CENTER FOR DRUG EVALUATION AND RESEARCH

Guidance for Industry

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

guidelines for the clinical evaluation of Hypnotic Drugs

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
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GUIDELINES FOR THE CLINICAL EVALUATION OF HYPNOTIC DRUGS

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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 HYPNOTIC 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.

I. EARLY PHASE I

A. Objectives

In early Phase I the overall objectives are:

1. To provide evidence of safety, pharmacological effects and dose related side effects of the drug.

2. To provide information regarding drug absorption, distribution, metabolism and excretion when technically feasible.

B. Subjects

"Normal," alert, adult volunteers who have been fully informed about the nature of the experiment, the agents being studied, and have given written informed consent. The criteria for "normalcy" are normal baseline physical examinations and laboratory and other clinical studies.

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

The following are to be excluded from Phase I in studies of hypnotic compounds:

1. Those requiring concurrent medication

2. Geriatric subjects

3. Known active alcoholics, known drug addicts or abusers, those with a past history of psychosis and those who are generally unreliable

C. Setting

Usually a confined setting in which provisions are available for close supervision and treatment on a 24-hour basis. Facilities selected should be capable of performing the required laboratory tests or have proper facilities for storing and shipping specimens for analysis.

D. Investigators

Competent individuals with experience in clinical pharmacology, psychiatry, or internal medicine who will conscientiously carry out frequent and thorough evaluation of all study subjects.

E. Study Design

Prior to receiving the study drug, all subjects should receive no other drug for a period appropriate to insure that there will be no metabolic or symptomatic carry-over 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 the others it would be much longer.

1. Single-Dose Trials

In evaluating safety and tolerance of hypnotics in normal humans, it is virtually impossible not to consider sedative-hypnotic effects. Therefore, many of the early studies will evaluate pharmacological activity as well as safety in normals. Since hypnotic drugs are generally given as a single bedtime dose, the single dose evaluation may provide data concerning the potential clinical dose. Divided daily dosage studies will not be needed. Studies may be open, single or double-blind and placebo or active drug controlled in balanced or imbalanced parallel groups.

Each study should encompass the following general principles:

(a) The initial dose in the first subject should be minimal and based on animal toxicity studies, e.g., a fraction of the maximum non-toxic dose in animals.

(b) Monitoring should be done before and after each dose (hence, the term single dose study) to determine that each dose level is safe before administering a higher single dose to the same or other subjects.

(c) Before repeating the same or higher dose in a subject, a sufficient interval should be allowed to insure "washout" (as determined by animal and evolving human pharmacokinetic and pharmacologic data).

(d) Residual effects of drug on alertness, mood change, judgment, muscle coordination, reflex changes, reaction times, memory and other adverse effects should be determined during the intitial studies if a placebo controlled design is employed.

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. Administer the initial dose to one subject in the morning, after a "normal" night's sleep. Monitor the effects for an arbitrarily set period of time, e.g., 2-3 days. If no pharmacologic or toxic effects occur, increase the dose in the first subject and start the second subject on the initial dose. Utilizing this technique, all subjects continue to receive increments of the drug until their maximum tolerated dosage is reached.

Studies of this type would provide a safe dose range and a rough estimate of the effective dose range.

The following is an example of another possible study design to determine a pharmacological profile of a proposed new hypnotic. In a single or double-blind study using groups of 4 to 6 subjects per dose start with a presumed subclincial dose and proceed through a series of doses which cause daytime sedation and daytime hypnosis, and stop with a dose which produces stage I anesthesia characterized by analgesia and arousable sleep. One or two subects of each group should receive a standard hypnotic such as sodium pentobarbital.

Effects of the drugs on the CNS can be determined by:

(a) Observation of behavior by a trained observer

(b) Drug effect on various tests of coordination, balance and reaction time

(c) Interpretation of scalp EEG recordings taken at the height of drug action and at intervals until normal

(d) Testing for lack of recall or amnesia

(e) Determining effects on the resting minute volume and the ventilatory response to CO_2

Effects of the drug on the cardiovascular system may be examined, for example, by determining the effect of 70^{o} tilt on cardiac output and peripheral resistance, by measuring systolic time intervals and by interpretation of standard 12 lead ECG's.

