INADEQUACIES IN THE REPORTING OF CLINICAL DRUG RESEARCH*

BY BURTON S. GLICK, M.D.

In a previous paper,[1] pertaining to the chlorpromazine treatment of chronic, hospitalized schizophrenics, the author discussed the influence of experimental design on clinical outcome. That paper comprised data derived from 34 published reports. The present study is based upon 28 of those reports[2-29] and excludes six, which might arbitrarily be defined as clinical notes, because of their brevity. This study constitutes an attempt to discover certain omissions in the descriptions of these experiments. It should be noted at the outset that some of the papers provided sufficient information to warrant consideration as examples of adequate reporting.

Material and Method

The present paper consists of an appraisal of the descriptions, and to a lesser extent, of the research designs, of 28 published papers (actually 29 separate studies, since one paper describes two different methods) dealing with the chlorpromazine treatment of chronic, hospitalized schizophrenics.[2-29] In all of these studies treatment outcome was described, in accordance with the writer's original criteria for paper selection, in global, clinical terms. Clinical notes, arbitrarily defined as papers of no more than two pages in length, are not considered in this report. The 28 papers that were considered varied in length from three to 40 pages. Fifteen of them came from the United States (14 state hospitals, and one Veterans Administration hospital). Of the remaining 13, eight came from mental hospitals in Great Britain, and one each from Finland, Switzerland, Greece, Australia and Norway.

The number of schizophrenic patients seen in these studies ranged from 16 to 1,091. Many of the accounts indicated that other drugs (including placebos) were tested besides chlorpromazine. The degree of illness for the entire series ranged from moderately to severely ill, with a marked preponderance of the latter. A great many of the patients had been refractory to previous somatic therapies of all types, including ECT, insulin treatment and psychosurgery.

*From the Psychopharmacology Research Unit, Department of Psychiatry, New York University School of Medicine, New York 16, N. Y. This research was supported by U. S. P. H. Grant No. MYP4669.

Of the 29 studies, 11 made use of the double-blind technique. All of the double-blind investigations were placebo-controlled, but only two of the 18 single-blind studies were thus controlled (χ^2=18.37, $p<.001$).

In each study, the writer was concerned with the following categories of data: extent of blindness; nature of the controls; dosage of chlorpromazine administration; duration of chlorpromazine treatment; duration of hospitalization and illness; severity of illness, and patient-types; definition of criteria of improvement; identity of the evaluating personnel; standard laboratory procedures; patient-interview or patient-observation schedules; extent of concurrent therapies; and, consideration of side effects.

Data

Extent of Blindness

All but one of the 28 papers indicated directly, or seemed to permit the inference of, conditions of blindness; i.e., whether single-blind (medication known to investigators but not to patients) or double-blind (medication known neither to investigators nor patients). However, a strong word of caution is in order here. It is assumed (none of the papers in question offers definite information on this point) that the 18 single-blind studies were truly such, but it is suspected that in not a few instances they were advertently or inadvertently nonblind, the patients knowing the nature, and even the name, of the drug they were receiving. It might conceivably make a considerable difference in clinical results if patients had this information and used it as a basis for biased therapeutic self-expectancy. There is a necessity for stating clearly the attempted methodological extent of blindness and for estimating relative success in attaining it. Two of the studies were apparently only partially double-blind, the identity of the drug being known to some of the observers but not to others.

Nature of the Controls

Here the writer is interested in statements or permissible inferences concerning the kinds of control grouping used; that is, whether placebo-controlled (own-control or separate-group control) or non-placebo-controlled (own-control or separate-group control).

All of the 11 double-blind studies were placebo-controlled. Two of them used both own-control and separate-group control methods. The final figures for these studies show nine instances of own-control and four of separate-group control.

In the 18 single-blind studies, the two which were placebo-controlled used the own-control technique. Of the remaining 16, which were non-placebo-controlled, 15 used the own-control method, and one employed a separate-group control. Concerning the 15 instances of single-blind, non-placebo, own-control, the quality of control in 14 of them is questionable. Any idea one might entertain that the patients in these studies were "untreated" before administration of the test drug can be presumptive only. That is, these papers did not indicate up to what point, if any, other medication had been given prior to the onset of test drug administration. Thus, the extent of the drying-out period and therefore the validity of base-line measures are unknown to the readers of these reports.

