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A Model for Pharmacological Research-Treatment of Cocaine Dependence

Ivan D. Montoya, MD, MPH, Judith M. Hess, MA, Kenzie L. Preston, PhD, and David A. Gorelick, MD, PhD

National Institutes of Health, National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD

Abstract

Major problems for research on pharmacological treatments for cocaine dependence are lack of comparability of results from different treatment research programs and poor validity and/or reliability of results. Double-blind, placebo-controlled, random assignment, experimental designs, using standard intake and assessment procedures help to reduce these problems. Cessation or reduction of drug use and/or craving, retention in treatment, and medical and psychosocial improvement are some of the outcome variables collected in treatment research programs. A model to be followed across different outpatient clinical trials for pharmacological treatment of cocaine dependence is presented here. This model represents an effort to standardize data collection to make results more valid and comparable.

Keywords

clinical trials; cocaine; dependence; pharmacotherapy; model

INTRODUCTION

Controlled clinical trials are the best method available to determine the efficacy of a medication, but the heterogeneity of methods used frequently does not allow comparisons of the results across studies. In the pharmacotherapy of cocaine dependence, many agents have been investigated (Gorelick, 1995) using dissimilar research methods which hamper direct comparisons of the results (Levin & Lehman, 1991). Positive results from open trials may be reported by the popular and medical press as a “cure” for cocaine dependence (Halikas, Kemp, Kuhn, Carlson, & Crea, 1989) even before completion of double-blind clinical trials which may not confirm the early positive findings (Montoya, Levin, Fudala, & Gorelick, 1995). Overt as well as hidden bias observed in open-label studies may explain the differing outcomes in the experimental and control groups (Rosenberger, 1991). Recently, the establishment of a structured reporting of randomized controlled trials has been proposed to improve the reporting of these trials and solve the problem of heterogeneity of reports (The Standards of Reporting Clinical Trials Group, 1994).

Failure to replicate results in cocaine dependence treatment research may be due not only to lack of an effective medication but also variations in study quality and design. Differences in study population, definitions of outcome variables, methods for data analysis, and length of

treatment are some of the major obstacles to cross-study comparisons and generalizability of study results. In some cases, the relevant factors may often not be described in the published reports (*e.g.*, patient sociodemographic characteristics) (Gorelick & Montoya, 1994). Double-blind, random assignment, experimental designs, using standard intake and assessment procedures, help to reduce these problems (Ashery, 1993).

The following are the usual phases of testing medications for treatment of cocaine abuse: *Phase 1*: Medication is administered to normal volunteers to establish safety and approximate dose ranges. Metabolic and pharmacokinetic studies are conducted and potential adverse effects are evaluated. Comparison with placebo is preferable. Medications such as mazindol, carbamazepine, and bromocriptine are at this testing phase (Schuster, 1993). *Phase 2*: Medication is administered for a limited period of time to patients to evaluate the potential therapeutic usefulness, comparing with placebo. Desipramine and imipramine are at this testing phase (Schuster, 1993). *Phase 3*: Medication is administered to a larger and more varied population of patients for a longer period of time to get a more representative evaluation of efficacy and safety. *Phase 4*: After a new medication has been commercially available, rare and/or serious adverse events are evaluated through "post-marketing surveillance." No medication for treatment of cocaine dependence is at phase 3 or 4 of research (Schuster, 1993).

The results of most cocaine pharmacotherapy studies are still inconclusive. Medications such as bupropion or bromocriptine with dopaminergic effect, fluoxetine or buspirone with serotonergic effect, or carbamazepine with anticonvulsant effect have been investigated for treatment of cocaine dependence (Gorelick, 1995). Desipramine is one of the medications more thoroughly studied for treatment of cocaine dependence, however, its proposed efficacy has neither been conclusively documented nor refuted. A meta-analysis of six double-blind desipramine studies showed that desipramine was better than placebo in promoting cocaine abstinence but similar to placebo in improving retention in treatment. The authors found that one of the major difficulties in conducting the meta-analysis was the great differences in study quality and design (Levin & Lehman, 1991). Later double-blind studies have failed to demonstrate the efficacy of desipramine (Arndt, Dorozynsky, Woody, McLellan, & O'Brien, 1992; Kosten, Morgan, Falcione, & Schottenfeld, 1992; Covi, Montoya, Hess, & Kreiter, 1994).