A study of this type will determine whether the drug has the proper onset and duration of action for a hypnotic, will predict the usual hypnotic dose for the general population, provide the margin of safety in dosage and point out possible side effects which may be different from those of known sedative-hypnotics.

2. Repetitive Dose Tolerance Studies

After determination of one or more potentially effective doses to be evaluated further (e.g., the expected therapeutic dose and one or two other possibly therapeutic doses), the determined fixed doses should be administered begining with the smallest and increasing to the largest, as a single daily dose for varying periods of time (3 to 4 weeks). See Section II (Late Phase I and Phase II) for discussion of more extended safety studies.

At least two such studies should be performed in institutions with controlled environment employing a small group of normal volunteers in each study. The studies should be double-blind, placebo-controlled in balanced or imbalanced parallel groups. If more than two fixed doses are evaluated, additional studies of this type will have to be performed (one study for each dose). As in the single dose trials, residual effect of drug on alertness, mood change, judgment, coordination, reflex changes, reaction time, memory and other adverse effects can be determined.

On completion of a given study, the effects of withdrawal should be determined, preferably by substituting placebo without the patient's knowledge, for a period of 1 or 2 weeks.

F. Assessment of Safety Parameters

Safety and/or toxicity are usually assessed by baseline and repeated extensive physical examinations: vital signs assessments; laboratory tests to assess the hematopoietic, hepatic, renal and cardiovascular systems. It is beyond the scope of these 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 during at least the first week after discontinuation of the drug.

G. Documentation

Basically all study documentation should include the following:

1. Subject identification, demographic data, pertinent medical history, vital statistics

2. Pre-and post-treatment physical examination results

3. Details of administration of medication and dosage adjustment

4. All behavioral and emotional effects observed or reported

5. All adverse reactions reported or observed, the date, the severity and duration of such reaction, the investigator's judgment of whether drug-related

6. All laboratory reports, including normal range for the particular lab used

H. Pharmacokinetic Studies

During the initial single and multiple dose safety studies, the absorption, metabolism and half-life of the drug should be determined, if feasible, since these data are 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.

II. LATE PHASE I AND PHASE II

A. Objectives

In Phase II the overall objectives are:

1. To identify types of insomnia which may be responsive to the drug

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

3. To identify adverse effects

B. Subjects

Late Phase I and early Phase II studies can be conducted primarily with inpatient or outpatient adult males and females of non-childbearing potential, depending upon the degree of supervision feasible. For example, outpatients may be utilized in sleep laboratory studies because of the high degree of supervision and monitoring which is involved. The sample should be as homogeneous as possible, considering the following: age, sex, weight, and treatment setting. Patients should continue to be monitored for safety of the drug, as described in the early Phase I outline. The use of normal or good sleepers is not warranted in efficacy studies.

Patients evaluated in late Phase I and early Phase II should require no concomitant medication and have no organic diseases that may obscure clinical observations or laboratory test interpretations.

1. Patients, in general, should be inpatients with varying types of insomnia, such as difficulty falling asleep, difficulty staying asleep, premature final awakenings or a combination of these complaints and:

   a. Stable medical conditions

   b. Post-operative status without significant discomfort, and not requiring concurrent medication which would interfere with the evaluation of a hypnotic

   c. Rehabilitation status with similar criteria as given in b, above

   d. Freedom from hepatic and renal dysfunction and cardiopulmonary decompensation

   e. A negative history of drug reactions

2. For sleep laboratory trials, patients can be medical or psychiatric outpatients with varying types of insomnia and:

   a. Same as a-e, above

3. Exclusions (in addition to considerations listed above):

   a. Known active alcoholics, drug addicts or drug abusers, mental retardates and those with a past history of psychosis

   b. Patients using other hypnotic or CNS drugs

C. Setting

1. Clinical trials - Late Phase I and Phase II determinations of efficacy require regular monitoring (observation) at regular intervals throughout the night. As such, inpatient settings should be used.

2. Sleep Laboratory Trials - Since the sleep laboratory provides a setting in which sleep is continuously monitored throughout the night, outpatients or volunteers with insomnia may be used.

D. Investigators

The investigators should be competent in clinical pharmacology, psychiatry or internal medicine and have experience in evaluating CNS 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. The investigators must carry out frequent and thorough evaluations of all study subjects. In the case of sleep laboratory trials, investigators should also be qualified and experienced in sleep laboratory methods.

