnostic classification has certain inadequacies, it is probably the best nomenclature now available. It might be used to describe the patients in a study.

Other Relevant Variables

Criteria for selection. The method by which patients are selected for study, whether on a random basis, by psychiatric symptomatology, or by diagnosis, should be explicitly described. The desirability of selecting controls by some explicit method was discussed, and such selection was recommended by the majority of the committee.

Patient population. The total number of patients in the hospital and the number of patients of similar diagnostic grouping available for treatment, with some notation as to age and duration of hospitalization, should be mentioned.

Description of professional personnel. For proper evaluation of the observations, it would be desirable to state who selected the subjects for study; for example, senior psychiatrist, psychologist, resident, nurse, or attendant.

Pilot studies. When pilot or exploratory studies are made, these should be described.

We recognize that accumulation of all these data represents an ideal which can be more easily accomplished in studies on small groups than on large ones. Nevertheless, the reporting of information suggested should be the aim. Such data could be easily tabulated on machine punched cards.

Committee on Evaluation of Change

Ivan F. Bennett, chairman

Although changes in individual symptoms do not necessarily imply a change in the basic processes of the mental illness itself, the action of a drug seems to be best described and measured in terms of its effects on specific symptoms. Since drug therapy is aimed at modifying these symptoms, they can be referred to as "target symptoms." The degree of accuracy in reporting changes will depend on how well these target symptoms are defined and described. Quantitative changes in severity and frequency should be considered. There should be a clear distinction between patients in whom there is a change in all target symptoms toward recovery and those in whom there is only a partial change in some or all of them.

Inasmuch as all symptoms are interrelated, the committee believes that the clinician should be the principal interpreter of the whole configuration of symptom changes. Studies pertaining to therapeutic efficacy should therefore

include clinical screening by means of psychiatric evaluation.

Although the ultimate goal of any therapy should be the restitution of the "well" state, limited goals may be the only ones practical. These goals should be clearly specified in the report. They could include such changes as control of undesirable behavior, elimination or alleviation of subjective discomfort, better hospital adjustment, and so on. It should also be recognized that the permanence of the symptomatic effect may have nothing to do with the effect of the drug as such. A result can be reported as excellent, for example, if the patient responds initially to the drug but later relapses.

It is highly desirable to define the criteria for improvement or change and also to state clearly the method used to measure and evaluate such change. The degree of change of the target symptoms must be measured and described in the areas of motor behavior, social functioning, mentation, and mood and affect. It is important to define clearly the specific variables that were measured. Any disturbances that are reportable and that can be considered the target symptoms should be categorized by these symptoms and clearly described. Diagnostic terms or special terminologies peculiar to certain schools of thought or to certain hypothetical preconceptions as to how drugs act do not belong in the description of the target symptoms. It is necessary that all data from which conclusions are drawn be clearly and specifically documented. If certain diagnostic categories alone are used, one might not be able to distingush, for example, between a retarded and an agitated depression or between an aggressive and a withdrawn catatonic schizophrenic patient.

For proper reporting of evaluation of changes, it is necessary to have a stable baseline study on each patient. Because of the well-known day-to-day variations in symptomatology shown by patients, multiple baseline observations should be reported. These, along with all other observations, should include, whenever feasible, not only systematic observations by the physician, but also evaluations by the patient himself, by ward personnel, and, if possible, by the family of the patient and others. These observations and evaluations may be difficult or impossible to make, of course, when acutely ill hospitalized patients or outpatients are being studied.

A study should include a series of observations made at appropriate intervals. The report should specify the time intervals of these observations, in addition to the times at which the pretreatment and post-treatment observations were made.

The report should describe clearly the actual training of personnel (aides, nurses, physicians, psychologists, social workers, and others) in the specific techniques used in the study. For example, the report could tell the amount of instruction given concerning the definitions used in a rating scale and the number of trial runs before actual use of the scale.

Whenever possible, several techniques should be combined and used as a battery because at the present time no technique has been accepted as being sufficiently reliable to stand by itself. When rating scales are used, the test-retest reliability and the interrater reliability should be reported.

