Management of Clinical Trials With New Medications for Cocaine Dependence and Abuse

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INTRODUCTION

Clinical trials of medicines for cocaine dependence are extremely complex to conduct because of the varied nature of cocaine abusers, imprecise methods of diagnosis, lack of well-defined endpoints that can be measured independently of the subjective judgment of the clinician and subject, lack of standardized rating scales, and lack of interrater reliability. Additional problems in doing such studies pertain to site selection, patient recruitment, patient compliance, and study management.

This chapter examines some of these issues and offers important management guidelines that may prove useful as cocaine abuse trials move toward larger placebo-controlled Phase III studies.

CLINICAL TRIAL MANAGEMENT ISSUES

Clinical trials represent a significant departure from the ordinary routines of clinical practice, so it is imperative that efforts be made at the outset of a study to address all of the potential problems that may occur in the course of a study.

Essentially, clinical trials require a proactive management approach where the study objectives determine the steps to take to execute the study rather than passively accept results and breakdowns as inherent in the process, or in the patients, or in the condition. It is essential to review every breakdown in the study process from recruitment to maintenance of patients in the study for solutions that may increase participation: Why did the patient drop out? How could that patient have been kept in the study? What are the differences between patients who stay in and who drop out? How many were in previous studies? How are potentially noncompliant patients who drop out shortly after starting recognized? Are there any differences between different screening personnel and enrollment rates and retention rates

of different raters? What role did the staff play in the process in terms of attitudes, neglect, failure to follow up, or failure to go the extra mile?

Proactive management means clear-cut responsibilities, clear lines of communication, high levels of accountability, designated personnel, and clear definition of duties for managing the project. It also means a willingness to commit to objectives by doing whatever additional steps it takes to produce the result and not simply attributing poor results to the patient population. This may mean, for example, having someone available in the evening in the early phases of a study who knows inclusion/exclusion criteria so as not to lose eligible patients at the moment when the patient first calls about participating in the study—a telephone call may be the only available window in which to enroll the caller.

It also means focusing on other measures to increase retention, such as telephone calls and home visits between office visits, a regular review of all breakdowns in communication, and introduction of essential procedures to prevent breakdowns such as training staff in the subtleties of study etiquette to bolster patient compliance.

The more complex the inclusion and exclusion criteria, the less well-specified the diagnostic subtypes of patients being studied. This is a special problem because it has not yet been determined how to differentiate different types of patients in terms of type of drug use, frequency of use, route of administration, and the various stages of withdrawal, each of which may require a different treatment strategy and a different model of psychotherapeutic management. Also, it becomes especially difficult to train the staff in terms of the appropriate attitudes and procedures to routinely maintain to ensure participation and compliance with the study protocol.

The deficiencies demonstrated in data audits of clinical trials generally reflect failure in communication among responsible parties and a general breakdown in the process of total quality management.

The most common deficiencies in data audits are the absence of informed consents, inadequate drug accountability, nonadherence to protocol, inadequate and inaccurate recordkeeping, failure to obtain approval from the institutional review board (IRB), and failure to inform the IRB of protocol changes.
Adherence to a higher standard of quality control than what exists in most practice settings requires a clarification of study objectives,

commitment to the objectives, and a willingness to keep searching for steps that are missing or procedures and personnel that must be installed whenever problems are encountered. Since it is difficult to anticipate all the possible potential patient presentation problems that must be questioned in light of the inclusion/exclusion criteria, or all the procedural breakdowns that may occur along the way that become protocol violations, it is essential that a mechanism be included for constant monitoring of the process as well as quality control of the case report forms to ensure that as much as possible common problems in data audits, and problems that ensue when applying a theoretical protocol to real-life patients, are recognized early so that corrective measures can be put in place.