E. Study Design

1. Short-Term Clinical Trials

Patients should be selected to provide an unbiased sample of the population of interest and should be assigned to treatments at random or in a stratified random design. Pre-drug history and type of insomnia, according to criteria set forth in study protocols, should be documented and recorded.

Each study subject who is receiving a drug which could interfere with evaluation of safety and efficacy of the investigational hypnotic drug 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 which the subject had been receiving. Those subjects in whom this is not feasible should be excluded.

Baseline testing 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.

In late Phase I, several uncontrolled trials may be desirable to allow investigators sufficient flexibility to explore all 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 double-blind 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 among investigators in order to facilitate the interpretation of results.

In Phase II studies, the investigational new drug should be compared in double-blind fashion to a matching placebo control to establish its efficacy. Other studies should include an active treatment control and placebo. Packaging and coding of medications should be performed on an individual patient basis rather than on a treatment group basis. Other psychoactive and CNS depressant drugs are to be avoided. If other drugs are used, this should be carefully documented.

At least three, multiple, consecutive night, randomized, double-blind, placebo-controlled, balanced parallel group studies, using adequate numbers of insomniac patients, should be carried out to compare drug and placebo in a between-groups design. If a comparison of drug and placebo in a within group design is desired, at least three placebo baseline nights should precede the 3-5 consecutive nights of test medication. One or two of a few estimated effective doses should be selected for use in each study. The necessity for more than three studies at this stage will partially depend on the doses selected, how definitive are the results, and the type and severity of the side effects produced. If the latter are pharmacologically related, further studies should include lower doses.

The planning of this design, including the number of subjects to be studied and other aspects of these studies, should, whenever feasible, involve consultation with a biostatistician. There should be full awareness of the advantages, disadvantages, and criteria for validity regarding each possible design before selecting one.

a. Dosage

(1) Exploratory, open 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 is indicated.

(2) Double-blind, controlled studies

Dosage should be fixed.

b. Assessment of Efficacy Parameters

(1) Subjective (patient's evaluation) - post-sleep questionnaire filled out after morning toilet and dressing.* The most important, analyzable parameters are:

(a) Sleep induction time or sleep latency (time to fall asleep)

(b) Number of nocturnal awakenings after onset

(c) Presence or absence of premature final awakening

(d) Total sleep time

(e) Drug "hangover"

(f) Other parameters may be added, i.e., quality (soundness or patient satisfaction) of sleep, dreams, etc.

(2) Objective (nurse/monitor evaluation). Observations made at regular, frequent intervals from lights out until resumption of routine A.M. hospital activity. A total sleep period of 7-8 hours should be made possible. Parameters measured are the same as given in a-e, above.

C. Assessment of Safety Parameters

Physical examinations and clinical laboratory tests are basically the same as those for Phase I.

Adverse reactions due to drug and those due to other causes, e.g., concurrent medication, placebo reaction or treatment must be carefully documented, evaluated and analyzed. If the side effects are severe enough to discontinue the subject from the study, this should be stated.

Appropriate and validated rating scales as well as global assessment may be used. If an investigator has rating scales or methods which have been validated and tested for reliability and with which he is thoroughly experienced, it may be preferable for him to use them. The use of rating scales may allow a determination as to whether a hypnotic drug has an effect on emotional symptoms during the day.

2. Short-Term Sleep Laboratory Trials

In an attempt to ascertain as early as possible whether the compound is an effective hypnotic, sleep laboratory studies should be carried out as soon as a rough therapeutic dosage range is known and short term safety is assured. The sleep laboratory offers a reliable objective method for screening the effects of the drug.

*It is suggested that the post-sleep questionnaire be administered after, rather than before, morning toilet and dressing. This may help to differentiate between residual morning sedation due to test medication and somewhat similar manifestations which may occur as part of the normal awakening process. If symptoms of sedation continue after toilet and dressing into the late morning and persist or recur later in the day, they should be considered as drug-related adverse effects. Additional questions relative to adverse effects, mood and performance should also be answered later in the day.

At least two sleep laboratory drug evaluation studies should be carried out using a total minimum of 12 insomniac subjects. The study should include a series of at least four consecutive placebo nights to allow for adaptation to the laboratory effects and the ascertainment of baseline sleep measurements.

