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Guidance for Industry

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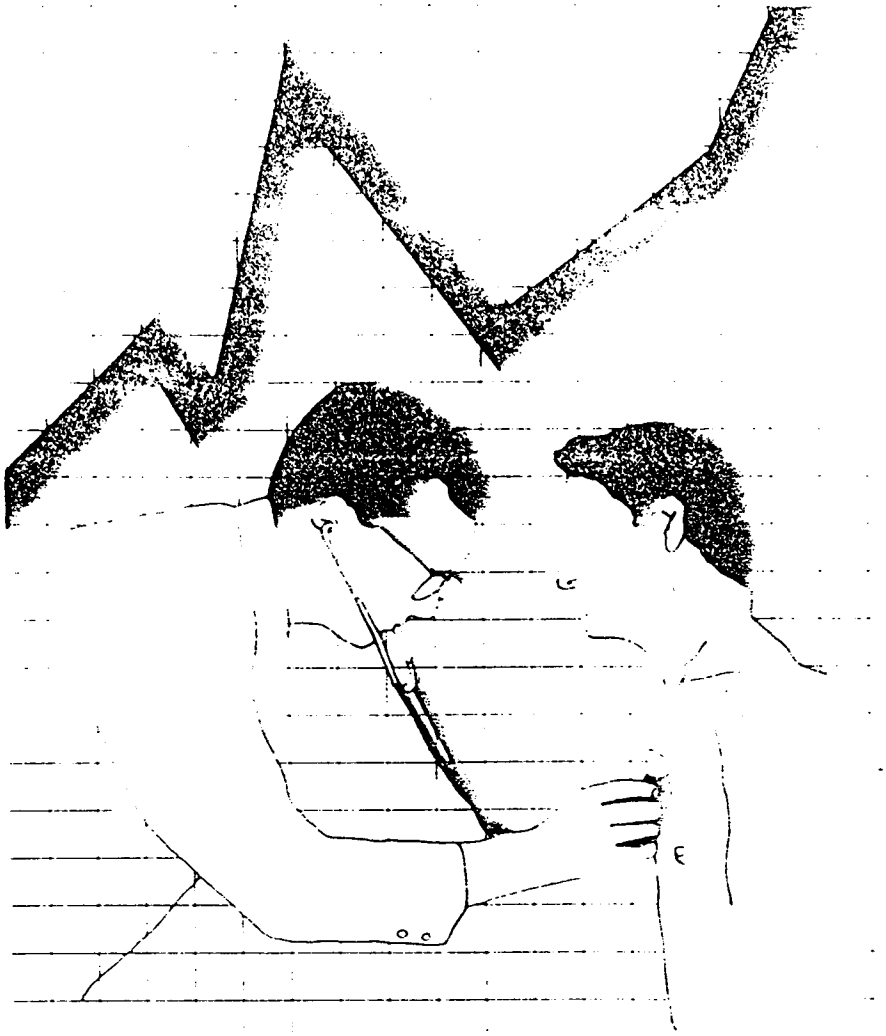

guidelines for the clinical evaluation of Antidepressant Drugs

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Food and Drug Administration

(This list is incomplete. Additional Guidelines will be published in early 1978)

FDA 77-3040	General Considerations for the Clinical Evaluation of Drugs
FDA 77-3041	General Considerations for the Clinical Evaluation of Drugs in Infants and Children
FDA 77-3042	Guidelines for the Clinical Evaluation of Antidepressant Drugs
FDA 77-3043	Guidelines for the Clinical Evaluation of Antianxiety Drugs
FDA 77-3044	Guidelines for the Clinical Evaluation of Radiopharmaceutical Drugs
FDA 77-3045	Guidelines for the Clinical Evaluation of Anticonvulsant Drugs (Adults and Children)
FDA 77-3046	Guidelines for the Clinical Evaluation of Anti-Infective Drugs (Systemic) (Adult and Children)
FDA 78-3047	Guidelines for the Clinical Evaluation of Anti-Anginal Drugs
FDA 78-3048	Guidelines for the Clinical Evaluation of Anti-Arrhythmic Drugs
FDA 78-3049	Guidelines for the Clinical Evaluation of Antidiarrheal Drugs
FDA 78-3050	Guidelines for the Clinical Evaluation of Gastric Secretory Depressant (GSD) Drugs
FDA 78-3051	Guidelines for the Clinical Evaluation of Hypnotic Drugs
FDA 78-3052	Guidelines for the Clinical Evaluation of General Anesthetics
FDA 78-3053	Guidelines for the Clinical Evaluation of Local Anesthetics
FDA 78-3054	Guidelines for the Clinical Evaluation of Anti-Inflammatory Drugs (Adults and Children)
FDA 78-3055	Guidelines for the Clinical Evaluation of Psychoactive Drugs in Infants and Children

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GUIDELINES FOR THE CLINICAL EVALUATION OF ANTIDEPRESSANT DRUGS

September 1977

Comments on the contents of this publication are invited and should be addressed to the following office:

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ABSTRACT

The Food and Drug Administration, with the assistance of its scientific Advisory Committees and other outside consultants, the American Academy of Pediatrics' Committee on Drugs, and consultants to the Pharmaceutical Manufacturers' Association has developed guidelines for the clinical evaluation of new drugs. These guidelines present acceptable current approaches to the study of investigational drugs in man, and pertain to Phases I through III of the investigation. They represent generally accepted principles for arriving at valid conclusions concerning safety and effectiveness of new drugs, as well as the views of outstanding experts concerning appropriate methods of study of specific classes of drugs.

The FDA welcomes comments on the guidelines, and expects to keep them current by review and update at approximately two-year intervals.