It is especially critical to spend time in identifying patterns and sources of problems such as the high rate of dropouts in cocaine abuse drug trials and to determine whether they are due to the unreliability of the patient population or to failures in management. Here it is critical to know more about the different types of cocaine patients and withdrawal patterns so as to ensure that the patients recruited are suitable for the study. It is also important to train the staff in ways of handling the variety of problems that frequently surface in this patient population so that patterns of patient care at the site that may not be entirely suitable for the proper conduct of a study can be identified. It is critical to keep asking what is missing in the staff procedures rather than simply attributing problems of dropouts and no-shows to the underlying condition.

CLINICAL OBJECTIVES

A number of objectives have been pursued in the search for a medication for cocaine dependence, no doubt because of the different patterns of efficacy and pharmacological and theoretical considerations associated with the different drugs tested (Adams and Durell 1984).

Perhaps the most common objectives sought in most studies have been the cessation or reduction of drug use and drug craving. Other studies have sought to compare the efficacy of a single agent against placebo or against a known drug such as desipramine or bromocriptine, neither of which has achieved the status of a standard as yet.

Additional objectives have included the retention of patients in treatment, as has been demonstrated with desipramine; changes in the patients' occupational, legal, financial, medical, or psychological status (McLellan et al. 1980); a reduction in the use of other drugs of abuse; and a change in risk-taking behavior such as the sharing of needles and unprotected sex with multiple partners (Battjes and Pickens 1988).

Most pharmacological studies for cocaine abuse have focused either on blocking cocaine euphoria with drugs such as imipramine, bromocriptine, trazodone, or neuroleptics like haloperidol, or dealing with withdrawal and craving during the first several weeks of abstinence from cocaine as in studies with desipramine, imipramine, bromocriptine, amantadine, carbamazepine, flupenthixol decanoate, buprenorphine, and fluoxetine (Weddington 1992). While a number of pharmacological agents have shown some promise in leading to a reduction of craving and use among cocaine users, there have been few placebo-controlled trials and no drug has been approved for use in cocaine abuse, nor is there a standard drug against which to run clinical trials.

The best results appear to have been with desipramine, which increased periods of abstinence and decreased cocaine craving in the early phase of outpatient treatment (Gawin and Kleber 1984; Gawin et al. 1989*a*, 1989*b*). In a double-blind randomized trial, 59 percent of patients treated for 6 weeks with desipramine achieved 3 or more weeks of continuous cocaine abstinence compared to 25 percent of those treated with lithium and 17 percent treated with placebo. But desipramine had little effect on reducing attrition and did not decrease relapse to cocaine abuse.

SITE SELECTION

While much of the recent work in cocaine dependence has been done in university settings or in special settings devoted to the problems of cocaine dependence, larger scale studies will have to expand to other locations as well. It is critical to select sites that are organized for research in a highly regulated environment with dedicated personnel able to pay adequate attention to issues of informed consent, adequate documentation, drug accountability, and recordkeeping.

Site selection is critical to the success of clinical trials. In the prestudy phase it is important to establish that the sites have access to the

necessary patients, whether in their own patient pools or from referral sources. Too many studies fall short of their required quotas because of the optimism of clinicians or investigators eager to participate in clinical trials without carefully reviewing whether they have the requisite patient numbers, specifically patients who will meet the inclusion criteria, who will be willing to take a new investigational drug, who will participate in a placebo-controlled study, who will stop taking an existing medicine, who will be subjected to repeated venipunctures, who will make the necessary periodic visits, and so forth.

Patient recruitment, in line with enrollment quotas, is especially important and may be problematic for a given site and investigator. Some clinicians hesitate to enroll patients in placebo-controlled studies. They also may be reluctant to try to overcome the patient's resistance to enroll in a study, equating a proactive approach to enrollment with coercion. Clinicians also may be reluctant to advertise for symptomatic volunteers because of certain long-held beliefs about the unprofessionalism of advertising or the self-selected nature of such patients, even though in many studies this may be the only way to recruit sufficient numbers of appropriate patients.