The drug administration period should extend for at least 5-7 consecutive nights allowing for the determination of initial and short term effects of the drug. Immediately following this, there should be a placebo withdrawal period of at least three consecutive nights.

Recordings should begin immediately at lights out and extend for a 7-8 hour period with total bed time being held constant throughout the study.

Subjects in this design are used as their own controls as all comparisons are made to baseline. Crossover studies comparing the experimental drug to a reference drug can be carried out providing an adequate washout is observed and repeated design with a placebo baseline and withdrawal is included.

a. Dosage

Dosage should be fixed.

b. Assessment of Efficacy Parameters

(1) Subjective

Assessment is the same as described under Short Term Clinical Trials.

(2) Objective (polygraphic recordings)

The most important parameters are:

(a) Sleep induction time or sleep latency (time to fall asleep)

(b) Number of nocturnal awakenings after onset of sleep

(c) Early final awakening

(d) Total wake time after sleep onset

(e) Total sleep time

(f) Sleep stage alterations, e.g., REM or NREM sleep, REM latency, etc.

Data should be analyzed for each night and by segments of the night for each night across all conditions. Data should be collected for a 7-8 hour period. Each drug and withdrawal condition should be contrasted with baseline.

c. Assessment of Safety Parameters

Assessment is the same as described under Short Term Clinical Trials.

d. Sleep Laboratory Methods

Detailed descriptions are available in published medical literature for recording and sleep scoring techniques used in the sleep laboratory and for the methods of sleep laboratory drug evaluation studies.

3. Chronic Tolerance Studies (Safety)

Ordinarily this type of study is performed during Phase I before early efficacy studies are conducted. However, with a hypnotic, where early efficacy studies are of a few days duration, chronic safety studies in humans can be postponed until it has been determined on the basis of short-term safety and effectiveness information that the investigational drug is of interest.

The purpose of these studies is to further evaluate safety in a larger number of volunteer subjects.

Adequate numbers of subjects must be studied, preferably by two investigators. Studies should be randomized, double-blind, placebo or active drug-controlled in balanced or imbalanced parallel groups. Because of the duration of these studies it is desirable to use volunteers with insomnia rather than normal sleepers. Likewise, it may not be feasible to keep insomniacs on placebo for the length of these studies so that use of an active control may be considered.

Pretreatment physical examination similar to that mentioned under early Phase I, "safety" lab batteries for hematopoietic, renal and hepatic functions and special evaluations, e.g., EEG, ECG, eye exams, respiratory and cardiovascular function tests should be carried out as indicated by the nature of and previous experience with the drug. Even if previous studies do not indicate the necessity for special tests noted above, a certain proportion of subjects in both groups should be so studied. All of the above observations should be repeated at appropriate intervals during the course and after withdrawal of treatment, the intervals depending on the nature of and previous experience with the drug.

Pretreatment evaluations of alertness, mood, judgment, coordination, reflexes, reaction time and other performance tests, with repeat evaluations at appropriate intervals to test daytime residual effect of different dosages of the drug during administration and after withdrawal, could, if feasible, also be carried out.

Studies should run between 8-12 weeks starting with the estimated minimal effective dose and increasing to the highest tolerated therapeutic dose to be given at bedtime. At the end of the trial, withdrawal by placebo substitution for two weeks should be carried out. Special monitoring for a potential seizure disorder or other withdrawal phenomena is desirable and should continue for periods of time determined by data obtained from pharmacokinetic studies.

III. PHASE III

A. Objectives

1. Extend and confirm the drug's clinical efficacy and duration of efficacy in heterogeneous patient populations.

2. Provide more specific information about the types of insomnia for which the drug is especially effective.

3. Establish optimal dosage in the population(s) for which it is intended under conditions which more closely resemble those of actual therapeutic use.

4. Establish the duration of continued effectiveness of the drug when given up to 6 months.

5. Establish the safety of the drug when given daily for up to 6 months.

B. Subjects

The same comments apply as in Phase II. In Phase III, larger and more heterogeneous population samples may be studied. In such studies the investigator may employ sample characteristics in his analysis or results to provide more precise estimates of drug effects, to learn more about the effects of the sample characteristics themselves, and to delineate the most responsive subsamples. The five conditions which account for the vast majority of difficulties with insomnia are situational stresses or crises, medical conditions, psychiatric disorders, drug-withdrawal insomnia, and aging. Most outpatients with chronic or severe insomnia fall within the diagnostic category of the neuroses or personality disorders and have a history of chronic anxiety or depression or anxiety mixed with depression. The use of normal or good sleepers is not warranted in efficacy studies.

