FDA-ACNP TASK FORCE ON GUIDELINES FOR THE
EVALUATION OF ANTI-ANXIETY AND ANTI-DEPRESSANT AGENTS

COMMITTEE ON EVALUATING ANTI-DEPRESSANT DRUGS

SEPTEMBER 11, 1972
MINUTES

ATTENDING: Gerald L. Klerman, M.D., Chairman
Jonathan O. Cole, M.D.,
Alberto DiMascio, PhD.
Edgar Grunwaldt, M.D.
Douglas McNair, PhD.
Allen Raskin, PhD. (NIMH)
Barrett Scoville, M.D. (FDA)
Myrna Weissman, MSW
J.R. Wittenborn, PhD.
Eleanor Seaton

INTRODUCTION

The meeting began with a review of the background of the project. Emphasis was placed on the previous NIMH-ACNP project which resulted in the "bluebook" Principles and Problems in Establishing the Efficacy of Psychotropic Agents, edited by Levine Schiele, and Bouthilet and the guidelines for psychoactive drugs developed by FDA with consultation from ACNP and the Pharmaceutical Manufacturers Association (PMA). The overall goals of the project and its long-term implications were discussed.

STATUS OF THE CONTRACT BETWEEN FDA AND ACNP

Dr. Wittenborn reported on the status of the contract between FDA and ACNP, which will define the scope of the project and provide financial support for its activities. The contract has been signed by ACNP but has not yet been signed by FDA. Individuals have been undertaking work for the project in the name of ACNP, and Dr. Wittenborn expected that there would be no difficulties with funding. Members of the Task Force were instructed to submit their travel expenses and related finances to Dr. Wittenborn.

GOALS OF THE PROJECT

Four goals were specified in the contract between FDA and ACNP:

1. To develop minimal standards for defining suitable and appropriate patient populations for clinical trials and appropriate related instruments which would be useful for the selection of samples for these trials.

2. To identify specific methods and instruments for the assessment of change.

3. To develop criteria for defining clinically meaningful change as distinct from statistically significant change.

4. To study the need to improve the training of raters so as to increase the level of reliability.

There was uniform agreement that these goals were of high priority. However, consensus was not reached as to the feasibility of achieving each of these goals. All the participants agreed that the most difficult goal would be that of developing criteria for defining clinically meaningful change as distinct from statistically significant change.

FDA VIEWS

Barrett Scoville, M.D., Deputy Director, FDA Division of Neuropharmacology, attended the meeting and participated actively. In response to questions, he expressed the high expectation of the FDA for the success of this project. He said that the FDA has been pleased with the close liaison with the ACNP in recent years and the free exchange between ACNP members and the staff of the Division of Neuropharmacology

He identified three specific questions about anti-depressants that arise within the overall goals of this project:

1. What rating scales and related techniques are most appropriate for evaluating anti-depressants?

2. What criteria should be employed for subjects entering various studies for anti-depressant drugs? Can there be minimum levels or "cut-off points" for entrance?

3. The issue of clinical versus statistical significance.

THE PROJECT'S FINAL PRODUCT AND ITS AUDIENCES

In response to these introductory discussions, the Committee members discussed the project's ultimate end product and the probable audiences. It was agreed that the report would be aimed at a wide range of audiences but probably in a defined sequence. Obviously, FDA and ACNP members will be the first recipients of the project reports. Pharmaceutical firms and their related investigators will also be an important audience. Ultimately; practicing physicians and the public at large should be reached.

It was uncertain as to whether or not a single report or a series of reports will be developed. At a minimum, a report including a catalog and listing of various scales and other techniques that are valid and reliable will be produced along with a specific discussion of diagnostic criteria and statements concerning training and criteria for determining clinically significant change.

Finally, in the spring of 1973, these general reports will be collated, and carefully worded specific guidelines for use in evaluating IND and NDA submissions will be published. Dr. Grunwaldt, representing the PMA Committee, indicated that these guidelines need to be equally applicable to staff at FDA, investigators, and staffs of pharmaceutical firms.

INVOLVEMENT OF PHARMACEUTICAL FIRMS

The question was raised as to how and when staff from drug companies and investigators should be brought into the work of the committee. It was decided that Dr. Grunwaldt will participate actively in the Committee's work over the next few months. He was invited to communicate the activities of the group to date and the discussions at this meeting to his associates.

Dr. Cole suggested that the ACNP call a meeting in Washington soon after the December meeting in Puerto Rico for general discussion of the material presented at ACNP in order to get reactions and responses from interested investigators, physicians, and pharmaceutical manufacturing firms.

REPORTS ON INDIVIDUAL PROJECTS

Dr. Klerman reviewed the activities of the June, 1972 meeting and indicated that individual members of the Task Force have been active over the summer. Drs. Cole, DiMascio, and McNair and Mrs. Weisman were identified as active in specific areas.

DIAGNOSTIC CRITERIA

Dr. Cole reported on his activities over the summer in developing criteria for diagnostic selection. All agreed that rating scales such as the Beck, Hamilton, and Zung should be reviewed for determining minimal levels of psychopathology for entrance into the studies of anti-depressant drugs.

Dr. Cole said he is reviewing recent controlled studies to ascertain which types of criteria have been utilized. Mention was made of the approach developed by the St. Louis group (Robins, Guze, Feigner, and Winokur). This approach employs what Dr. Klerman called the "Chinese menu approach" to diagnosis, in which necessary criteria, such as level of depression, are joined with a list of secondary criteria. To be included in any study, these patients must have a certain number of symptoms other than mood disturbance in itself. Criteria of intensity of symptoms and their duration were discussed. (Dr. Guze, who is working with the Committee on Anti-Anxiety drugs, developed a report for Dr. Uhlenhuth's Committee and a copy of his memo is attached.)