FOREWORD

The purpose of these guidelines is to present acceptable current approaches to the study of investigational drugs in man. These guidelines contain both generalities and specifics and were developed from experience with available drugs. It is anticipated that with the passage of time these guidelines will require revision. In order to keep them current a re-review will be performed approximately every 18 to 24 months.

These guidelines are not to be interpreted as mandatory requirements by the FDA to allow continuation of clinical trials with investigational drugs or to obtain approval of a new drug for marketing. These guidelines, in part, contain recommendations for clinical studies which are recognized as desirable approaches to be used in arriving at conclusions concerning safety and effectiveness of new drugs; and in the other part they consist of the views of outstanding experts in the field as to what constitutes appropriate methods of study of specific classes of drugs. In some cases other methods may be equally applicable or newer methods may be preferable, and for certain entirely new entities it is possible that the guidelines may be only minimally applicable.

Under FDA regulations (21 CFR 10.90(b)) all clinical guidelines constitute advisory opinions on an acceptable approach to meeting regulatory requirements, and research begun in good faith under such guidelines will be accepted by the Agency for review purposes unless this guideline (or the relevant portion of it) has been formally rescinded for valid health reasons. This does not imply that results obtained in studies conducted under these guidelines will necessarily result in the approval of an application or that the studies suggested will produce the total clinical information required for approval of a particular drug.

Many of the clinical guidelines have been developed largely, or entirely, by FDA's Advisory Committees and consultants. Others were originally developed by intramural committees and consultants of FDA and of the Pharmaceutical Manufacturers Association; in these cases the guidelines were reviewed and revised, as appropriate, by FDA's Advisory Committees.

The general guidelines for the evaluation of drugs in infants and children and most of those for study of various drug classes in children were developed by the Committee on Drugs of the American Academy of Pediatrics (AAP). Some of the pediatric guidelines for specific classes were written by FDA's Advisory Committees. There was cross review and comment on the pediatric guidelines by both the Committee on Drugs of the AAP and FDA's Advisory Committees.

The Bureau of Drugs of the FDA wishes to thank the many individuals who devoted so much time and effort to the development of these guidelines.

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GUIDELINES FOR THE CLINICAL EVALUATION OF ANTIDEPRESSANT DRUGS

"General Considerations for the Clinical Evaluation of Drugs" is an important companion piece and should be reviewed prior to reading these guidelines. It contains suggestions which are applicable to investigational drug studies for most classes of drugs and enables elimination of repetitious material in each of the specific guidelines.

1.0 INTRODUCTION

1.1 Purpose: Psychotropic drug guidelines have been developed to clarify the planning, monitoring, analysis, and evaluation of clinical studies of investigational new drugs with anticipated efficacy in the treatment of anxiety, depression, and psychosis. These particular guidelines represent a reasonable set of considerations in planning and executing appropriate clinical studies at various stages of drug development and in documenting and evaluating the results of individual studies as well as groups of studies relevant to establishing safety and efficacy. Attention to these guidelines by investigators, drug company staff, and FDA hopefully will provide a common basis for planning, evaluating, and interpreting clinical studies and will facilitate the development of new and effective drugs. Time and energy invested in unnecessary or inappropriately designed and executed studies also should be reduced at all levels. The guidelines will be particularly helpful to staff (investigational, industrial, or governmental) not yet expert in the area of clinical psychopharmacology. More detailed discussions of clinical drug evaluation can be found in recent publications.[1,2,3]

The guidelines are not intended to be immutable nor are they to be used to stifle innovative approaches to clinical research. They are intended neither as minimal standards nor as unrealistic standards of excellence but are written with the hope of improving the quality and meaningfulness of clinical studies designed to evaluate new psychotropic drugs. Although detailed guidelines are written only for antianxiety, antidepressant, and antipsychotic agents, the general issues discussed should be useful in planning studies of drug efficacy for other psychiatric indications.

1.2 Phases of Clinical Drug Evaluation: The guidelines specify the purposes of each of the phases of drug development and suggest characteristics of studies designed to provide the necessary information for proceeding to the next phase of study. The phases (I, II, III) are not entirely separable, and data collected in one phase will be relevant to decisions made in the next phase.

1.21 Phase I, human pharmacology, follows completion of appropriate pharmacological and toxicological studies in lower animals. A reasonably safe initial dose for use in man should be inferable from the data available. Although animal pharmacology may suggest that a new compound resembles existing drugs with known efficacy in specific psychiatric states, adequate animal models of human psychiatric illnesses are nonexistent, and the initiation of Phase I studies could be based on considerations other than specific pharmacological activity in animals

(e.g., a possible effect on brain biochemistry). Phase I studies should provide evidence as to the safety, pharmacological effects, and dose-related side effects in normal volunteers and/or psychiatric patients based on both single dose and time-limited multiple dose studies. Evidence as to drug absorption, distribution, excretion, and metabolism is also desirable. Obviously, if data documenting drug effects on mood or behavior in normal volunteers or on symptoms in patients can be obtained during Phase I studies, this is highly desirable.

1.22 Phase II studies are designed to provide reasonable evidence of clinical efficacy and usually proceed from carefully conducted open or single-blind studies in appropriate patient groups toward controlled studies designed to clearly establish efficacy in well-defined patient populations. Obviously, knowledge of the effective dose and side effects and some indication of therapeutic potential must be obtained from early Phase II studies before more formal controlled studies are worthwhile.

1.23 In Phase III, more extensive controlled studies are conducted to confirm and extend the findings in Phase II, aiming at more extensive evidence of efficacy under a wider range of patient groups and settings as well as more specific information about the incidence of both common and rarer adverse effects. Controlled studies can provide the kinds of information needed to assess the causal relationship between the investigational drug used and the adverse somatic or psychiatric events (e.g., jaundice, dermatitis, and suicidal attempts). Uncontrolled studies of the drug in a wider range of clinical settings may be useful in assessing its safety, particularly the rarer adverse reactions.