After controlled studies have indicated the drug's basic hypnotic activity, later studies in this Phase may explore its efficacy and safety in patients with organic or functional disease requiring concomitant medication.

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

Children may be studied in separate trials provided the clinical picture warrants drug administration and safety is assured to the fullest extent possible. Geriatric samples generally also should be studied separately, as responsiveness in different age groups can vary greatly.

C. Setting

May be varied, e.g., inpatient, outpatient, private practice, psychiatric, non-psychiatric, any specialty or general practice.

D. Investigator

Qualified physicians in various specialities with an interest in the clinical evaluation of hypnotics or other CNS-active drugs. They should have ready access to the appropriate population group for whom the drug may be indicated. The investigators must be able to carry out frequent and thorough evaluations of all study subjects.

E. Study Design

A major area of importance during Phase III evaluation of a hypnotic drug is the performance of controlled studies designed to further confirm the drug's basic hypnotic efficacy. The design guidelines for Phase III are generally the same as those discussed in Phase II. However, in order to accommodate greater variations in purpose of studies, settings, investigators and subjects, adjustments may be made in controls, duration of study, dosage and design which do not interfere with validity. (Biostatistical consultation is recommended.)

When it is concluded that the drug's basic hypnotic efficacy has been clearly established by controlled studies, consideration may be given to undertaking further studies on an open trial basis. 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 can lead to hypotheses which can be confirmed or refuted by reviewing already completed studies 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 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 basic hypnotic claim. For each of these other areas, a few 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 (such as the geriatric) carefully edited clinical pharmacology and therapeutic trials (i.e., they need not include all parameters of other studies) may be carried out to establish tolerance, efficacy and safety.

Long-term safety evaluations may be performed in both open trials and controlled parallel groups design. For controlled studies, imbalanced groups may be used, e.g., 30 drug and 20 controls.

Data regarding long-term safety should 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.

All controlled trials should be randomized and double-blind. Short-term, intermediate term and long-term studies should be controlled with placebo and/or a standard reference. Dosage is to be indicated by type of population and setting.

1. Short-Term Clinical Trials

   a. The sleep on a placebo night can be affected by the administration of a hypnotic drug on the previous night, e.g., carryover effect may improve sleep while certain withdrawal effects may worsen sleep. Therefore, for these studies, a single, paired night (2 consecutive nights) design, in which a placebo is either followed by a second placebo night (PP) or a drug (PD), should be used. Several hundred insomniac patients, both inpatient and outpatient, should be evaluated, the exact number in each study to be determined by biostatistical consultation.

   b. Multiple, consecutive night (3-7 drug nights), randomized, double-blind, balanced, parallel group studies using an adequate number of insomniac patients to compare drug and placebo in a between groups design. For comparison of drug and placebo in a within group design, at least three placebo baseline nights should precede the 3-7 consecutive nights of test medication. If a crossover design is used, there should be an adequate no-drug period between treatments.

2. Intermediate Term Clinical Trials

   Studies in which the drug is administered for 2-3 consecutive weeks should be carried out using an adequate number of insomniac inpatients or outpatients. The studies may be of a within-group or between-groups design but all studies should include up to 3 placebo baseline nights and 3 placebo withdrawal nights so that withdrawal effects can be properly evaluated, e.g., drug withdrawal

may result in a worsening of sleep beyond baseline levels. When inpatients are utilized and it is feasible, nurse-monitor objective data should be collected, and all patients should report subjective estimates of sleep duration and quality on a daily basis each morning.

3. Intermediate Term Sleep Laboratory Trials

A minimum of 2 separate sleep laboratory studies in at least two different laboratories should be carried out with a total minimum of 12 subjects. Designs should be similar so that data can be analyzed separately or as a pooled sample. Drug administration period of at least 2 weeks should be preceded by at least 4 placebo nights for purposes of adaptation to the sleep laboratory and baseline measurements and followed by at least 3 placebo nights to evaluate withdrawal effects, if any.

It is not necessary to record all nights in the sleep laboratory. However, selected sampling for each condition, i.e., short-term drug, intermediate term drug and withdrawal should allow for readaptation and include a minimum of 3 consecutive nights of recording.