The Treatment Branch of the Division of Intramural Research, National Institute on Drug Abuse, National Institutes of Health (NIDA-DIR) has established a model that is followed across different studies in its outpatient research clinic to standardize the collection of data, make results more comparable across studies, and to realistically model conventional (nonresearch) treatments as delivered in the community. This article presents these methods, describing the selection of subjects, active treatment, follow-up evaluations, research instruments, data analysis, and result reports. The methods suggested here represent an empirical proposition that is useful at our center but have not been scientifically validated. They are open for improvements or modifications to meet the specific requirements of those who might use them.

INTAKE EVALUATION

A comprehensive intake assessment is essential for determining the eligibility and comparability of applicants for the study and to collect baseline data. A balance should be established between strict eligibility criteria that may limit the generalizability of results and the great heterogeneity of applicants to clinical trials for cocaine dependence, which may complicate data analysis and interpretation of results. In this model, applicants are screened according to the inclusion/exclusion criteria defined by the protocol. In general, subjects are

at least 18 years old, and meet clinical history and *DSM-III-R* (American Psychiatric Association, 1987) criteria for cocaine dependence. *DSM-IV* criteria will be adopted in future studies.

Common exclusion criteria are: (a) current dependence on other psychoactive substances except for caffeine and tobacco, defined by *DSM-III-R* criteria (this criterion is modified in studies of multiple dependency); (b) inability to read or understand the consent form or questionnaires; (c) severe medical or psychiatric illness that in the judgment of the investigators would impair the subjects' ability to safely participate in the studies; (d) legal problems that would prevent the subjects' completion of the study.

The intake process takes approximately two 4-hour sessions. It is recommended that these sessions be no more than 30 calendar days apart and as close as possible to avoid losing applicants and maintain validity of psychological and laboratory data. On the first day of intake, the applicant gives consent for assessment, is interviewed to determine his/her admissibility to the treatment research, and provides sociodemographic information. The applicants undergo laboratory testing including urine drug testing, routine urinalysis, blood count, blood chemistry profile, HIV antibody test (with pre-test counseling), hepatitis B surface antigen, RPR, PPD, and any other test needed to determine both medical eligibility and baseline measures pertinent to the particular protocol.

Cocaine-dependent subjects often present with comorbid disorders that may affect the outcome of the pharmacological treatment being tested (Blaine, Ling, Kosten, O'Brien, & Chiarello, 1994). A battery of tests are used to assess subjects' past and current psychiatric status, drug use and craving, and comprehension of study material. The instruments used are: the Shipley Institute of Living Scale (SILS) (Shipley, 1940), Symptom Check List-90-Revised (SCL-90R) (Derogatis, 1983), Addiction Severity Index (ASI) (McLellan et al., 1986), Diagnostic Interview Schedule (DIS) (Helzer, Croughan, Robins, & Ratcliff, 1981), Personality Diagnostic Questionnaire-Revised (PDQ-R) (Hyler, Skodol, Kellman, Oldham, & Rosnick, 1990), Beck Depression Inventory (BDI) (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), and Minnesota Cocaine Craving Scale (MCCS) (Halikas, Kuhn, Crosby, Carlson, & Crea, 1991). The results of these tests can provide a profile of the psychosocial characteristics of the research subjects. Stratification by some of these characteristics (either prospective or post-hoc) can help to control for the potential confounding effect of major differences in the study groups on factors such as dual diagnosis or dual dependence.

The SILS is used as a screening tool to assess cognitive functioning and intellectual ability. The test yields 6 summary scores:

1. Vocabulary score,
2. Abstraction score,
3. Total score,
4. Conceptual quotient and impairment index,
5. Abstraction quotient,
6. Estimated full-scale IQ score based on the Wechsler Adult Intelligence Scale (WAIS).

The SCL-90R is a multi-dimensional self-rating scale of current (past 7 days) psychopathology that consists of 90 items each measured on a 5-point scale, yielding 9 subscales and a summary score of psychiatric symptomatology. The subscales are: somatization, obsessive-compulsive, interpersonal sensitivity, anxiety, hostility, depression, psychoticism, phobic anxiety, and paranoid ideation.

Subjects are interviewed using the ASI, a semi-structured clinical/research interview that evaluates medical condition, employment, finances, drug use, alcohol use, illegal activity, family relations, and psychiatric condition. The number, extent, and duration of each problem area are assessed both for lifetime and past 30 days. The ASI has concurrent and discriminant validity among substance abusers applying for treatment. The ASI is also utilized to systematically collect demographic information.