1.3 General Methodology: The principles for "adequate and well-controlled clinical investigations" (Code of Federal Regulations, Title 21 Section 314.111(a)(5)(ii)) are applicable to the classes of drugs covered in these guidelines. Difficulty frequently will be encountered in establishing an unequivocal diagnosis, since psychiatry lacks clear, quantitative, universally accepted diagnostic criteria. Both anxiety and depression are subjective symptoms occurring in association with a variety of other types of psychopathology, and both symptoms often occur in the same patient in varying proportions. This makes it impossible to define clear, universally applicable diagnostic criteria for use in each of the three classes of drugs for which guidelines have been prepared. Thus, it is even more necessary that individual study protocols describe explicitly their operational criteria for selection (and exclusion) of patients and that each patient be characterized as to the presence and intensity of various aspects of psychopathology commonly observed in anxious, depressed, or psychotic patients. Otherwise, the results of several studies cannot be compared or pooled.

Although existing assessment measures and study designs are often capable of detecting clear evidence of clinical drug efficacy, the state-of-the-art in clinical psychopharmacology still requires the development of new and better techniques. The development of new, potentially useful approaches to drug evaluation are to be encouraged by the investigators, the industry, and the FDA. Evidence of clinical efficacy derived from such new approaches will be given sufficient weight to encourage further improvements in the tools of clinical psychopharmacology. The absence of useful laboratory measures of anxiety or depression is regrettable. The absence of reliable methods for measuring blood levels of almost all existing psychoactive drugs is equally regrettable, since it suggests that absorption, distribution, metabolic, and excretion studies of future investigational agents may be very difficult to conduct. Limited studies using radioactively labelled compounds, of course, may be possible.

1.4 Monitoring: The task of monitoring the progress of an investigational new drug through the three phases rests primarily on the professional staff assigned by the drug company to the particular drug. In carrying out this role, close contact between industry monitors and clinical investigators is vitally needed as are well-planned, realistic study designs. The Food and Drug Administration also is responsible for reviewing clinical research plans. Ideally, there should be continuing contact between

the industry monitor and the FDA staff to help insure that studies will provide acceptable evidence for the decision to advance the drug to the next phase of evaluation or to final marketing. Using these guidelines, requirements can be formulated and made available to the clinical investigator which may serve to assist the industry monitor in motivating the investigator to adhere carefully to protocol requirements and data-collection procedures. On the other hand, some leeway must be provided clinical investigators to let them follow up unanticipated leads growing out of adequately designed formal studies. Only good communication between investigator, company monitor, and FDA will enable the monitoring of an investigational drug through its several phases to be sensible, reasonably efficient, and productive of the data necessary to competently evaluate both the drug's efficacy and its safety. There must be sufficient allowance for flexible, exploratory studies to insure that a compound which might be effective in condition A is not restrictively consigned to evaluation only in condition B where it is ineffective.

1.5 Ethics: The possibility of teratogenicity frequently makes it necessary to avoid involving female patients of childbearing potential in studies of investigational drugs. Women with childbearing potential should be included only when results of required reproduction and teratologic studies in animals have been reviewed by the pharmacologist and are considered to be satisfactory. However, in some institutionalized severely ill female patients, the clinical setting provides sufficient insurance against the risk of pregnancy to make their inclusion in studies justifiable.

Investigational drugs should be administered to children and minor adolescents only with parental consent. Such studies should not be initiated until safety and efficacy studies in adults are well advanced. Studies in children of drugs likely to be used in the treatment of the hyperkinetic syndrome, or adolescent forms of adult illnesses should not be unduly delayed since the drug, once marketed, may well be used in such patients without the physician having the benefit of knowledge obtained from careful clinical studies. Patients with a history of drug dependency usually should be excluded. Since the elderly and patients with cardiovascular, hepatic, renal, or other organic diseases also would be potential recipients of these drugs, if marketed, it is desirable that they be cautiously included in Phase III studies unless contraindicated by the nature of the drug. The use of placebo in clinical trials of psychotropic drugs poses a special problem. In conditions such as depression and anxiety states, the superiority of standard existing drugs over placebo is of sufficiently modest extent to make the administration of placebo to some patients in a study entirely justifiable, particularly if there are explicit provisions for removing from the study patients whose clinical condition worsens or fails to improve in a reasonable period of time.

1.6 Data Collection and Recording: Definitive, accurate, and appropriate documentation of clinical trials is an absolute necessity if valid conclusions regarding safety and efficacy are to be made by investigators, the industry, and the FDA. A perfectly designed and executed clinical trial without adequate documentation is wasted effort. The details for adequate documentation need not be specifically defined in this brief guideline. In general, it is necessary to document (1) the samples studied and the nature of the population or populations to which the results of clinical trials may be generalized, (2) the procedures followed during the trial, (3) the "case history" of each patient, (4) the criterion measures (for psychopathology, laboratory and physical examinations, and side effects), and (5) other variables which may have an influence on the results of the trial. To the extent that previously standardized and validated forms and measures are available and appropriate to assess the populations and drugs being evaluated, these are preferred since results are then more easily interpreted. The emphasis or extent of documentation for measures of safety versus efficacy or degree of specificity regarding efficacy will obviously and appropriately vary from Phase I to Phase II to Phase III. These will be in keeping with the objectives of the phases and the hypotheses of the individual studies.