4. Long-Term Clinical Trials

Long-Term Phase III clinical trials of hypnotic drugs have never been well defined. In the past, it was customary to perform a chronic trial with a new drug that used a historic control as comparison for efficacy. Even when a standard hypnotic is employed as a parallel control, problems arise from the difficulty inherent in proving a null hypothesis and from the lack of knowledge as to whether the patients required hypnotic therapy during the entire duration of the trial.

Nevertheless, it is important to attempt to establish when tolerance to the hypnotic effect begins to occur following chronic use. It is also necessary to obtain safety data on long term use by patients of various age groups with and without concurrent disease.

Several types of chronic studies of up to 24 weeks duration may be considered:

a. Double-blind parallel studies using a standard reference agent or, in the shorter trials, placebo

b. Double-blind crossover studies using a standard reference agent

c. Double-blind crossover studies using a standard reference agent and a placebo

d. A within group design which would include at least 3 placebo baseline nights and placebo withdrawal nights so that withdrawal effects can be properly evaluated. Further, since most hypnotic drugs lose much of their effectiveness within two weeks of consecutive nightly use, the inclusion of a placebo baseline period provides a better means of evaluating whether tolerance or loss of effectiveness begins to develop.

In a and c, above, the use of a long-term placebo control may be quite unfeasible due to a high dropout rate. Thus, it may be necessary in conducting long-term clinical trials to use a standard reference agent.

With outpatients, daily logs or telephone reports should be obtained. The log should provide not only for efficacy data but also for information which

could impact on efficacy, e.g., temporary emotional upsets, mental stimulation, excess caffeine consumption, alcohol intake, ingestion of antacids, a large meal prior to bedtime.

5. Long-Term Sleep Laboratory Trials

Because sleep laboratory trials require a smaller number of subjects and compliance is less of a problem, long-term sleep laboratory trials are more feasible than long-term clinical trials. Long-term sleep laboratory studies of hypnotic drugs are necessary both to determine whether the effectiveness of a hypnotic drug is maintained and whether extended use produces sleep alterations not found in shorter term studies.

A minimum of two separate sleep laboratory studies in at least two different laboratories should be carried out with a total minimum of 12 subjects. Designs should be similar so that data can be analyzed seaparately or as a pooled sample. Studies should include at least 4 nights of placebo for adaptation and baseline purposes, at least 4 weeks of consecutive drug administration and at least 3 nights of placebo withdrawal to evaluate withdrawal effects if any. It is not necessary to record all nights in the sleep laboratory. However, selected sampling for each condition, i.e., short-term drug, intermediate term drug, long-term drug and withdrawal should allow for readaptation and include a minimum of 3 consecutive nights of recording.

F. Assessment of Safety Parameters

This is generally similar to that outlined for Phase II. The usual "safety" laboratory tests should be performed at weekly intervals for the first month and less frequently thereafter while on the drug, with similar monitoring continuing during an extended withdrawal period.

G. Special Studies

1. In vitro protein binding studies

2. Interaction of the drug with alcohol. Other drug interaction studies may optionally be performed

3. Studies of the effects of the drug on vital processes (e.g., respiration, blood pressure and circulation). Much of this information can be obtained in the studies described in Phase I

4. Tests for dependency-producing properties and abuse potential. These should be preceded by appropriate animal testing for dependency-producing potential. e.g., in dogs or monkeys

   a. Clinical trials should be done to evaluate hypnotic-like subjective effects and reinforcing characteristics. Preferably, subjects with prior drug experience should be used. A standard hypnotic (usually a barbiturate) should be used for comparison. Both subjective effects (i.e., "liking") as well as objective measurements should be monitored.

   b. Direct testing of physical dependence capacity in humans should probably not be done on a routine basis because of the hazards and difficulties involved. Direct testing of physical dependence capacity should be done in animals rather than man.

5. Tests of the effects of the drug on performance following an intervening sleep period. These tests may include evaluations for motor coordination, reaction time, memory, etc.

6. Sleep laboratory studies of neuroendocrine function may be carried out with drugs found to alter specific sleep stage characteristics associated with hormonal release patterns. For example, growth hormone secretion patterns suggest a relationship between plasma peaks and slow wave sleep. In turn, drugs that suppress slow wave sleep may have an effect on growth hormone release.

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