It is also important at the outset to establish the availability of dedicated staff to ensure adherence to protocol inclusion criteria, to maintain adequate source and regulatory documents, and to keep abreast of the numerous changes and amendments to the protocols that occur during the course of a study. These changes and amendments must be coordinated among the site personnel as well as the sponsor and IRB. In this regard it is critical that onsite staff participate in startup meetings and that a complete meeting of all staff take place at the site at the start of the study to ensure that all logistical details are worked out.

It is important to choreograph patient flow, and to recognize the importance of the right attitude of empathy and interest from the telephone screening person to the lab technician, both of whom are critical for enrolling patients, just as they may unwittingly say the wrong thing to patients and encourage withdrawal. All staff members must be familiar with the focus and philosophy of the project, and scripts should be prepared if necessary so that the limits of what to communicate are known.

Because patient screening is often done by nonclinical personnel, it is important that they be made a central part of the research team and

trained in the inclusion/exclusion criteria. Their first contact with the patient establishes a bonding with the site that is necessary to ensure complete participation during the course of the study.

EXPERIENCED INVESTIGATORS

While independence and self-reliance are highly valued characteristics of physicians in general, the clinical investigator may have to learn certain new skills in teamwork to participate in research in a highly regulated and closely managed framework. While the clinician's medical judgment is ultimately critical, it is crucial to always be assessing activities in the framework of protocol requirements. This means learning to feel comfortable in maintaining close communication with the sponsor or clinical research organization managing a trial, and learning not to hesitate to inquire about uncertain issues so as to avoid making protocol errors.

It is especially important to ensure the availability of the targeted population, as access to depressed and anxious patients and even other difficult-to-locate groups such as schizophrenia and Alzheimer's cases does not necessarily prepare the investigator for the special problems associated with recruiting and maintaining cocaine-dependent patients. The demonstration of past experience, a continuous patient pool, or a proven network of referrals is critical in collecting sites even among experienced investigators. It may be desirable to begin building such a cadre of investigators by initiating smaller studies, in anticipation of the larger scale studies that will be needed in the future.

This will help the investigator build a pool of compliant patients who are not placebo responders and who may be willing to participate in subsequent clinical trials. These small-scale studies may also make it possible to explore different methods of recruitment at particular sites and establish actual numbers of screening calls, the percentage of telephone-screened subjects who keep their appointments, the rate of enrollment of telephone-screened subjects to studies, and the dropout rate. This would help establish a measurable basis for site selection for future large-scale studies.

A significant percentage of cocaine-dependent patients deviate from protocols by dropping out because of cocaine craving, other drug dependencies, and psychiatric illness. Experienced investigators are essential in these studies because of their ability to select compliant

patients and to maintain compliance without being overly "psycho-therapeutic" and without putting patients at risk. The experienced investigator is also alert to the early warning signs of noncompliance, such as missed first appointments, inconsistencies in the information given on the telephone screen and office screen, ambivalence about signing the informed consent, and a past history of noncompliance or nonresponsiveness to a variety of medication programs. The investigator can make the decision not to include selected patients in a study even though there is pressure to enroll them in terms of a highly demanding timeline. The larger the investigator's network, the easier it is to be selective in including patients to increase full participation and lower the dropout rate.

PATIENT SELECTION

It is important to identify the best geographic locations and investigative sites where the targeted population can be located. There are geocoded databases that can help with this. Given the high dropout rates in cocaine dependence studies, it is best to locate patients who are working and living with significant others who can facilitate followup.

This is especially true for Phase II and Phase III efficacy studies but less relevant in Phase I studies with less stable chronic users who are needed for safety and interaction studies involving the administration of cocaine. Chronic nontreatment-seeking abusers are suitable for early Phase I studies especially when drug challenges are given or controlled access to the abusable drug is available in a behavioral paradigm to measure directly the effect of the medication on drug-seeking behavior (Fischman et al. 1990). These individuals are not generally included in or suitable for controlled clinical trials of medication because they generally do not want to stop drug use.