1.7 Data Presentation: Once the individual appropriate items of information have been accurately collected during the clinical trial (documentation), it then becomes necessary to organize and present the data in a form which allows results to be viewed and conclusions to be reached. For a single clinical trial or study, this is done by: (1) preparing an individual case record for each patient, (2) summarizing data according to the treatment groups (or other meaningful groupings) in tabular and graphic form(essentially showing frequencies), and (3) performing appropriate statistical inference tests which indicate whether observed results are (un) likely to have occurred by chance. The ways in which the data may be presented cannot be detailed here but should be appropriate to the measures employed and the design of the trial. The use of well-validated and documented statistical procedures enhances the interpretation of results, but novel (well-documented) approaches which enhance the understanding of the results of a trial are encouraged. It should be possible in a well-documented and well-presented study to trace an individual patient's raw data through to its contribution in arriving at a probability statement.

1.8 Interpretation: While the previous section dealt with data presentation from single clinical trials, it is usual that evidence for safety and efficacy is acquired over the course of many studies carried out over considerable periods of time and at different geographical locations. Interpretation refers to the process by which the evidence from these various studies is considered together in reaching a conclusion. This may be done by comparing the results of one study to another or, where appropriate, by actually combining or pooling the data from several studies into a larger analysis. Where efforts of this type are undertaken the reasons for this and the procedures employed should be clearly given. The "picture" resulting from pooling of data should be clearer or more comprehensive than the results from the component individual studies.

EARLY CLINICAL PHARMACOLOGY

2.0 PHASE I

2.1 Objectives: To determine human tolerance of a new agent and when technically feasible, its absorption, distribution, metabolism, and excretion. Early studies in patients to determine whether the drug exerts a pharmacologic effect on the disease may be considered late Phase I studies.

2.2 Subjects: Adults; age 21 and over. Women of childbearing potential, children, and individuals with serious diseases usually should be excluded. May be confined "normals" or institutionalized patients. Should be informed volunteers and have normal baseline physical examinations, laboratory, and other clinical studies. Generally should require no concomitant medication.

If normal volunteers are used, it must be recognized that the findings may have little relevance when compared with some psychiatric patients, particularly in their ability to tolerate side effects or larger doses of the drug.

2.3 Setting: Usually a confined setting in which provisions are available for close supervision and treatment on a 24-hour basis.

2.4 Investigator: An especially competent individual with experience in clinical pharmacology, psychiatry, or internal medicine who will conscientiously carry out frequent and thorough evaluation of all study subjects.

2.5 Study Design: Prior to receiving the study drug all subjects should receive no other drugs for a period appropriate to insure that there will be no metabolic or symptomatic carryover effects. For example, if the previous drug has a relatively short half-life, the necessary drug-free period may be only several days while for phenothiazines, it should be much longer.

2.51 Single-Dose Study: It is beyond the scope of these guidelines to list the many variations in study designs that may be appropriate for the first trials of a new drug in humans. However, each should encompass the following general principles: First dose in the first subject should be minimal and based on animal toxicity studies (e.g., 1/5 to 1/10 of the maximum nontoxic dose in animals); monitoring before and after each dose (hence, term single-dose study); determination that each dose level is safe before administering a higher single dose to same or other subjects; interval before repeating same or higher dose in same subject sufficient to insure "washout" (when feasible as determined by animal and evolving human pharmacokinetic and pharmacologic data).

The following, which is to serve only as an example of one possible study design, may be accomplished with approximately six subjects in an open trial. The first subject receives a minimal single dose determined as stated above. The same subject is then given increments at three-day intervals. The second subject receives the maximum dose given the first subject. Each additional subject then starts at the maximum dose administered to the prior subject. All subjects continue to receive increments of the drug to the maximum tolerated dosage. Monitoring is conducted of clinical, laboratory, and when feasible, pharmacokinetic parameters at baseline, prior to receiving increments, and at follow-up intervals.

2.52 Multiple-Dose Study: Preferably double-blind with placebo control. Numerically balanced or imbalanced parallel group design may be used, e.g., 20 drug vs. 20 placebo, 12 drug vs. 8 placebo, or 30 drug vs. 10 placebo. Dosage increased at appropriate intervals (if possible, based on pharmacokinetics of single-dose study). As a precaution, may use subgroups starting at day or week intervals. When treatment emergent symptoms or side effects prohibit further increases, cut back to maximum tolerated dose and continue for at least 14 days. By this method, a total duration of approximately six weeks is usual, although it may often take longer. In any case, the duration of administration should be appropriate to the intended duration of further studies with recognition that additional and longer term safety data will evolve from them.

2.6 Assessment: Safety and/or toxicity usually assessed by: baseline and repeated extensive physical examinations; vital sign assessments; laboratory tests to assess the hematopoietic, liver, renal, and cardiovascular system. It is beyond the scope of guidelines to list all the specific tests that might be indicated. The type, extent, and frequency of testing will depend in part upon the type of drug, the preclinical information available, evolving information, and the eventual intended use of the compound. However, follow-up data usually should be obtained at least weekly during administration and whenever possible for at least one week after discontinuation of drug.

2.7 Documentation: Basically all study documentation should include the following:

a. Subject identification, demographic data, pertinent medical history, and vital statistics.

b. Pre- and post-treatment physical examination results.

c. Details of administration of medication and of dosage adjustment.

d. All behavioral and emotional effects observed or reported.

e. All adverse reactions reported or observed, the date, the severity and duration of such reactions, the investigator's judgment of whether drug-related, the control measures utilized, and the results of such measures.

f. All laboratory reports, including normal ranges for particular lab used.

2.8 Absorption and Metabolism: When initial safety studies have been completed, the absorption and half-life of the drug should be determined, if feasible. Such data might be relevant to the evaluation of safety and efficacy. More complicated metabolic studies can be postponed until Phase II when the utility of the drug will be more certain.

3.0 PHASE II

3.1 Objectives: In Phase II the overall objectives are:

3.11 To identify conditions or symptoms which may be therapeutically responsive to the drug.

3.12 To estimate the appropriate clinical dosage and duration of effect.

3.13 To identify adverse effects.

3.2 Sample Selection: Early Phase II studies can be conducted with in-patient or out-patient adult males (and females who are not of childbearing potential), depending on the degree of clinical supervision possible. Patients should be continually monitored for safety of the drug, as described in the Phase I outline.

