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The FDA published Good Guidance Practices in February 1997. This guidance was developed and issued prior to that date.

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, FOOD AND DRUG ADMINISTRATION

guidelines for the clinical evaluation of **Antiepileptic Drugs (Adults and Children)**

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

FDA BUREAU OF DRUGS CLINICAL GUIDELINES

(This list is incomplete. Additional Guidelines will be published in 1981)

Guidelines May Be Ordered From: Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402.

FDA 77-3040 General Considerations for the Clinical Evaluation of Drugs (GPO 017-012-00245-5, $0.90).

FDA 77-3041 General Considerations for the Clinical Evaluation of Drugs in Infants and Children (GPO 017-012-00246-3, $1.10).

FDA 77-3042 Guidelines for the Clinical Evaluation of Antidepressant Drugs (GPO 017-012-00247-1, $1.00).

FDA 77-3043 Guidelines for the Clinical Evaluation of Antianxiety Drugs (GPO 017-012-00248-0, $1.00).

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FDA 78-3053 Guidelines for the Clinical Evaluation of Local Anesthetics (GPO 017-012-00255-2, $0.80).

FDA 78-3054 Guidelines for the Clinical Evaluation of Anti-Inflammatory Drugs (Adults and Children) (GPO 017-012-00258-7, $1.50).

FDA 78-3065 Guidelines for the Clinical Evaluation of Antacid Drugs (GPO 017-012-00261-7, $.90).

FDA 78-3066 Guidelines for the Clinical Evaluation of G.I. Motility-Modifying Drugs (GPO 017-012-00262-5, $.90).

FDA 78-3067 Guidelines for the Clinical Evaluation of Laxative Drugs (GPO 017-012-00263-3, $.90).

FDA 79-3055 Guidelines for the Clinical Evaluation of Psychoactive Drugs in Infants and Children (GPO 017-012-00281-1, $4.75).

FDA 79-3073 Guidelines for the Clinical Evaluation of Bronchodilator Drugs (GPO 017-012-00271-4, $.80).

FDA 79-3074 Guidelines for the Clinical Evaluation of Drugs to Prevent, Control and/or Treat Periodontal Disease (GPO 017-012-00272-2, $.80).

FDA 79-3075 Guidelines for the Clinical Evaluation of Drugs to Prevent Dental Caries (GPO 017-012-00273-1, $.90).

FDA 80-3093 Guidelines for the Clinical Evaluation of Analgesic Drugs (GPO 017-012-00283-8, $1.50).

FDA 80-3094 Guidelines for the Clinical Evaluation of Drugs Used in the Treatment of Osteoporosis (GPO 017-012-00284-6, $1.25).

FDA 80-3103 Guidelines for the Clinical Evaluation of Lipid-Altering Agents in Adults and Children (GPO 017-012-00288-9, $1.50).

FDA 81-3110 Guidelines for the Clinical Evaluation of Antiepileptic Drugs (Adults and Children) (GPO 017-012-00292-7).

HHS (FDA) 81-3110

GUIDELINES FOR THE CLINICAL EVALUATION OF ANTIEPILEPTIC DRUGS (ADULTS AND CHILDREN)

PRINTED September 1977
REVISED January 1981

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

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For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402

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 acceptable 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 acceptable 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 ANTIEPILEPTIC DRUGS (ADULTS AND CHILDREN)

"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 applicable to most investigational drug studies and enables elimination of repetitious material in each of the specific guidelines.

ADULT SECTION

I. INTRODUCTION

These guidelines are concerned with drugs used in long-term therapy of seizure disorders. Evaluation of drugs used in acute situations (e.g., status epilepticus, withdrawal convulsions, febrile convulsions, etc.) may require modification of these suggestions.

II. EARLY-PHASE I STUDIES

(See "General Considerations for the Clinical Evaluation of Drugs")

A. Investigators

Phase I studies should be performed by investigators skilled in safety evaluations of new compounds.

B. Subjects and Setting

"Normal" adult male volunteers are suitable subjects. Pretreatment physical, neurological and laboratory examinations are necessary to ascertain "normality".

Subjects should preferably be in closed environments permitting close observation. Abstinence from alcohol must be observed for at least two weeks and from other drugs for a period necessary to prevent carry-over effects. No alcohol or other drugs should be permitted during the test period.

Subjects with known seizure disorders generally should not be included in early-Phase I studies. However, if a promising drug with significant potential for adverse effects is developed, it may be necessary to use highly refractory patients with frequent seizures and poor prognosis.

C. Observations

Neurological examinations should be performed in addition to the usual clinical and laboratory observations during the test period.