In Phase II studies of drugs like flupenthixol, which block the effects of cocaine, crack cocaine users theoretically may use more cocaine to get high and counteract the effects of the medication, as has been demon-strated in lab animals. As such it is usually necessary to include some form of psychotherapy to ensure compliance with such studies, of course possibly adding its own confounding effects.

Ideally the best Phase II studies of safety and efficacy are done with small numbers in controlled inpatient settings for several days to determine tolerance to the medication followed by outpatient

treatment. Here the criteria for inclusion are less stringent, and recreational users are often included with chronic users to increase compliance, perhaps at the cost of increasing the variability of the results.

When moving to later Phase II studies and Phase III studies, patient selection becomes more important especially because there are no well-validated rating scales and no standard drug against which to compare new drugs. Without such standardization, trends in decreased cocaine usage at particular sites in multisite studies may sometimes be attributed to the inclusion of nonhomogeneous patient populations or to different treatment approaches at the different sites.

The clinical condition must be defined as precisely as possible. In Phase III trials there is a need to distinguish between recreational and chronic users whose patterns of usage and attitudes toward participation in a study may be significantly different. It is difficult to differentiate between subtypes of patients in terms of type of drug use, frequency of use, route of administration, and the various stages of withdrawal, each of which may require a different treatment strategy and a different model of psychotherapeutic management, making it especially difficult to train staff in terms of the appropriate attitudes and procedures to routinely maintain to ensure participation and compliance with the protocol. It is also important not to define exclusion criteria too rigidly and to leave a large window or grace period for followup visits so that missed visits do not constitute protocol violation.

Local newspaper or radio advertising, which is often essential to recruit the large numbers needed for Phase III trials, may be less useful with the cocaine-using population than is true for symptomatic volunteers with depression and anxiety symptoms. This requires further study. It is also necessary to find new ways of working with traditional sources of referral from other community medical or psychiatric agencies, which oftentimes for philosophical reasons do not support the concept of “testing” new medications in placebo-controlled clinical trials, or are threatened by issues of territoriality. It may be necessary to begin to build relationships with other agencies, including the drug-free therapeutic communities, which seem to have a large number of cocaine-dependent patients in their patient and graduate networks, many of whom may be interested in and may benefit from participation in clinical trials with new medications for cocaine dependence.

Problems at the time of recruitment pertain to problems in diagnosis and making certain only to include those patients who fit the protocol. The same applies to the care with which past medical histories are obtained, so as not to include patients who after starting may reveal the existence of conditions that would exclude them. The initial interview must be extremely thorough and designed in anticipation of subtleties about participation that are not generally considered in the course of routine psychiatric care.

It is important to recruit patients who will be cooperative, compliant, and willing to participate for the duration of the study. Patients must also be capable of following instructions, returning medications, making regular appointments, and adhering to the protocol. Meeting these criteria is especially difficult in the case of cocaine abuse where the condition itself seems to impinge on the very qualities necessary for participation.

The same may be said for certain Axis II personality disorders such as borderline personality and paranoid personality, which may be particularly prevalent among cocaine-abusing patients and which also may contribute to noncompliance in the study.

HOSPITAL OR OUTPATIENT SETTINGS

There are obvious advantages to hospital settings in terms of the severity of withdrawal patterns, the control over medication and retention, the measurement of side-effect profiles, and the monitoring of plasma levels, all of which are more easily measured because of increased compliance. Hospitals are also better environments in which to conduct challenge studies where patients are given the test medication and then are able to select differing amounts of the drug of abuse in a patient choice paradigm designed to measure the blocking effect of the test medicine.

Chronic users who are most suitable for these studies are easier to find and easier to induce to remain in an inpatient facility than recreational users, but they are often less motivated, have more medical problems, are polysubstance abusers, and when moved to outpatient status may rejoin the ranks of the homeless and be difficult to find for followup visits.