As determined by comprehensive clinical and laboratory evaluations, patients evaluated early in this phase should require no concomitant medication and have no organic disease that may obscure clinical observations, laboratory tests, or interpretations.

In early Phase II studies, heterogeneous samples may be useful to determine range of implications. Later in Phase II, the sample should be as homogeneous as possible, considering the following: age, sex, weight, treatment setting, and socio-occupational group.

3.21 Criteria for Selection: Carefully specified criteria for selection of subjects for antidepressant drug trials are desirable for two reasons:

1. The greater the homogeneity of the sample, the greater the likelihood of obtaining reliable and valid results in comparing a new compound with placebo or standard drug.

2. In generalizing the results of clinical trials to therapeutic practice, it is necessary to have an adequate description of the patients' characteristics to provide assurance they are representative of some clinically relevant population.

In evaluation of antidepressant drugs, major problems arise from the semantic confusions associated with multiple meanings of the term "depression." Depression has different usages in various scientific fields, including physiology, psychology, and psychiatry. In clinical psychiatry, the two uses that are most pertinent to drug investigations are depression as a symptom and as a syndrome. As a symptom, depression may occur in association with other mental, behavioral, and psycho-physiological manifestations in various, and as yet poorly understood, complex combinations.

Failure to clarify the purpose of the study may lead to difficulties in patient selection, in design, in execution of the study, and in unnecessary problems in the interpretation of the data.

3.22 Depression as a Symptom as a Target for Drug Therapy: Depression as a symptom occurs in a wide variety of clinical conditions. Antidepressant drug

treatment may be useful in such conditions. However, research and clinical experience have not clearly demonstrated that drug treatment of depression as a symptom can be generalized across all states.

We also do not have normative data for distinguishing between the normal depressive state and the pathologic symptom. Some preliminary psychometric studies have been undertaken by Beck, Katz, Zung, and others; and research efforts are underway using population survey and epidemiologic techniques to generate such norms.

The following recommendations seem appropriate:

1. Depressive symptoms occur in many transient conditions, such as post-partum, following coronary disease, and also as significant accompaniments of many chronic medical ailments of the cariovascular, musculoskeletal, and gastrointestinal systems. Where a drug is being evaluated for depression in these states, the pharmaceutical firm and the investigators should specify the population, and the criteria for the primary medical diagnoses should be described in detail.

2. Symptoms required to be present at entrance to the study should be specified in the protocol. Two alternative procedures have been used successfully.

   They are:

   a. Listing of target symptoms, e.g., depression, crying, agitation, insomnia, etc., with a statement as to their frequency in the sample studied, measure of severity, and the duration prior to entrance into the study.

   b. Where established scales are used, pretreatment level should be established below which patients will not be admitted to the study.

3. Where antidepressant drugs are being used for depressive symptoms accompanying other psychiatric conditions, this indication should be specified in the protocol, and the diagnosis criteria identified. In practice, three such populations have been involved in antidepressant drug trials. These are:

   a. Alcoholics. Care should be taken to exclude patients who are or have only very recently experienced acute withdrawal symptoms such as DT's, tremulousness, or seizures.

   b. Schizophrenic or schizo-affective states. The criteria for the diagnosis should be specified.

   c. Aged patients, including those with CNS disease in whom depression is a frequent concomitant.

3.23 The Depressive Syndromes and Drug Evaluation: The most common clinical conditions for which antidepressant drugs are evaluated are the various depressive syndromes. Syndrome refers to the temporal coexistence and covariation of related symptoms and behaviors. Patients with a depressive syndrome usually manifest depressed mood (as described below) plus a significant number (4-5) of associated symptoms.

1. Depressed mood characterized by any of the following: sad, low, blue, despondent, hopeless, gloomy

2. Anhedonia - inability to experience pleasure

3. Poor appetite or weight loss

4. Sleep difficulty (insomnia or hypersomnia)

5. Loss of energy; fatigue; lethargy

6. Agitation

7. Retardation

8. Decrease in libido

9. Loss of interest in work and usual activities

10. Feelings of self-reproach or guilt

11. Diminished ability to think or concentrate such as slowed thinking or mixed-up thoughts

12. Thoughts of death and/or suicide attempts

13. Feelings of helplessness and hopelessness

14. Anxiety or tension

15. Bodily complaints

Since these symptoms will occur together at greater than chance, factor analysis and correlational statistics are useful to identify symptom groupings. Depressive syndromes usually involve various complex patterns or configurations. It is important to acknowledge that there is no one depressive syndrome. There is no agreement as to the basis upon which the various depressive syndromes should be identified and separated. Most investigators currently accept the concept of heterogeneity within the affective disorders and employ various pluralistic or dualistic diagnostic distinctions. The most used pluralistic distinctions are embodied in the official APA-WHO nomenclatures which designate multiple affective states such as manic depressive illness, involutional states, psychoneurotic depression, etc. The dualistic distinctions involve the primary-secondary separation developed by Robins and Guze, the unipolar-bipolar distinction developed by Perris, Leohard, and Winokur, and the endogenous-neurotic distinction recently revised by Kiloh, Mendels, Klein, and others. Older distinctions, which have also been used in drug evaluations, are the retarded-agitated typology and the psychotic-neurotic forms.

In addition, there are statistically derived typologies, which utilize computer programs for assignment of patients to multiple groups. The Overall-Hollister typology has been used in antidepressant drug studies. Techniques developed by Paykel, by Grinker and associates in Chicago and by Friedman in Philadelphia have not yet been widely applied to drug evaluation.