One notes in the over-all figures a marked preference for the own-control over the separate-group-control method (26 as compared to five cases).

Dosage of Chlorpromazine Administration

In 17 of the 29 studies the mean daily milligram dose of chlorpromazine was stated directly or could be calculated with a fair degree of accuracy by making use of the dosage schedule included in the report. An additional 10 studies, which did not give, nor permit the calculation of, mean dosage values, indicated the maximum dose used. Unfortunately these values could not be equated in any sensible manner with the mean values. Of the two remaining papers, one gave the "average maximum" dose and the other gave no indication of dosage whatever.

Duration of Chlorpromazine Treatment

Two of the 29 studies did not indicate in any manner the duration of therapy. One of these was the paper which had given no dosage data. Thus 27 studies were left wherein there was some notation of duration. However, in four of these, duration was mentioned in such a vague or ambiguous way as to be unsuitable for comparative purposes. For instance, the duration of treatment might be given as "at least two months," or, "from one to several months."

Duration of Hospitalization and Illness

There seems to have been a certain reluctance toward presenting information on both duration of current hospitalization and duration of illness. This was done in only two papers, the remainder being divided into 15 papers that indicated in some way the duration of hospitalization, 10 that described the duration of illness, and one that made no statement about either. The over-all figures, therefore, show that 27 of the 29 studies mentioned one or the other, or both, of these indices.

Of the 17 papers that described duration of hospitalization 12 provided, or allowed for the calculation of, mean figures, and two permitted estimation of the mode, a not particularly useful comparative measure here. The remaining three papers used such unsatisfactory phrases as: "long history of hospitalization," "the majority of patients hospitalized seven years or more," and "at least six months."

Of the 12 papers that described duration of illness, five provided, or permitted the calculation of, the mean, and one of the mode. The others, in three instances gave the range, and in the three remaining cases, statements such as: "about 90 per cent ill for at least two years," "73 per cent ill for more than five years," and "two-thirds had a duration of illness of more than five years."

Severity of Illness, and Patient-Types

Even in applying the most liberal standards of judgment to the adequacy of information concerning severity of illness and behavioral or symptomatic types of patients (liberal in this instance signifying acceptability for the writer's purposes where there is some indication of severity of illness without necessarily a specification of patient-types), one finds that 10 of the 28 papers must be categorized as poor or inadequate in this respect. As examples of such descriptive failures there are the following: "chronic cases," "chronic schizophrenics," "chronic in-patient population," and "mentally disturbed." As adequately elucidated examples of severity of illness and patient-type, one sees: "The most deteriorated and apathetic patients were chosen; most were totally unoccupied, withdrawn and unsociable; a few were noisy and destructive"; "chronically nude, incontinent, combative, destructive and noisy," "noisy, confused, agitated, denudative, assaultive, smearing," "inappropriate affect, disorders of association and apathy."

Definition of Criteria of Improvement

Since the writer was interested, in accordance with the original criteria for the selection of papers only in studies which made use of global, clinical assessments of patient progress, all of the papers indicated this factor, and did so by means of the usual "marked," "moderate," "slight," etc., improvement, or by minor variants thereof. However, only 10 of the 28 papers offered any specific definitions of these various categories.

Identity of the Evaluating Personnel

Five of the 28 papers gave no indication as to the evaluating personnel. In these cases one would assume that the author or authors were the raters, but one cannot be sure.

Standard Laboratory Procedures

The routine pathological examinations done on most hospitalized patients at or soon after admission, or at the first sign of new or recurrent physical symptoms, are termed here standard laboratory procedures. Among these would be included complete blood counts, white blood cell counts, urine analyses, liver function tests, BUN's, etc. Nine of the 28 reports gave insufficient or no data regarding the extent of these tests (that is, whether done routinely, p.r.n., or not at all). Here too one would assume that in a state hospital setting (the usual one for the patients in this series), with many patients under study, the usual laboratory tests would be done at least p.r.n., but again one cannot be certain. Therefore, these data are lost for purposes of the study of research designs.

Patient-Interview or Patient-Observation Schedules

It is, of course, important to know the frequency of contact between patient and evaluating staff because each of these meetings may easily assume for both parties the nature of a therapeutic relationship. In addition, the reported incidence of drug treatment benefits, detriments and side reactions may well be a function of such frequency, since a large number of contacts or observations will provide greater opportunity for a more comprehensive and precise study of clinical alterations. On examining the 28 reports one finds the poorly, or not at all, described interview or observation schedules outnumber the adequately described, 15 to 13.