A disadvantage of hospital settings is that they lack the environmental cues and stimuli that often provoke a return to drug abuse and therefore are not realistic settings in which to measure the control of

drug dependence with medication. The severity of the patient's illness and the stage of drug testing are critical factors here. To measure cocaine use, craving, and the responsivity to environmental cues, it is preferable to conduct a trial to measure the control of drug dependence with medication in an outpatient department, despite the risk of greater dropouts.

Because patients, especially recreational users, do not want to be confined, there is a need for fast-acting drugs. While these may work, the long-term beneficial effects that may be even more dramatic may be hard to establish because of the problems of following up patients after they have left an inpatient facility.

COMPLIANCE

Various attempts to increase compliance have been tried. The anecdotal evidence on putting a computer chip in the medicine bottle to see if the patient took the test medicine suggests that these bottles are often opened as much as 25 times a day, making this virtually useless as a measure of compliance. The use of depot flupenthixol to circumvent the issue of compliance has been tried, but it raises ethical questions of inducing in high doses dopamine (DA) side effects such as tardive dyskinesia, which may not be justifiable in this population as it is in patients with psychotic symptomatology. Moreover, some patients may theoretically try to overcome the DA blockade by taking more cocaine and risking overdose. The dropout rate in one such study was 60 percent as compared to a dropout rate of 20 percent on a 6- to 8-week trial of methadone main-tenance patients with cocaine abuse. Another way to lower dropout rates is to exclude hardcore patients who are more likely to use other drugs and take more cocaine and to rely more heavily on more motivated individuals who may be living with family members and working, which also may add to compliance. Another approach is to design feasible studies, for example by allowing a wider window for drug administration to accommodate missed visits by patients.

PSYCHIATRIC DIAGNOSIS

The difficulty of making precise diagnoses often leads to heterogeneous patient samples, which in turn makes it difficult to accurately test the efficacy of new compounds. This is seen in traditional psychiatric trials where there is often difficulty in

distinguishing schizophrenia from schizoaffective illness or manic-depressive illness, or in distinguishing discrete episodes of major depression from chronic low-grade depressive mood of dysthymia. The heterogeneity of drug users makes it especially difficult to find treatments that may be effective with a selected portion of the drug-using population that enter into a study. On the other hand, limiting study samples to homogeneous ones may limit the rate of enrollment and generally slow the progress of comparable research at other sites. It is therefore often essential to find some compromise between the two extremes.

In cocaine studies there may be difficulty differentiating chronic users from heavy recreational users. This is especially significant in Phase I safety and interaction studies where it would be acceptable to use chronic users who do not want to stop cocaine, but unethical to use cocaine for nondependent recreational users who are motivated to stop the drug. The distinction between chronic users and heavy recreational users is less significant in Phase II dose-ranging and efficacy studies where the use of recreational users is likely to make it easier to show a response. These patients are usually more compliant and motivated but harder to convince to stay in a facility for the intense tests such as Holter monitoring required for such studies. Differences among patients is also important in Phase III studies attempting to differentiate active drug from placebo and measuring it against a comparator. Fortunately, the problems of diagnosis can be controlled to some extent by the use of standardized criteria and standardized interview schedules, a number of which are available.

DEFINING THE COCAINE DEPENDENCY SYNDROME

The importance of defining specific diagnostic subgroups to study is underlined by clinical findings of Weddington and his group that cocaine addicts who sought treatment in his research facility reported greatest craving for cocaine during the 24-hour period immediately before admission and the greatest severity of mood distress on day 1 (Weddington et al. 1990). Mood states, craving, and reports of waking during the night and of clearheadedness on awaking improved gradually during the study and were not cyclical or phasic during the first 4 weeks of abstinence. According to Weddington, the absence of cocaine and other drugs as well as drug-taking stimuli in a controlled environment may account for the lack of a classical postabuse abstinence syndrome.