D. Duration of Treatment

Test drug administration should eventually be extended to a minimum of four weeks.

E. Study Design

Multiple-dose studies should be single-blind and may be double-blind. Placebo controls are highly desirable to eliminate bias in the reporting of subjective phenomena.

F. Drug Dynamics

Evidence that the drug is biologically available at the administered dosage must be presented during Phase I. This may be accomplished by absorption and excretion studies. (See "General Considerations for Clinical Evaluation of Drugs" for a detailed discussion.)

G. Pilot Efficacy Studies

None are recommended.

III. LATE-PHASE I AND PHASE II STUDIES

A. Objectives

Objectives of the study should be stated clearly.

B. Investigators

Investigators should be physicians experienced in the medical evaluation and management of epilepsy. They should have appropriate support facilities.

C. Setting

Subjects in late-Phase I and initial-Phase II studies should be hospitalized for a pretrial period of observation adequate for pharmacological and clinical stabilization. Further inpatient observation may be necessary for certain patient populations, drugs or study designs.

In later-Phase II, outpatient epileptics may be included, allowing observation in more natural settings and inclusion of patients with varying severities of epilepsy.

D. Patients

Patients with incomplete control of seizure disorders are suitable subjects for late-Phase I and Phase II testing. Patients failing to respond satisfactorily to adequate dosages of standard therapy, in whom compliance seems likely and for whom adequate plasma drug concentrations of standard therapy have been documented should be chosen.

Patients well-controlled on current therapy are not suitable subjects for late-Phase I or Phase II unless experiencing excessive side effects from current medication.

Factors to be considered in patient selection:

1. Classification of seizures according to the International Classification of Epileptic Seizures (including electroencephalography). Types of seizures to be studied should be chosen with consideration of animal seizure models in order to facilitate selection of fairly homogeneous patient populations. Seizures of a given type may progress to generalized tonic-clonic seizures* and patients with such seizures may be included.

2. Number of seizure types. Preferably, patients should have only one seizure type. Those with more than one type generally should be reserved for later studies. If different seizure types are likely to occur in the studied population, measurable endpoints should be decided upon prospectively to distinguish efficacy.

3. Current therapy. Existing therapy preferably should consist of only one drug (but not more than two) which has remained at constant dosage for several months. Previously untreated patients with absence seizures may be utilized in Phase II.

4. Age. Adult subjects are preferable in late-Phase I and early-Phase II testing unless the seizure type is restricted to the young-age period, e.g., absences, infantile spasms or atonic seizures (drop attacks, akinetic seizures). Children with other forms of epilepsy must be selected on the basis of extreme refractoriness to current medicine or with control obtained only at the cost of unsatisfactory levels of side effects, with full evaluation of the legal and ethical implications of such testing.

5. Presence or absence of cerebral lesions. If lesions are present, the type and natural history should be considered.

*This term is used interchangeably with grand mal seizures throughout these guidelines.

E. Exclusions

1. Use of drugs (other than concomitant antiepileptic drugs) which would interfere with safety or efficacy evaluations of the drug under study.

2. Presence of associated disease. Before the drug trial begins, patients should be examined to rule out treatable causes of seizures. Laboratory tests should be performed to document the pretreatment status of the subjects. It must be recognized that in chronically treated seizure patients some of the results may deviate from accepted normal standards.

F. Observations

Measurements of efficacy should be documented objectively. These may include :

1. Reduced seizure frequency.

2. Increased seizure-free intervals, e.g., time between seizure clusters.

3. Decreased total seizure time. (This parameter has been successfully determined only in absence.)

4. Improved functional capacity.

5. Decreased incidence of adverse reactions. In patients experiencing adverse reactions to previous medication, effectiveness of the new agent may be demonstrated by decreased adverse reactions, even if no improvement in seizure activity is manifested.

6. Decreased generalization of focal seizures. This parameter has not yet been used in a quantified fashion, however, such qualitative measures are desirable supplements to quantitative data.

Particular attention should be given to the method of recording these measures of efficacy. Pretrial observation of seizure frequency is usually obtained. Length of this observation depends upon the seizure frequency and the study design. Ideally, patients with frequent seizures which can be monitored objectively should be selected.

In seizure types other than generalized tonic-clonic seizures, newer methods of quantitation are highly recommended. Telemetry, for example, has revealed drug-related changes in the frequency of absence seizures far more precisely than clinical observations or patient reports, permitting more efficient study designs.

Electroencephalography and psychological testing are desirable but not mandatory unless there are specific indications for performing these tests.