Extent of Concurrent Therapies

There is reason for feeling that a certain amount of reportorial negligence attended the question of the use of concurrent therapies (for example, electric-convulsive, insulin, sedative, soporific, psychotherapeutic, occupational). The use of other drugs or therapeutic techniques with the test drug could conceivably alter treatment outcome to a considerable extent, yet fully 19 of the 28 papers presented no information about this aspect of the problem.

Consideration of Side Effects

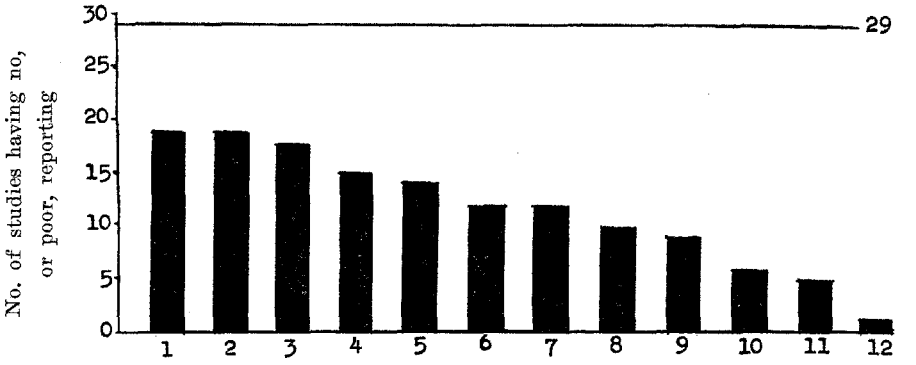
The important area of side effects in clinical drug investigation was noted, to a greater or lesser extent, in almost all of the papers, 25 of the 28. Reasons for the omissions were given in the cases of two of the abstainers. In one case, side reactions were deliberately not studied, in order to maintain blind conditions as much as possible. The other report indicated that the side effects observed were to be the subject of another communication. One may, therefore, rightfully conclude that they were carefully studied during the course of that experiment.

The accompanying diagram presents the results of the survey in graphic form.

Another approach to the situation is to consider the 29 studies individually regarding their relative completeness of reporting in the 12 categories of data. Table 1 indicates the frequency distribution of this approach.

It is rather doubtful if all of the data-categories are of equal importance in the design or the reporting of an experiment, but it is a somewhat subjective matter as to which should be accorded prominence. For operational purposes, the writer is considering them all of equal value, and, for a study to be considered well-reported, he is arbitrarily fixing the required minimum number of adequately reported categories at 9. In this light, 10 (or 34.5 per cent) of the 29 studies may be considered well reported. Nine of these 10 are double-blind studies, and 1 is single-blind. Using the value of 9 as a cut-off point, below which a study may be considered inadequately reported, a 2 x 2 distribution of the entire series (Table 2) reveals that double-blind studies were significantly better reported than single-blind ($\chi^2=14.36$, $p<.001$).

Incidence of Inadequacies in Drug Research Reporting, by Categories of Data
(Based on 29 studies of chlorpromazine-treated, chronic, hospitalized schizophrenics)



Code:

1. Extent of blindness
2. Extent of concurrent therapies
3. Definition of criteria of improvement
4. Patient-interview or patient-observation schedules
5. Nature of the controls
6. Chlorpromazine dosage
7. Duration of hospitalization or illness
8. Severity of illness, and patient-types
9. Standard laboratory procedures
10. Duration of treatment
11. Identity of evaluators
12. Side effects

Table 1. Frequency Distribution of 29 Studies of Chlorpromazine-Treated, Chronic, Hospitalized Schizophrenics Arranged According to Adequacy of Reporting in 12 Data-Categories

No. Categories Adequately Reported	Studies by Categories (N=29)
11	2
10	7
9	1
8	6
7	2
6	1
5	5
4	1
3	3
2	1

Table 2. Relationship Between Extent of Blindness and Adequacy of Reporting in 29 Studies of Chlorpromazine-Treated, Chronic, Hospitalized Schizophrenics

	Single-Blind	Double-Blind	Total
Adequately Reported	1	9	10
Inadequately Reported	17	2	19
Total	18	11	29