Elsewhere, Meyer and Mirin have proposed that drug craving is an appetitive response: Where drugs are available to addicts, craving is likely (Meyer and Mirin 1979). Wikler demonstrated that craving and physiological responses to drugs and drug-taking cues are affected by classic conditioning of exteroceptive stimuli (Wikler 1973). Other work by Jaffee demonstrated the role of internal stimuli associated with cocaine administration by demonstrating that giving cocaine to experienced cocaine users increases their craving for the drug (Jaffee et al. 1989).

All of this underscores the importance of studying the behavioral and psychological components as well as the physiological components and emphasizes the importance of clearly defining the parameters of the study so as to take these factors into consideration and not simply bunch people all together in heterogeneous samples.

PATTERNS OF DRUG ABUSE

It is also essential to differentiate among patterns of drug abuse, routes of administration, the frequency of drug use, and the consequences of use in terms of physical dependence, tolerance, craving, drug-induced problems, and neurobiological system dysfunction, such as in the adrenergic, dopaminergic, and serotonergic systems where these drugs act (Blaine et al. 1994).

The stage of drug use is also an important variable. People in the earliest stages of dependence who are more difficult to find are more likely to respond to antagonist medications than those in later stages, and they may be more suitable candidates for testing efficacy than chronic long-term users.

Other factors to consider in differentiating among patients is the nature of prior treatment, prior success in achieving abstinence, time to relapse, or early treatment termination. Additionally, motivation for treatment is a critical variable to assess. Here are encountered the problems of denial and the desire to continue the drug-using pattern. There may also be difficulty in distinguishing the effects of various anticocaine medications when the patient populations are heterogeneous. A review of some of the recent research literature suggests that diagnostic distinctions must be made between nasal and intravenous users who seem to respond differently in some studies, patients on methadone maintenance as compared to those who are not, and patients suffering from depression and cocaine abuse as in the

studies at Yale where depressed cocaine abusers certainly showed some response to desipramine.

Of course it is easier to recommend these finer diagnostic distinctions than it may be to find homogeneous samples of cocaine abusers. The reasons for this are severalfold:

1. Many patients are polysubstance abusers. Even if screening out patients with positive drug screens for opiates or other substances, patients are often unreliable and noncompliant and investigators cannot be certain patients will use only cocaine in the course of the trial. Moreover, the interaction of prescribed opiates such as methadone with cocaine may further compound the results.

2. It is sometimes difficult to differentiate between treatment-resistant chronic users who may be motivated by a need for food and shelter and treatment-seeking chronic users who may qualify or be appropriate for early Phase II studies but not for later studies.

3. Some patients may have multiple psychiatric diagnoses that may not be identified at the screening interview. In addition to cocaine abuse, patients may suffer from major depression or schizophrenia, conditions that may respond to the test drug resulting in some improvement of symptoms and a reduction of the motivation for cocaine without directly impacting on the cocaine abuse itself. This can create obvious problems in the interpretation of the data.

TREATING PATIENTS WHO ARE CODEPENDENT OR ON OTHER MEDICATION

A number of studies have been conducted with cocaine-dependent individuals who were receiving methadone for opiate abuse. Using such individuals for study can be problematic for several reasons. Multidrug users are less likely to be compliant than single-drug abusers and more problematic to maintain in an outpatient study (Mirin and Weiss 1987). Additionally, the drugs may interact, producing problems in interpreting the data. It has been reported that methadone raises blood levels of desipramine thereby making for complicated dosing of desipramine to control cocaine use and cocaine craving (Kosten et al. 1987). Nevertheless, there is some strong evidence that desipramine and amantadine may be helpful in reducing cocaine use, craving, and depressive symptoms in a group of

methadone maintenance patients and that desipramine may be helpful in keeping patients in treatment and cocaine-free at the end of the study (Kolar et al. 1993).