It is suggested that:

1. The investigator should specify the classification approach used and the criteria for assignment of patients to designated groups.

2. Among the assignment and selection techniques shown to have been effective in drug studies are those developed by Raskin for the NIMH collaborative study, by Overall and Hollister for VA studies, by the UK-MRC studies, and by Kiloh and Roth for endogenous-reactive types.

3. Investigators are encouraged to make use of scales which have already been used in drug research. For a number of scales, such as the Raskin, Beck,

Wittenborn, MMPI, Hamilton, and Zung, information exists as to the range of scores expected in populations, such as out-patient and in-patient, and for grades of severity.

4. The degree of severity of a patient's illness should be described using global scales.

5. The patient's status should be described, i.e., out-patient, day, or in-patient and whether the patient is seen in private practice or in group practice, a clinic, or institutional setting.

6. It is desirable that a variety of socio-demographic and clinical characteristics of the patients be reported. These characteristics include age, sex, racial or ethnic background, social class, previous hospitalization, previous diagnoses of mania or schizophrenia, and previous major therapies, i.e., ECT, phenothiazines, etc.

7. It is recommended that the criteria for exclusion be identified particularly for patients in the borderline between schizophrenia and the affective diseases.

8. Problems in design of studies and in selection of patients with anxiety and depression will be discussed elsewhere in these guidelines.

3.24 Sample Size: In early Phase II studies, sample size may vary since actual numbers depend on the problems to be investigated and on the magnitude of difference between the treatment and control groups that is to be expected or is actually observed. There should be sufficient numbers of subjects to assure a reasonable likelihood of demonstrating differences if they exist.

In later Phase II or Phase III studies, a minimum of twenty patients per treatment group are necessary if drug-placebo or drug-drug differences are to be demonstrated.

3.3 Setting: In early Phase II studies, in-patient setting should be used when feasible. If other settings, e.g., out-patient clinic, day hospital, private clinic, or private office are necessary, these should be described and justified.

3.4 Investigators: The investigators should be experienced in evaluating psychiatric drugs and in the conduct of clinical trials; they should have ready access to the appropriate population group for whom the drug may be indicated.

3.5 Design: Patients should be selected to provide an unbiased sample of the population of interest and should be assigned to treatments at random. Predrug severity of the disorders to be measured should be recorded and included as part of the design.

3.51 Drug-Free Period: When safe and feasible, each study subject should have a drug free period for several days prior to receiving the study medication. The number of days would depend upon the prior medication received by the subject and its duration.

There are two reasons for this procedure. One, rapid remitters and placebo responders can be detected and eliminated from the study, thus maximizing the likelihood of establishing drug effect. Second, during the "washout" period, patients who have been taking drugs with potential for dependence or withdrawal will manifest these behaviors.

If patients' symptoms decrease to a level below criteria for entrance into the study during this "washout" period, they should not continue in the study.

3.52 Uncontrolled Trials: In early Phase II, several open or uncontrolled trials may be desirable to allow investigators sufficient flexibility to explore possible aspects of a new drug's activity and to allow for the determination of an appropriate dosage range for use in double-blind studies. It must be kept in mind that information obtained from these early open studies can only form hypotheses which must then be tested in controlled studies. The open studies may be of small sample size; however, it may be desirable for validated clinical measures and selection of patient samples to be consistent between investigators in order to facilitate the interpretation of results.

3.53 Controlled Trials: Hypotheses evolved from open studies can be confirmed or refuted only by controlled double-blind studies. In at least some Phase II studies the investigational new drug should be compared to a matching placebo control to establish its efficacy. Other studies may include only an active treatment control or both.

Parallel groups, crossover, intensive, and other designs may be used. The planning of this and other aspects of these studies should, whenever feasible, involve extensive consultation with a biostatistician. There should be full awareness of the advantages, disadvantages, and criteria for validity regarding each possible design before selecting one. Comparisons between two active drugs usually require much larger sample sizes than active drug-placebo comparisons.

Packaging and coding of medications should be performed on an individual basis rather than on a treatment group basis. Other psychoactive drugs are to be avoided. If other drugs are used, this should be carefully documented.

3.6 Dosage

3.61 Open or Uncontrolled Studies: After selection of initial dosage based on all previous data (including pharmacokinetic), dosage in open trials is usually increased until a satisfactory therapeutic response is observed. If adverse effects are a significant problem, further increases may be precluded and dosage reduction or discontinuation indicated.

3.62 Double-blind, Controlled Studies: Dosage may be fixed; however, because of individual metabolism and tolerance, a flexible dosage may be necessary.

A specified range may be used (as determined in earlier trials) within which adjustments are made individually according to specified clinical criteria.

The mode of administration, range, schedule of administration, and criteria for dosage adjustment should be stated in each protocol.

3.7 Duration of Trial: The duration of individual clinical studies in Phase II may vary from days to weeks depending on their purpose and the nature of the drug. The therapeutic activity of antidepressant agents usually can be established in trials of approximately four weeks duration. However, to allow for a further assessment of safety beyond that obtained in Phase I, at lease one of the first several Phase II studies should be continued for six weeks with appropriate laboratory monitoring if preliminary data have indicated satisfactory support of efficacy.

3.8 Assessment: Physical exams and clinical laboratory tests are basically the same as those for Phase I, but may be modified according to the findings in Phase I. Appropriate and validated rating scales should be made for recording symptom emergence which may represent side effects or possible new uses for a drug. The reliability of the ratings may require more than one rater.

Baseline observations should be carried out in all patients immediately before their initiation into the study. The frequency of follow-up determinations may then vary from days to weeks.

All adverse reactions reported or observed should be part of the record. Include the dose of the drug at the time of appearance of the side effect, the duration of the side effect, severity, judgment as to whether the drug is responsible for the side effect, method of treating the side effect, and the results of the treatment. If the side effect was severe enough to discontinue the subject from the study, this should be stated.