The reports should include not only a description of the measuring instruments used, but also the manner in which they were used. One of the following statements might be made: "Assessments of mental condition of the patient were made on the basis of clinical interviews of 30 minutes' average duration conducted by a third-year psychiatric resident." "Assessments of hospital adjustment were made by attendants. Three attendants from the patients' ward, working as a group, rated each patient on the hospital adjustment scale, basing their rating on the behavior exhibited by the patient during the preceding 2-week period." "Assessments of social and recreational adjustment were made from the reports of the chief recreational therapist, who reported on each patient every 2 weeks."

Psychosocial factors which are nonspecific to the drug but which are operative in the process of the psychiatric remission are important and cannot be ignored. Two errors are commonly made in regard to these factors. One is continuously to rediscover and report their operation when in fact they have been recognized in the literature for years. The committee

realizes, however, that most research workers doing drug studies have not paid much attention to psychosocial factors. The other error is to overestimate the importance of psychosocial factors. When the outcome of drug administration on target symptoms is marked, psychosocial factors may play a secondary role. Nevertheless, the appropriate recognition of these factors is essential in the evaluation of changes due to the drugs.

For full understanding of the nature of the change in the patient, the characteristic pharmacological effects of the drugs must be determined by clinical or laboratory procedures, or both. When appropriate, these effects should be reported. Nonpsychological effects, such as sleepiness, Parkinsonian symptoms, or diarrhea, may have a significant bearing on the behavioral or psychopathological features that were measured, and they should therefore be noted in the report. Other pharmacological indicators that may be relevant to such problems as adequacy of dosage should be included if available.

Finally, a research design gains in value if there is a person on the research team who evaluates the patient but who is not a member of the treatment team. Similarly, a research design is improved if the individual who collates the multiple individual observations is not himself a member of the treatment team.

A description of these research team variables is therefore useful in a drug evaluation report.

Committee on Description of the Treatment Setting

Jay L. Hoffman, chairman

Patient behavior is a response not only to the drug which is administered, but also to the total milieu in which the experimental design is established and the experiment carried out. Therefore, the committee believes that descriptive data relative to the setting is essential to appraisal of psychopharmacological research and its validity by the reader.

We have listed a number of items that in the aggregate serve to describe the setting in which drug evaluation studies are conducted. We do not expect that the investigator will slavishly adhere to this list. Rather, we hope that he will select those items that are most closely applicable to the circumstances in which his study was carried out, or which can be described within the space he is willing to allot to this phase of his report.

In selecting these items we restricted ourselves to types of data which could be expected to be available to most investigators without onerous or expensive effort. Our inclusion of the listed items does not necessarily signify that they have proved relevance to those factors that are significant in the evaluation of a therapeutic agent. Admittedly, we are here expressing personal biases, but these biases are shared by many of our colleagues. We hope that recording these items in a succession of studies will stimulate the further investigation of the value and meaning of these factors per se.

It has been pointed out that consideration of any large number of items will take more space than most editors will permit. We are not certain that this is so if the items are chosen with some discrimination and if the writer has learned the art of brevity. At any rate, such descriptions need to be repeated in subsequent papers from the same hospital only to the extent of significant changes in the setting.

It is of some importance to emphasize that the report writer should be concerned not only with a description of the setting as it was at the beginning of the study, but also with any alterations in the setting introduced by the investigator or by circumstances after the study was begun.

We have categorized about 20 items under 3 headings. Initially, we had a fourth category, attitudes. We soon found that almost every item we considered reflected attitudes of staff, administration, patients, or community. We would expect, however, that attitudes as such of both staff and patient would be mentioned when such data are available to the investigator. We also found that with most items we were concerned not only with a description of that item for the hospital as a whole, but also for the unit in which the study

was carried out if that was not the entire hospital. These modifications apply to all items that follow.

We appreciate that the list we offer is not complete or final. Further experience will probably indicate the need for additions, deletions, or modifications.