Dr. Scoville pointed out that in recent NDA submissions, subjects have been included in clinical trials whose level of depressive symptoms was extremely low or non-existent. He reiterated a feeling that some minimal levels of symptoms are necessary for inclusion in the study.

The distinction between symptom and syndrome generated considerable discussion. The recent paper by Simpson in the Archives of General Psychiatry was distributed, and there was brief discussion of the implications of the use of tricyclic drugs on schizophrenics. Simpson reported negative findings in that the tricyclics aggravated the overall clinical picture of the schizophrenic syndrome, even though they may have influenced one or two affective components.

This discussion of syndrome led to a comparison of dimensional versus typological approaches. Dr. Wittenborn discussed the importance of factors such as age, sex, previous history, and personality patterns, which serve as modifiers or qualifiers of prediction response. Dr. Al Raskin related some of the findings of the NIMH Collaborative Depression Study to these ideas. In response to this discussion, Drs. Raskin and Wittenborn agreed to work together on this area to review variables which had been identified as qualifiers, modifiers, or predictors. Dr. Cole welcomed this approach as parallel to his. One of the specific outcomes might be a list of descriptive information which would be collected on all subjects entering into drug trials for possible subsequent analyses as predictors.

INTERVIEW AND HOSPITAL BEHAVIOR

Alberto DiMascio, PhD., has agreed to review various techniques used for the assessment of interview techniques such as the Hamilton, Beck, Wittenborn, and Overall scales. He indicated that he is actively involved in this project and has undertaken literature review and has written to various pharmaceutical firms. He also reported on preliminary efforts to review techniques used for hospital behavior, particularly by nurses. It was agreed that scales such as the NOSIE, which have been developed for hospitalized schizophrenics has limited usefulness for depressives. The scale developed by Weschler in the Massachusetts collaborative study was discussed. Dr. DiMascio will pursue this matter further.

SELF-REPORT FOR SYMPTOMS AND MOOD

Dr. McNair reported that he has reviewed about 100 controlled studies which showed some form of self-report for assessing symptoms and mood. His preliminary conclusion was that these are commonly used techniques and have appeal because they do not require trained professionals or raters. He was confident that meaningful trends will be identified by his efforts during the fall.

SOCIAL ADJUSTMENT BEHAVIOR

Mrs. Weissman gave a detailed report on her survey of the techniques of social adjustment. She was commended by members of the Committee for the thoroughness of her efforts to date and the scope of her endeavors. The question was raised as to the level of functional improvement that might be considered meaningful. It was agreed that assessment of social behavior might not be useful for acute studies, either as outpatients or inpatients, but were highly desirable, if not necessary, for long-term maintenance studies aimed at prevention of relapse and promotion of social adjustment.

COGNITIVE AND PERFORMANCE BEHAVIOR

There was a discussion of various techniques used for testing psychomotor, cognitive, and learning behavior. It was agreed that these would not be pursued at this time since they are not considered direct criteria for the evaluation of efficacy. It was hoped that future research in this area would provide performance measures to complement or even replace subjective or behavior methods.

PSYCHOPHYSIOLOGICAL METHODS

Similar conclusions were reached about the relevance of psychophysiological methods. It was agreed that further research in this area is desirable, using techniques such as muscle tension, salivation, and pulse rate. However, it was not felt that these techniques currently have reached the stage where they can be utilized as criteria for significant change.

CLINICALLY MEANINGFUL VERSUS STATISTICALLY SIGNIFICANT CHANGE

The Committee discussed in some detail the issue raised by Dr. Gardner distinguishing between clinical and statistical significance. There was feeling that the "state of the art" has not yet reached the point where it is possible to specify such criteria. Dr. Grunwaldt expressed his doubts about the feasibility of defining these criteria and was concerned lest arbitrary control be extended over the activities of investigators and the pharmaceutical industry. Dr. Uhlenhuth and his associates working on the problem of anti-anxiety drugs have also been involved in this area, and in a recent letter to Dr. Klerman, Dr. Uhlenhuth stated "It seems doubtful that any number of messaging techniques as such can get us much further with the problem of clinical significance at this time. Perhaps we simply need more experience in translating the result of controlled studies into clinical practice to get a 'feel' of what a particular significance level or percent variation means to the practitioner.... Our biggest problem, however, is that none of our group seem really convinced that the current state of the field enables us to made recommendations as detailed as Al Gardner wants." (A copy of Dr. Uhlenhuth's letter and Dr. Klerman's reply are attached).

There was some feeling that it might be desirable to devise a research program in which existing data were reviewed to ascertain how much change in various scales was equivalent to clinical judgments of improvement. Techniques such as discriminate function or multiple regression might be included in such analyses. One of the possible outcomes of this study would be to project areas of research to be undertaken between FDA-ACNP and NIMH to develop such criteria.

FUTURE TIMETABLE

At the ACNP meeting, there will be a workshop, and it is planned that documents will be distributed prior to the meeting. It was recommended that a meeting be set up in January or February, 1973, at which investigators, clinicians, and pharmaceutical firms could respond to material presented at the December ACNP meeting.

The group agreed that there would not be a total meeting before the ACNP meeting in December. Dr. Klerman will work with individual members for progress reports.

Spring, 1973, will be devoted to collating the reports and translating the general reports into specific guidelines.