3.81 Techniques for Assessment of Change: There are a number of techniques which can be applied in assessment of change with antidepressant drugs. No one technique in itself is considered sufficient. Not all techniques are required. Varying combinations may be employed depending on the phase of investigation and the types of patients.

These techniques include:

1. Global measures. The NIMH and VA studies have used 5-7 point scales. The Menninger Health-Illness Scale may also be used. Categories of improvement (marked - moderate - some - none - worse) are widely used.

2. Clinical Interview Scales. The scales developed by Hamilton, Levi, Overall, Spitzer, Wittenborn, and others are of demonstrated reliability, validity, and sensitivity to drug effects.

3. Self-report techniques. These have gained wide acceptance in out-patient samples. Among those frequently used are the Zung, the Beck, the MMPI, the Symptom Check List (SCL), the Clyde Mood Scale (CMS), and the Adjective Check List.

4. For in-patients and day patients, direct observational approaches to behavior rated by nurses or other personnel have been used. The most common scales are those of Lorr, Burdock, the NOSIE, and the Grosser-Wechsler scales.

5. Social adjustment. Assessment of social adjustment seems most appropriate for drug maintenance trials where patients are followed into the community after discharge from the hospital. In these studies, drug therapy attempts at demonstrating efficacy in the prevention of relapse and recurrence in prophylactic or maintenance therapy. This need occurs in long-term trials with lithium or tricyclics.

6. Psychological techniques, such as projective methods and tests of intelligence, have not been used widely as measures of efficacy. They are useful as associated data, and further research may demonstrate their validity.

7. Verbal sample techniques and content analysis, such as those developed by Gottschalk and associates, have proven sensitive to drug response.

8. Psychophysiological measures, including EEG, pulse rate, blood pressure, EMG, GSR, and pulse volume do not in themselves provide evidence of efficacy but may be useful as associated indices of change. However, pulse, BP, and weight are valuable clinical indicators and suggested for studies, even though they may not be criteria of efficacy. Specialized psychophysiological methods, such as quantitative EEG analysis, while still in the investigational stage, may provide valuable data.

Other techniques including rating scales developed by the investigator may be employed providing evidence for their reliability and validity is available.

Efforts should be made to establish agreement on the use of diagnostic and descriptive terms as well as the handling of assessment instruments. This may be accomplished by investigator meetings or in-depth discussion by the monitor with each investigator.

3.82 Interpretation: In addition to clinical considerations, the interpretation of studies in this difficult area may involve extensive statistical analysis which often cannot be predetermined. Rather than interpreting studies only individually, it is also important to consider all information available concerning a drug, including preclinical studies, before making final positive or negative conclusions regarding it.

Insofar as possible, it is desirable to demonstrate efficacy within the unit study. However, it may be difficult to obtain enough patients in a unit study to achieve strong statistical evidence of efficacy therein, particularly when two active medications are involved. This may result simply from a scarcity of patients or from particularly strong placebo effects in the type of patient and/or the setting involved. Under such circumstances, it may be necessary to pool data from several studies to provide convincing statistical evidence of efficacy. This decision should be made in research protocol planning. The pooling of data from different investigators can be of definite value but requires special consideration.

4.0 PHASE III

By the middle or end of Phase II, sufficient information should be available to formulate hypotheses as to types of patients and their clinical conditions which may respond to the investigational drug. For testing these hypotheses, controlled trials are necessary. This is the major purpose of Phase III studies.

4.1 Specific Objectives:

4.11 Therapeutic Studies: Extension of comparative controlled studies are used to fully confirm the drug's basic antidepressant activity in heterogeneous patient populat ons and to provide more specific information about symptoms and patient types in which the drug is especially effective. Placebo controlled trials are necessary as are comparisons with standard drugs of established efficacy for the clinical condition.

4.12 Long-Term Safety Studies: To establish the safety of a new antidepressant agent when given daily for 3 to 6 months or longer, long-term safety studies are undertaken with particular regard to the nature, incidence, and control of side effects.

4.2 Patient Selection: Similar considerations apply as in Phase II. In this Phase, patients with the diagnosis of primary depressive syndrome of some form are usually selected. Populations with other than primary depressive disorders, such as depression with schizophrenia or in association with anxiety or with medical conditions, may be studied in separate trials.

A greater variety of populations differing as to age, sex, diagnostic categories, social class, treatment setting, previous treatment, etc., may be studied. Within each study (or subgroup in studies of sufficient size), patients should be selected to be as homogeneous as possible regarding the above variables. In any case, full reporting of patient characteristics is necessary to allow for adequate interpretation of results.

Exclusions should be stated. Exclusion of placebo responders may strengthen a trial. The placebo response for a particular patient population should, at least, be known to the investigator.

Females of childbearing age may be included if results of animal reproductive and teratologic studies are satisfactory.

4.21 Sample Size: While it may be possible to demonstrate drug effects in samples as small as twenty patients per treatment group, experience has shown that samples in the range of thirty to fifty patients in each treatment group provide greater assurance.

4.3 Setting: A number of settings may be used, e.g., in-patients, out-patients, and private practice.

4.4 Investigators: Because the extension of claims into other areas involves a variety of types of investigators, it is important to consider the investigator's capability and experience in evaluating and working with patients with depression, his provisions for needed safety precautions, his access to laboratory facilities with suitable controls, and the appropriateness of his clinical setting to allow for valid drug evaluation.

4.5 Design: Of primary importance during Phase III of a drug's evaluation are controlled studies designed to fully confirm the drug's basic antidepressant efficacy. The design guidelines are generally the same as those discussed in Phase II. However, adjustments may be made in controls, duration of study, dosage, and design which do not interfere with validity to accommodate greater variations in purpose of studies, settings, investigators, and subjects as discussed under the respective headings in Phase II.