χ^2 (Yates Correction)=14.36, $p<.001$

Discussion

The reporting of psychopharmacological research projects and clinical trials involves two areas besides the fundamental one of imparting information to the scientific community. The first, which is perhaps the more obvious and readily appreciated, is extrinsic to the immediate experimental situation and is concerned with the comparative approach (that is, with comparative evaluations between and among studies). It might be termed *inter-experimental.* The second, which is significant in its own right, has to do with inferences concerning design and description, drawn from the account of a study and peculiar to that particular study. It might be called *intra-experimental.* For instance, if the experimenters pay no attention to (and therefore, do not discuss) the factor of the rigorousness of single-blind control, they are ignoring a potentially important variable in treatment outcome. The same may be said in the case of initial non-treatment, own-control studies. If the extent of lack of drug treatment before the administration of the experimental medication is not stated, one has a certain right to assume that this factor may have been not only not reported by the authors, but also may have been ignored by them.

In instances where severity of illness and patient-types are poorly or vaguely described, there is the possibility that the observers paid as little attention to this variable as they did to the reporting of it, and that diverse kinds of patients were grouped together in the treatment process, thus giving a very distorted picture of a drug's therapeutic potential. The issue of the identity of rating personnel assumes importance when one realizes that findings may be entirely different, depending on whether observations are made by trained and experienced psychiatrists or by relatively unsophisticated ward attendants or inexperienced nurses. Certainly this information should be included in an experimental

report. The extensive use of various laboratory procedures, or conversely, their neglect, may also have different meanings for different patients, some of whom may view them as signs of attention and regard, and others who may see in them unwarranted, occasionally painful or frightening, intrusions into their heretofore comfortable and routine mode of life. These varying feelings may then be reflected in the response to the medication under examination and should be noted in an adequate report.

Other instances of derelict intra-experimental description have already been mentioned. Such poor reporting makes one wonder about the possible existence of certain inadequacies and deficiencies in experimental design and control, and tends to make the claimed clinical results suspect.

As for the inter-experimental, comparative approach, it is perhaps sufficient to say that lack of a complete and detailed description of experimental design constitutes a truly destructive element in the field of research on methodology. One would be hard put, for instance, to construct some sort of research design complexity index on the basis of the limited information available in many of the studies under consideration. It is believed that such critiques as the present one will be of some use, if, through consideration of them, future drug studies will be so constructed and reported as to be readily assimilable into the great mass of data that is constantly accruing on the clinical, psychological and physiological effects of psychoactive agents.

Summary

Twenty-eight published papers dealing with the chlorpromazine treatment of chronic, hospitalized schizophrenics were scrutinized for completeness of reporting under the following categories of data: extent of blindness; nature of the controls; dosage of chlorpromazine administration; duration of chlorpromazine treatment; duration of hospitalization and illness; severity of illness, and patient-types; definition of criteria of improvement; identity of evaluating personnel; standard laboratory procedures; patient-interview or patient-observation schedules; extent of concurrent therapies; and, consideration of side effects.

Although some of the studies considered in this paper were adequately reported, the data in a majority of them and in a considerable number of the categories were found wanting. Double-blind

studies were significantly better reported than single-blind studies. The importance of a complete and detailed description of experimental design in order to avoid confusion about significant variables and to facilitate research on methodology was stressed.

New York University School of Medicine
Psychopharmacology Section
Bellevue Hospital Mental Hygiene Clinic
550 First Avenue
New York 16, N. Y.