Serum level determinations of the subject's pretest antiepileptic medications are highly recommended. If the subject continues on pretest antiepileptics, serum level determinations of these drugs, as well as the test drug, are recommended at least twice weekly.

The usual "safety" laboratory tests should be performed, viz., hematopoietic (including platelet estimation), renal, hepatic and any others that may be indicated. Careful clinical observations should be made, with particular regard to disturbances of thought processes, gait, speech, coordination, nystagmus and lethargy.

Patients should be evaluated at least weekly during the first four weeks and at least biweekly for the next eight weeks.

G. Duration of Treatment

After initial Phase II studies have demonstrated relative safety and efficacy, studies may be extended to a duration of three to six months. Patients need not be hospitalized, provided close control can be maintained.

H. Study Design

Late-Phase I and initial-Phase II study designs are more rigid than those of later-Phase II studies.

Pilot or preliminary studies on small numbers of patients need not be blind. Objectives of preliminary studies must be stated clearly.

Crossover or substitution designs should be reserved for later-Phase II studies by which time some evidence of drug efficacy in human seizures will have been obtained. Late-Phase I and initial-Phase II studies generally should consist of addition of the new drug to existing therapy. Existing therapy should consist of one drug and not more than two drugs, as noted before, although more flexibility may be considered in later-Phase II studies.

Later-Phase II studies may include withdrawal of existing therapy if satisfactory control is achieved through addition of the new agent. With crossover or substitution studies, careful monitoring of serum drug levels and hospitalization or institutionalization with careful observation are indicated. Adequate safety precautions must be taken to prevent and immediately treat status epilepticus should it occur.

In later-Phase II trials, when there is reasonable evidence of efficacy, new patients may be started on the test drug as the sole medication to determine the effects when given alone.

If possible, objective evidence of seizure control should be determined in the presence of estimated therapeutic serum levels. For patients failing to show evidence of objective improvement in the estimated therapeutic range, dosage may be increased until the first signs of limiting side effects appear.

If the methods of efficacy evaluation are not subjective or not subject to error in observation, the test design may be single-blind. Placebo control is usually desirable.

Biostatistical consultation should be obtained from experts familiar with the state of the art of trial designs for antiepileptic drugs for help in formulation of study design, determination of adequate sample size, proper grouping of subjects and analysis of data.

I. Enzyme Induction and Drug Interaction Studies

It is recognized that during late-Phase I and initial-Phase II studies the investigational drug may be given in combination with other drugs, such as barbiturates, with the attendant possibilities of enzyme induction, altered metabolism and antagonism, inhibition or synergism between drugs. The ability to determine serum levels of the currently utilized antiepileptic drugs makes it possible to observe potential drug interactions during Phase II. Therefore, serum level measurements of the test drug are highly recommended.

IV. PHASE III STUDIES

A. Objectives

Objectives of the study should be stated clearly.

B. Investigators

The investigators should be qualified by training and experience to evaluate antiepileptic drugs.

C. Setting and Subjects

Ambulatory patients are the usual subjects of Phase III studies, although institutionalized patients must also be included at some time during this phase. Hospitalization or adequate observation in institutionalized patients may be required in withdrawal or substitution studies.

A varied patient population is desirable for Phase III studies for the following reasons: (1) there are many different types of seizures, 2) many patients have more than one type of seizure, 3) seizures of a given type may occur in patients of widely varying demographic and clinical characteristics and 4) a drug may not alleviate all forms of epilepsy. The investigational drug should be tried in patients with appropriate seizure types and in patients with more than one seizure type. The drug should be tested in sufficient numbers of patients with widely varying characteristics to warrant generalization of results to the population in which the drug may eventually be used.

Patients well-controlled on current medication should not be subject for Phase III trials unless experiencing excessive side effects from current medication.

Clinical studies of the test drug's safety and efficacy should ordinarily be undertaken in children since it is likely that the drug, once marketed, will be used in children.

Before the drug trial begins, patients must be examined to rule out treatable causes of seizures. Patients should be classified by all identifiable variables and assigned randomly, according to the study design. Three important variables should be considered:

1. Classification of seizure types according to the International Classification of Epileptic Seizures.

2. Age of patient.

3. Presence or absence of cerebral lesions. If present, type and natural history of lesion should be considered.

D. Observations

Accuracy of data collection is essential. Every effort should be made to quantify observations. In other than generalized tonic-clonic seizures, newer methods of quantitation are highly recommended. Telemetry, for example, has revealed drug-related changes in the frequency of absence seizures far more precisely than clinical observations or patient reports, permitting more efficient study designs.