There is wide agreement that a number (preferably three to five) of studies in Phase III should compare the new compound with a placebo and with an established drug of demonstrated efficacy in similar pharmacological class (tricyclic, MAO inhibitor, and psychomotor stimulant). These studies should be double-blind and utilize standard methods of assessment of change.

Crossover designs to control bias have major inherent difficulties because of carryover effects, both pharmacological and psychological, particularly in depressive syndromes (spontaneous remissions, self-limiting, response to attention, etc.).

When it is concluded that the drug's basic antidepressant efficacy has been clearly established by controlled studies, consideration may be given to undertaking further studies on an open trial basis with new populations. These, of course, carry with them the inherent risk, due to lack of a control group for comparison, of encountering difficulties in interpretation of unexpected findings. However, such findings, as stated previously, can lead to forming hypotheses which must be confirmed or refuted by reviewing already completed or establishing further controlled studies. In providing further experience with the drug (often under conditions of usual medical practice), these studies can be important in providing corroborative support of efficacy demonstrated by well-controlled studies and in adding valuable data regarding safety of the new drug. This is particularly true when a number of investigators working independently obtain similar findings.

Patients may also be evaluated in studies related to other than the major antidepressant claim. For each of these other areas, a number of double-blind studies should be sufficient. Prior to these, it may be necessary to carry out several open studies to familiarize the investigator with the drug's activity and appropriate dosage range in a particular therapeutic situation or special population. In these populations, carefully edited (i.e., they need not include all variables of other studies) clinical pharmacology and therapeutic trials may be carried out to establish tolerance, efficacy, and safety.

4.51 Long-Term Safety Studies: Long-term safety studies may be on an open trial basis or may be of a controlled parallel group design.

Data regarding long-term safety may also be obtained from a number of studies rather than from a single formally structured one. For example, provision may be made for patients in therapeutic trials to continue on the drug if it is indicated. Special attention will need to be given to children, elderly patients, and women who are of childbearing potential. As was done in Phase II studies in young and non-elderly adults, it is necessary to establish in children and the elderly in dose-response studies the dosage that gives adequate clinical response with a minimum of side effects.

In long-term safety studies, dosage should be of at least the level expected for eventual general therapeutic use. Allowance for adjustments to age, sex, and individual tolerance, of course, must be provided.

4.6 Duration: The duration of therapeutic trials (Phase III) may vary as in Phase II and, particularly regarding open trials, may often be longer. After baseline determinations in all cases, follow-up evaluations usually become less frequent as evolving data permit.

The duration of long-term safety studies is usally three to six months, and may be as long as a year for drugs indicated for such prolonged use. Baseline observations should be carried out in all cases and follow-up evaluations are usually at least monthly in the earlier stages and bimonthly thereafter.

4.7 Assessment: This is generally similar to that outlined for Phase II. Valid adjustments are permissible as indicated.

4.71 Interpretation: Since most Phase III studies will involve multiple trials, consideration must be given to problems of statistical analysis and interpretation within each trial, among various trials, and when data from a number of trials are grouped or pooled. These issues are reviewed in greater detail in the section on Documentation and Interpretation in: Levine, Schiele, and Bouthilet, Principles and Problems in Establishing the Efficacy of Psychotropic Agents, 1971, Washington, D.C., U.S.G.P.O. Publ. #2138.

4.8 Maintenance Studies and Long-Term Trials: Currently, there is considerable interest in long-term trials to establish the value of maintenance antidepressant therapy in prevention of relapse or recurrence. Whereas the treatment goal in acute episodes is the reduction of symptoms and the patient's return to a premorbid state, in long-term maintenance therapies the goals are more ambitious: prevention of relapse or recurrence after an initial episode, facilitation of the patient's social and vocational adaptation, relief from minor symptoms, enhancement of personal adjustment, and life satisfaction.

Research methodology in these studies is still in the developmental stage and there are many unsolved design and statistical problems.

A major problem is the identification of patients likely to suffer from multiple recurrences. While a significant number of patients with acute depressions are likely to have multiple recurrences, it is difficult on the basis of presenting clinical symptoms to predict which patients experiencing acute depressions are likely to have recurrences. The frequency of recurrence in a large population as well as the duration of intervals between relapse and recurrences is highly variable.

Given this lack of information, investigators have employed different strategies to select samples for long-term maintenance studies. Most investigators advocate selecting patients who have had two or more well-designed episodes and/or hospitalizations. Others have proposed selecting patients with salient symptoms or characteristics such as familial history, manic elations, clear-cut retardation, or well-defined periodicity.

In evaluating the efficacy of treatment, the criteria of effectiveness are different from those used in studies of acute treatment. Reduction of mortality, especially from suicide, is a major criterion. Another is prevention or reduction of rehospitalization rates. These effects are more easily identified but occur less frequently than minor relapses or recurrences that may not be of sufficient intensity to require hospitalization. For the detection of such symptomatic change, rating scales and systematic clinical observation are needed.

Moreover, for evaluating criteria in areas such as familial and marital functioning, social effectiveness, and vocational peformance, new techniques are needed in addition to the established rating scales whch assess psychopathology and mood.

Design problems for long-term maintenance studies are considerable. In the absence of established data as to the predictors of relapse and the frequency of rehospitalization and recurrence, a concurrent control group receiving no treatment or placebo is highly desirable.

There are significant statistical problems, particularly the need for statistical techniques for repeated measures. Various forms of trend analysis or stochastic models may assume an important role.

A related problem deals with attrition. The longer a trial continues, the greater the likelihood that patients will drop out; the sample finishing the trial will not be identical to that beginning the trial. Life-table methods and other statistical techniques derived from public health morbidity and mortality studies may have applicability in this area.

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