Structure of the hospital

1. Size of hospital and of research unit; percentage by which average daily population varies from "normal" bed capacity.
2. Location of hospital; accessibility to visitors.
3. Type of hospital: Federal, State, city, county, or private; general or specialized psychiatric.
4. Architectural characteristics; for example, cottage type or skyscraper.
5. Physical characteristics of wards and furnishings: type of furniture, presence of color, and decorations; accessibility of wards to grounds; number of beds per room or dormitory.
6. Per diem expenditure of hospital for total care of patients.
7. Quality and nature of relationships of hospital with community; extent and nature of participation by relatives in hospital program.

Personnel of the hospital

1. Various types of personnel, expressed both as numbers and as percentages of the numbers called for by American Psychiatric Association standards in the several major categories.
2. Predominant therapeutic orientation of psychiatric staff: eclectic, psychoanalytic, custodial care, somatic therapy, or other.
3. Description of major related therapy activities, such as social service, occupational therapy, and clinical psychology.
4. Training programs of hospital, including both identification of such programs and number of trainees in each.
5. Amount of freedom of action granted to nursing and other personnel, and the conditions thereof.
6. Rate of personnel turnover.
7. Social characteristics of ward personnel: drawn from farmer population, from urban population, or from displaced industrial workers, for example.
8. Research orientation of hospital: kinds of research and quantitative measure of hospital resources devoted to the total research program; person or persons responsible for administration of research unit; existence of a research committee.

Patient population

1. Special characteristics of the patients in the hospital: Are admissions "screened" through a psychiatric section of a general hospital? Are certain types of patients (for example, alcoholic or senile patients) excluded? Are patients segregated by color, sex, or religion? What is the socioeconomic status of the patients?
2. Percentage of voluntary admissions.
3. Percentage of privileged patients.
4. Amount of seclusion, restraint, destructiveness, assaults, injuries, incontinence, and the like; elopements and action taken; kinds and amounts of sedatives used.

Committee on Drug Therapy and Toxicity Reactions

Heinz Lehmann, chairman

In the clinical evaluation of psychiatric drugs many of the problems encountered are common to all types of drug therapy. With the rapidly increasing number of drug agents and of clinical reports in psychiatric therapy, new and specific problems have arisen.

We have found it difficult to dissociate completely our considerations from those of the other committees. We have, however, attempted to limit the scope of our discussions to (*a*) routes and modes of drug administration, (*b*) problems concerned with dosage and duration of treatment, and (*c*) drug-induced deviations from the physiological and psychological norms (complications, toxicity reactions, side effects).

It is outside the scope of this report to consider the basic conditions for experimental

evaluation of the drug. We agree unanimously, however, that prior to the initiation of clinical trials, adequate pharmacological and toxicological animal data should be made fully available to the clinical investigator. All studies on drugs with only animal toxicological and pharmacological data available prior to clinical tests should be supplemented with adequate equivalent human data obtained before or during the clinical study. Such data should be reported completely and in detail, although not necessarily in the same report. To this end, means might be found to arrange for closer coordination of pharmacologists and clinical investigators.

Routes of Administration

It is important to state clearly what route of administration is used and for what reason this route is chosen (oral, intramuscular, intravenous, or rectal). Although the oral route is the most widely used and has many advantages, it is not always controllable in some psychiatric conditions. Special precautions should therefore be taken by the investigator to insure actual ingestion of the agent. It should be clearly stated in the report that such precautions have been taken. In addition, the type of oral preparation used (tablets, capsules, or liquid) should be indicated.

In regard to parenteral administration, the presence or absence of local tissue irritation and pain must be noted since these might also have important psychological significance.

Dosage and Duration of Treatment

To permit proper assessment of the multiple problems concerned with dosage schedules, it is recommended (*a*) that specific individual dosages, preferably in metric units, not tablets or ampules, should be reported (for parenteral routes, the concentration and volume, as well as any other constituents injected, should be noted) and (*b*) that the frequency of repeated administration should be clearly indicated (for example, once a day) and the technical reasons be given (for example, duration of action or technical problems of administration).