Serum level determinations of both the investigational and concomitant antiepileptic drugs are highly recommended at appropriate intervals. Further information on the therapeutic and toxic ranges of the investigatonal drug should be obtained. Interactions with commonly used antiepileptic drugs should be studied to approximate actual conditions of use.

Electroencephalography and psychological testing before and during test drug administration are suggested if prior studies indicate that EEG's and emotional factors may be affected by the drug (e.g., psychotropic effects of the drug).

The usual "safety" laboratory tests (hematopoietic, renal and hepatic) and any others indicated should be performed at appropriate intervals.

E. Duration of Treatment

Some studies may be extended to six months and longer (one year or more) to evaluate long-term efficacy and safety.

F. Study Design

A variety of studies should be performed in Phase III, ranging from small, well-controlled, blinded studies comparing drug efficacies to large, open-label studies in situations similar to clinical use of antiepileptic drugs.

Evaluation of efficacy in less common seizure patterns may require collaborative studies in order to obtain significant data.

A variety of experimental designs may be used in Phase III. The following is an example of a potential study design :

> The minimum effective dose of the test drug, as established in Phase II, is added to existing medications and the dosage is increased sequentially to the desired seizure-control point or to the point of limitation due to side effects. The effective dose is continued for the period of the trial. Once the subject is stabilized, the frequency of seizures during treatment is compared to that of the pretrial period. After stabilization, withdrawal of pre-existing medication is attempted and further comparison of seizure frequency control is made.

An adequate number of studies should be controlled. A variety of controls are available, some of which are described below :

> 1. Historical control. The results of the new drug are compared with adequately documented histories of the untreated disease or with previous drug treatments. Because of the tendency of some patients to respond favorably to new drugs, the trial period should extend for at least six months and preferably for one year.
>
> 2. Active drug control. For shorter studies, an active drug control may be used. The effects of the new drug are compared to the effects of another known drug. The patient should not be able to distinguish between the drugs. Double-blind methodology should be used. Provisions should be made for breaking the blind in case of emergencies in which the test drug may play a role.
>
> 3. Placebo control. Placebo control is recommended when the test drug is added to existing therapy.

A well-controlled Phase III study of absence epilepsy or generalized seizures in institutionalized, brain-damaged patients, uncontrolled by present medication, could involve crossover or substitution from marketed antiepileptic drugs to the test drug. Such studies need adequate safeguards to prevent and treat status epilepticus.

Study designs which use placebos as the only medication in patients with a known seizure disorder are not recommended. Firm justification with specific indications is required to deprive a subject of all therapy in generalized tonic-clonic seizures. In some other forms of epilepsy (e.g., massive infantile spasms or absence), placebo may be justified as the sole source of therapy. Hospitalization is indicated in these situations.

PEDIATRIC SECTION

("General Considerations for the Clinical Evaluation of Drugs in Infants and Children" should be reviewed prior to reading this section.)

I. INTRODUCTION

Seizure disorders have certain age-specific phenomena and some types occur exclusively in children. In addition, an estimated 75 percent of seizure disorders have their onset in childhood. Since virtually all antiepileptic medications are eventually given to children, postmarketing studies designed to evaluate effects of the drug on growth and development of the brain and its cognitive functions should be considered.

II. CLINICAL STUDIES

Children should not be included in clinical trials until late-Phase II or Phase III unless the seizure type under study is restricted to the young-age period, e.g., absences, infantile spasmas or akinetic seizures. Even in these cases, safety studies should be performed first in adults. Children with other forms of epilepsy, considered for inclusion prior to late-Phase II or Phase III, should be selected on the basis of poor control on current medication or control obtained only at the cost of unsatisfactory levels of side effects. In such drug tests, full evaluation of the legal and ethical implications must be made. In cases where children are to be included in Phase I and early Phase II studies hospitalization or institutionalization with close and expert supervision is mandatory.

For study designs see the Adult Section of these guidelines. Studies should involve children and infants of varying ages and seizure types. In addition to safety and efficacy studies, pharmacokinetic studies should be performed.

Studies designed to test rates of learning and performance should also be included. Tests similar to those indicated in "Guidelines for the Clinical Evaluation of Psychoactive Drugs in Children" should be used.

Biostatistical consultation is recommended for help in designing efficient studies which maximize the amount of information obtained from the minimum number of subjects.

* U.S. GOVERNMENT PRINTING OFFICE: 1981 334-826/7021

UNITED STATES GOVERNMENT PRINTING OFFICE
DIVISION OF PUBLIC DOCUMENTS
WASHINGTON, D.C. 20402

OFFICIAL BUSINESS

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HHS Publication No. (FDA) 81-3110