The DIS is a structured interview used to determine *DSM-III-R* psychoactive substance use and other comorbid disorders and it is administered by lay interviewers. The DIS can be used to make diagnoses of most Axis I disorders (somatization, panic, generalized anxiety, phobic, obsessive-compulsive, post-traumatic stress, depressive and manic, schizophrenia, anorexia nervosa, bulimia, psychoactive substance use, psychosexual, organic mental, and dementia) and antisocial personality disorder.

The PDQ-R is a self-report instrument used to evaluate axis II disorders; it has high sensitivity, and moderate specificity and is useful as a screening tool which provides an overall total score as an indicator of global personality disorder. The BDI has been extensively used in substance abuse treatment research (Steer, Iguchi, & Platt, 1992). It provides a quantitative assessment of the severity of depression. The internal consistency and stability of the instrument and its agreement with clinicians' judgements illustrate its high reliability and validity. The MCCS is a reliable and practical tool for evaluating intensity, duration, and frequency of cocaine craving. The scale is recommended for studies testing anti-craving medications.

Cocaine use, as well as other drug use, is frequently inconsistently reported in clinical trials. At the NIDADIR, initial assessment of drug use uses parameters similar to those used by the NIDA National Household Survey on Drug Abuse (U.S. Department of Health and Human Services, 1991): ever used, and use in the past year and past 30 days. Drug use history is also collected in terms of the amount used in grams and the dollar value of the drug used, in the past 24 hours and past 7 days. This method using fixed, easy-to-anchor time intervals minimizes carryover and overestimation of drug use and reliance on subjects' memory. Because self-reported drug use is subjective and frequently unreliable, urine drug tests are necessary to document the recent use of cocaine.

On the second day of intake, subjects have a complete medical history and physical examination. Results of the laboratory tests are reviewed and discussed with the subject. At this time, HIV antibody test results are given to the subject along with post-test counseling. Other diagnostic procedures such as EKG or EEG are done if needed. Subjects who meet all the inclusion and exclusion criteria are consented to the study by an investigator. The IRB-approved consent form is read aloud to them and subjects answer a true-false consent-comprehension test to confirm full understanding of the consent form.

ACTIVE TREATMENT

Subjects who have consented to participate are scheduled to come to the clinic for treatment visits a specified number of times that varies according to the protocol design. The optimal frequency of clinic visits has not been established. For some medication studies subjects are scheduled to come 2 or 3 times per week to be medicated at the clinic and to pick up additional doses to ingest at home. Usually, counseling is provided during these medication visits, 1 or 2 times per week.

There is no established optimal length of initial active treatment. The research treatment model proposed here has a duration of 8–12 weeks. This duration was established to balance the need for sufficient time to allow treatment effects to become manifest versus the need to minimize the time and resources needed to complete a research study. For double-blind studies, the use

of an active placebo to evaluate psychotropic medications is recommended (Fisher & Greenberg, 1993) to limit medication discrimination by subjects and/or treatment staff, thus maintaining the double-blind nature of the study. Debriefing of patients and staff at the end of active treatment is also recommended to explicitly evaluate the success of the blinding.

Questionnaires, either computerized or pencil/paper, are administered during clinic visits to evaluate cocaine use and craving, mood state, and recent psychological functioning. The BDI, MCCS, and SCL-90R are self-administered every week. The drug use during the past 7 days is obtained by interview with a research technician. The systematic collection of these questionnaires before the counseling session helps clinicians and investigators to consistently assess treatment response and group differences in treatment outcome.

Vital signs, drug use during the past 24 hours, and side effects are collected at each clinic visit. A systematic approach to the detection, classification, and documentation of adverse events is recommended (Tangrea, Adrianza, & McAdams, 1991). Onset and resolution, type of report, relatedness to the medication, severity, action taken, and outcome of the symptoms are systematically collected using a standard questionnaire.

To insure compliance, medication is taken at each clinic visit in the presence of staff. Subjects are also given a medication diary to complete every time they take the medication, and medication blood levels are periodically checked. Some investigators have also used medication markers such as riboflavin to determine medication compliance (Satel & Kosten, 1991).