When possible, the range of effective dosage might be expressed as milligrams of the drug per kilograms of body weight. It is desirable that blood and urine concentrations of drugs be quantitatively determined as soon as methods are available and circumstances permit.

The reasons for the choice of a particular dosage schedule and for the length of treatment are of considerable importance and should be clearly specified. At this stage, a schedule appropriate to the needs, tolerance, and response of the individual patient is generally preferable to a routine fixed schedule. When a fixed schedule is used, the rationale should be stated explicitly.

The report should describe such factors as source of basic information on the drug, onset and duration of the illness (acute, subacute, chronic—clearly defined), and symptomatology and diagnosis.

All members of the committee strongly feel that the complexities of therapeutic objectives cannot yet be reduced to a definitive statement in view of the present incomplete knowledge. Nevertheless, reports should contain a clear statement of the basic concepts governing the investigator's therapeutic goals (symptomatic relief, increased responsiveness to other therapies, specific cure, or social rehabilitation, for example) because these therapeutic goals probably play an important role in regulating dosage and duration of the drug therapy.

Drug-Induced Deviations

All deviations from the physiological and psychological norms occurring during the course of drug therapy should be observed and recorded carefully. Statements regarding the reliability of the observer (physician, nurse, family, or patient), the clinical significance of drug reactions (annoying, or serious, or critical), and the incidence of reaction are desirable. Determination of the true frequency of any side reaction, however, cannot be reliably established until sufficiently large numbers of patients in various settings have been observed for an adequate period of time.

Careful consideration should be given to preexisting diseases, constitutional predispositions, and secondarily induced complications (for example, vitamin deficiency due to interference with appetite and food intake). If other drugs are employed to control disturbing side effects, full details as to type of drug, dosage,

and rationale should be provided since such drugs themselves might be responsible for additional side effects or otherwise interfere with the therapeutic response. It must be emphasized that absence of moderate side effects during treatment with a drug should not be considered too strongly in favor of its clinical desirability.

Medical participation is fundamentally important for the safe conduct of clinical evaluation of drugs, particularly with regard to the clinical assessment of the physiological deviations.

Finally, the committee strongly recommends that in reports of evaluation studies of drugs, extrapolations beyond the observed results, particularly with regard to dosage, range, duration of treatment, and significance of side effects, should be scrupulously avoided. All members agree that ex cathedra editorializing or moralizing would at this stage impede future scientific progress.

Advisory Committee on Community Air Pollution

A National Advisory Committee on Community Air Pollution has been set up by the Public Health Service. The first meeting was held June 17, 1957, in Washington, D. C. The committee was established to review the objectives, policies, and accomplishments of the program established by the Service under a 1955 act of Congress and to make recommendations to the Surgeon General.

In recognition of the primary responsibilities of the States and local governments in controlling air pollution, the Service's basic program has been one of research and technical assistance to areas coping with this problem.

Membership on the committee includes Surgeon General Leroy E. Burney as chairman, and 12 members representing State and local air pollution control agencies, universities, industry, professional associations, and private consulting firms in the field. Ten persons have already accepted membership on the committee; the other two will be named shortly. The 10 are Dr. James P. Dixon, health commissioner of Philadelphia, Pa.; Peter N. Gammelgard, vice president of the Pure Oil Company, Chicago, Ill.; Smith Griswold, director of the Los Angeles County Air Pollution Control District; Benjamin Linsky, air pollution control officer, Bay Area Air Pollution Control District, San Francisco, Calif.; Edward C. Legelin, vice president of the U. S. Steel Co., Chicago, Ill.; Dr. Louis C. McCabe, president of Resources Research, Inc., Washington, D. C.; Dr. Malcolm H. Merrill, director, California State Department of Health, Berkeley; Dr. Norton Nelson, associate professor of industrial medicine, New York University; Dr. Leslie Silverman, Harvard University School of Public Health, Cambridge, Mass.; Dr. Irving R. Tabershaw, associate professor of occupational medicine, Columbia University, New York City.