REFERENCES

1. Glick, B. S., and Margolis, R.: A study of the influence of experimental design on clinical outcome in drug research. Am. J. Psychiat., 118:1087, 1962.
2. Baker, A. A.: Observations on the effect of largactil in psychiatric illness. J. Ment. Sci., 101:175, 1955.
3. Barsa, J. A., and Kline, N. S.: A comparative study of reserpine, chlorpromazine, and combined therapy. A.M.A. Arch. Neurol., 76:90, 1956.
4. Blair, D., and Brady, D. M.: Recent advances in the treatment of schizophrenia: group training and the tranquillizers. J. Ment. Sci., 104:625, 1958.
5. Cares, R. M.; Asrican, E.; Fenichel, M.; Sack, P., and Severino, J.: Therapeutic and toxic effects of chlorpromazine among 3,014 hospitalized cases. Am. J. Psychiat., 114:313, 1957.
6. Dransfield, G. A.: A clinical trial comparing prochlorperazine ("stemetil") with chlorpramazine ("largactil") in the treatment of chronic psychotic patients. J. Ment. Sci., 104:1183, 1958.
7. Feldman, P. E.: A comparative study of various ataractic drugs. Am. J. Psychiat., 113:589, 1957.
8. ——: Clinical evaluation of chlorpromazine therapy for mental illness. J. Clin. and Exper. Psychopathol., 18:1, 1957.
9. Feldman, P. E.; Lacy, B. S.; Walker, A. E., and Garrez, N. J.: A controlled, blind study of effects of thorazine on psychotic behavior. Bull. Menninger Clin., 20:25, 1956.
10. Fleming, B. G., and Currie, J. D. C.: Investigation of a new compound, B. W. 203, and of chlorpromazine in the treatment of psychosis. J. Ment. Sci., 104:749, 1958.
11. Hall, R. A., and Dunlap, D. J.: A study of chlorpromazine: methodology and results with chronic, semi-disturbed schizophrenics. J. N. M. D., 122:301, 1955.
12. Hollister, L. E.; Jones, K. P.; Brownfield, B., and Johnson, F.: Chlorpromazine alone and with reserpine. Calif. Med., 83:218, 1955.
13. Hormia, A.: A comparison between combined reserpine-chlorpromazine and chlorpromazine therapies in psychiatry. Acta Psychiat. Scand., 31:437, 1956.
14. Kielholz, P., and Labhardt, F.: Treatment of mental disorders with chlorpromazine. J. Clin. and Exper. Psychopathol., 17:38, 1956.
15. Kokkoris, P.; Kordas, S.; Nikolopoulos, P., and Yanniris, M.: The results of chlorpromazine treatment with chronic psychoses in dromokaition. J.N.M.D., 125:102, 1957.
16. Kovitz, B.; Carter, J. T., and Addison, W. P.: A comparison of chlorpromazine and reserpine in chronic psychosis. A.M.A. Arch. Neurol., 74:467, 1955.

17. Kurland, A. A.: Chlorpromazine in the treatment of schizophrenia. J.N.M.D. 121: 321, 1955.
18. ——: Comparison of chlorpromazine and resperine in the treatment of schizophrenia. A.M.A. Arch. Neurol., 75:510, 1956.
19. Lomas, J.: Uses of chlorpromazine in mental hospital patients. Brit. Med. J., 1:879, 1955.
20. Morgan, D. R.: Chlorpromazine and reserpine in the treatment of chronic mental illness. Med. J. Austral., 2:57, 1956.
21. Pollack, B.: Preliminary report on 500 patients treated with thorazine at Rochester State Hospital. PSYCHIAT. QUART., 29:439, 1955.
22. Rinaldi, F.; Rudy, L. H., and Himwich, H. E.: Clinical evaluation of azacyclonal, chlorpromazine, and reserpine on a group of chronic psychotic patients. Am. J. Psychiat., 112:678, 1956.
23. Shepherd, M., and Watt, D. C.: A controlled clinical study of chlorpromazine and reserpine in chronic schizophrenia. J. Neurol., Neurosurg., and Psychiat., 19: 232, 1956.
24. Smith, J. A.; Gouldman, C.; Rutherford, A., and Wolford, J.: Comparison of two phenothiazine derivatives and a barbiturate in chronic schizophrenia. A.M.A. Arch. Neurol., 81:97, 1959.
25. Sundby, P., and Lien, J. B.: Prochlorperazine and chlorpromazine, a comparative clinical trial. Acta Psychiat. Scand. 34 (Suppl. 136):82, 1959.
26. Tenenblatt, S. S., and Spagno, A.: A controlled study of chlorpromazine therapy in chronic psychotic patients. J. Clin. and Exper. Psychopathol., 17:81, 1956.
27. Tuteur, W.; Stiller, R., and Whitehill, O.: Treatment of regressed schizophrenics with chlorpromazine, reserpine, and a combination of both drugs. Dis. Nerv. Sys., 18:100, 1957.
28. Vaughan, G. F.; Leiberman, D. M., and Cook, L. C.: Chlorpromazine in psychiatry. Lancet, 1:1083, 1955.
29. Walsh, G. P.; Walton, D., and Block, D. A.: The relative efficacy of "vespral" and chlorpromazine in the treatment of a group of chronic schizophrenic patients. J. Ment. Sci., 105:199, 1959.