Urine samples for toxicological analysis are collected under direct observation of a staff member. A cutoff of 300 ng/mL of cocaine metabolite benzoy-lechonine (BE) is currently recommended for defining a "positive" sample. Quantitative analysis of BE in urine samples has not yet been established as usefully worth the increased cost. The uncertainty of the number and timing of episodes of drug use, variations due to spot urine sampling, and individual differences in metabolism rate currently limit the interpretation of quantitative drug results (Cone & Dickerson, 1992).

A fixed time sampling scheme is preferable to a random time sampling scheme for collecting urine toxicology samples. The most efficient urine testing schedule without the risk of carryover effects is 3 days a week, e.g., Monday, Wednesday, and Friday or Tuesday, Thursday, and Saturday (Cone & Dickerson, 1992). The drawbacks of fixed time sampling are the potential to underestimate positive samples collected 72 hours after cocaine use, and to condition subjects' drug use to those days when they know cocaine will not be detected. This is especially true for treatments involving contingencies based on urine drug results. However, random urine testing is not recommended for clinical trials because of the potential heterogeneity that may result in nonanalyzable data (Jain, 1992a).

Counseling is an important component of the research treatment. The outcome of the pharmacotherapy can be greatly affected by the psychosocial treatment. Given the relatively modest effect obtained to date with medications for treatment of cocaine dependence, a controlled, standard, and well-documented psychosocial treatment should be equally available to all subjects (Blaine et al., 1994). In this model, all counselors are trained to provide a standardized counseling for all subjects. Periodic case conferences are used to maintain standardization of counseling and study methods. An integrated interpersonal/cognitive behavioral approach, with individual sessions once or twice per week, is currently being used. A summary of each session is documented in the subject's clinical chart.

The counseling treatment used in this model has three phases. The goals at each phase are: (a) to develop treatment alliance, review of personal history, and formulate problems and goals;

(b) to explore and modify problems on initial patient's list or newly identified problems, discuss and develop strategies for achievement of goals on initial list and newly identified goals, and learn how to manage drug cravings and use; and (c) to review changes that have occurred during treatment, new strategies and skills acquired or not achieved, review power hierarchy diagram and restructuring of habits and associations, explore vulnerabilities to relapse, resolve separation and termination issues, and review the use of available support resources. In general, 6 components are part of each counseling session: (a) events and problems since the last session and evaluation of progress, (b) use of drugs or alcohol since the last session, (c) recent urine drug test results, (d) cognition and affects accompanying the use of or abstinence from drugs, (e) exploration of foreseeable future events, and (f) discussion, conclusion and agreed on homework (Covi, Hess, & Kreiter, 1993).

The manual driven counseling used in this model has the important advantage of controlling many confounding factors (e.g., reducing variability across different therapists) involved in delivering psychotherapy as part of research and, unlike some other manual driven psychotherapies, it uses a wide-range of psychotherapy techniques. It has the clinical disadvantage of using a fixed method and being focused on stimulant abuse or dependence.

At the end of the medication treatment subjects receive a termination medical and psychological evaluation (exit interview) that consists of a complete physical examination, laboratory tests, and a semi-structured interview. The interview assesses: (a) the reasons why the subject stopped the treatment, (b) the subject's perception of the program and the medication, (c) the effect of the treatment on drug use and craving, and (d) the presence and intensity of medication side effects. Other baseline psychometric measures such as the MCCS, BDI, SCL-90R, as well as the ASI, are repeated. Reported drug use in the past 24 hours and past 7 days, and a urine toxicology test are also obtained. At the end of the exit interview, referral to community programs is offered to those individuals who wish to continue in treatment.

FOLLOW-UP

All consented subjects are asked to return to the NIDA-DIR for follow-up assessments at 3 months, 6 months, and 12 months after the end of the active treatment. The objective of the follow-up visits is to evaluate the long-term impact of the treatment. The subject meets with a research technician who collects data on the primary and secondary outcome measures. This evaluation takes about 2 hours. Subjects are paid for the exit interview and follow-up visits.

OUTCOME MEASURES

Outcome measures are physiological and psychological variables used to determine the therapeutic effect of a medication. Cessation or reduction of drug use and/or craving, subject retention in treatment, and changes in medical and psychological status are some of the outcome variables assessed in treatment research programs. The Food and Drug Administration recommends that clinical trials have no more than four primary outcome variables without penalizing for multiplicity. A pattern of similar results from different outcome variables strengthens the conclusions of a clinical trial. The primary outcome variable in most studies is toxicological analysis of observed urine samples, which provides safely and cheaply obtainable objective measure of drug use that can be analyzed either categorically (e.g., "positive" versus "negative" urines) or quantitatively.

Jain (1992b) postulated that if a proposed treatment has sufficient clinical robustness, clinical trials of different designs should lead to the same conclusions. However, cocaine treatment research is at such an early stage of development that the effect size of the medications studied is not sufficiently large to show consistent effects with different trial designs. The use of

comparable outcome measures, as well as appropriate statistical techniques, may help researchers to find differences that otherwise would not be detected.

DATA ANALYSIS

Data analysis of cocaine treatment double-blind clinical trials poses particular challenges (Lavori, Laska, & Uhlenhuth, 1994). One of the major problems is missing data, especially when the proportion of missing data is large and/or it is not randomly distributed across subjects and groups, as is too often the case. We present here some general methods to manage missing data and provide references for more detailed information (Little & Rubin, 1987; Simon, 1991; Laird, 1988).

There are 2 types of missing data: (a) subject early dropout from treatment (attrition), and (b) missing data time points. Missing data from early dropouts may be managed by carrying forward data from the last timepoint obtained, by including in the analysis only the timepoints obtained (i.e., using data from the remaining subjects at each data collection point), or by comparing the pre-treatment versus the last time-point. Other statistical approaches included standardized change scores, data replacement by regression, endpoint analysis by regression, and worst case scenarios (Flick, 1988). For missing data timepoints during treatment, a simplistic approach is to impute a specific value to all missing observations, e.g., imputing a positive urine toxicology result when the urine result is positive before or after the missing value. Newer, more sophisticated statistical methods make use of all within subject or within group data to impute missing values. Such methods include the rank test with Empirical Bayesian adjudication (Follmann, Wu, & Geller, 1992), mixed (Laird & Ware, 1982) and random regression (Gibbons et al., 1993) models, and generalized estimated equations (Zeger, Liang, & Albert, 1988). Although some guidelines have been proposed for statistical reporting in medical journals (Bailar & Mosteller, 1988), there is still no consensus on the best way to manage attrition and missing data. Some statistical software program packages, such as the Statistical Analysis System (SAS Institute Inc., Cary, NC) provide details on the way missing data is treated when using a statistical procedure. However, for most tests the missing value is excluded, often resulting in dropping that subject from the analysis as an incomplete case.

It is beyond the scope of this article to review in detail the analysis of clinical trials for pharmacological treatment of cocaine dependence. However, innovative methods for data analysis of this type of trial have been proposed. Investigators have recently reported three methods for data analysis of double-blind, placebo-controlled study of fluoxetine and placebo (Covi, Hess, Kreiter, & Haertzen, 1994). The first analysis grouped all valid subjects according to medication or placebo assignment; the second analysis grouped subjects by their plasma medication concentration (regardless of medication group), and the third analysis retrospectively grouped subjects by cocaine urine positivity status at the first clinic visit. Although all three methods of data analysis showed similar results, the study illustrated the potential of methods for analysis of cocaine dependence clinical trials. Given the large volume and complexity of clinical trial data, new computer software has been developed to visualize and recognize treatment outcome patterns in the data (Spilker, Crusan, Pool, Russell, & Fram, 1992).

COMMENTS

The model proposed here has been used in published clinical trials for pharmacological treatment of cocaine dependence conducted at the NIH-NIDA-DIR (Weddington et al., 1991; Covi et al., 1994; Montoya, Preston, Cone, Rothman, & Gorelick, 1995; Montoya, Levin, Fudala, & Gorelick, 1995; Covi, Montoya et al., 1994). This model can be applied to both pharmacological and nonpharmacological studies. It can be implemented in almost any clinical

and research setting, because it offers a framework that allows diagnosis, treatment, and follow-up of cocaine-dependent individuals.

The model uses a complete set of assessment instruments that have been demonstrated to be valid and reliable. Some of these instruments can assist clinicians in making diagnoses of mental disorders and particularly of substance use disorders. Additionally, data collected in a standardized fashion can be utilized by investigators for research purposes. The longitudinal follow-up provides a way to measure the long-term impact of the treatment research. The follow-up assesses all consented subjects, allowing a natural comparison groups of subjects who start and who do not start treatment. Finally, the important advantage of this model is that the data collected can be comparable across different studies, while still being flexible enough to meet the requirements of different protocols.

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