COMORBIDITY

There is an extremely high incidence of comorbid mental disorders among those with drug use disorders (Regier et al. 1990). In one survey, 76 percent of those with a cocaine abuse or dependence disorder gave a history of mental disorder. Recently Rosen and Kosten found that the incidence of panic attacks among methadone-maintained patients has increased over a 10-year period from 1 to 6 percent to as high as 13 percent as a result of cocaine use as well as environmental and constitutional factors (Rosen and Kosten 1992). Schizophrenic patients have a lifetime prevalence rate of cocaine abuse between 15 percent and 50 percent. In one study of schizophrenic patients in a dual-diagnosis program, patients receiving desipramine and antipsychotic agents were more likely to complete the study and demonstrate substantially decreased cocaine usage than did patients treated with antipsychotic medication alone (Ziedonis et al. 1992).

Other comorbid problems relate to issues of HIV infection, alcohol abuse, and multiple drug abuse patterns. In one study it was found that informing drug abusers in treatment regarding positive HIV serostatus was not associated with a lower treatment retention rate or adverse psychological reactions when counseling regarding HIV issues was integrated with drug abuse treatment (Weddington et al. 1991). Insofar as alcohol and cocaine abuse commonly occur together, it is of interest that treatment for both can be accomplished in the same setting if important demographic and pharmacological differences are addressed (Closser and Kosten 1992). As to multiple drug abuse there have been successful demonstrations of treatment with disulfiram for alcohol-abusing patients and amantadine for cocaine-abusing, methadone-maintained patients (Kosten 1991).

RATING SCALES

Efficacy of psychiatric medication is often difficult to measure because of the variability of patient responses to medication, especially when the patient sample is heterogeneous. The method of measuring efficacy by having the investigator question the patient and assign symptoms to a rating scale is fraught with error. There is often a high degree of variability in the ways that patients can respond to

cue questions and a minimum of interrater reliability regarding diagnosis, which makes for problems in multisite studies. Indeed, there are no validated or universal tools as yet for measuring issues relating to cocaine abuse.

The scales being used in cocaine studies, including the Visual Analog Cocaine Use Scale and the Visual Analog Craving Scale as well as various measures of mood states, are highly subjective and hard to validate without a standard drug against which to compare the test drug. One new test, the Self-Administration Paradigm, where patients get to choose one of two drug regimens after active medication, has some potential for being objective, but it has not been validated as yet.

A review of the literature suggests a wide variety of endpoints being used in studies that make comparisons among studies very difficult. Outcome measures include psychiatric outcomes, craving, subjective drug effects, patterns of drug use, and retention in treatment. The instruments and the data collection methods being used vary from study to study, making comparison of studies virtually impossible. There is an urgent need to standardize or at least reach some consensus on the methodologies, instruments, rating scales, and endpoints used in clinical trials so that cross-trial comparisons can be made, thereby facilitating advancement of knowledge in the field.

There is also the difficulty of differentiating between symptoms and side effects. Patients may be depressed before, during, and after using cocaine. In testing a DA antagonist like flupenthixol, for example, it might be difficult to test whether reports of depression were related to the cocaine use or to the DA depletion caused by the medication. The presence of side effects also may blunt the patient's report of symptomatology. The Hamilton Rating Scale for Depression often used in studies of cocaine dependence is heavily weighted with items relating to insomnia, GI disturbance, and anxiety—all three of which may be adversely affected by selective serotonin uptake inhibitors like fluoxetine, which is being studied at some sites for cocaine dependence. During a trial the scale may indicate an increase in depression when in fact the elevated scores may be due to common physiological side effects of the selective serotonin reuptake inhibitors (SSRIs).

DURATION OF CLINICAL TRIALS

Many studies have been done that did not last long enough to establish clinical efficacy. Studies must be designed in terms of the pharmacology and the intended use of the medication (Satel and Kosten 1991). The duration of the study needs to be long enough to demonstrate efficacy and yet short enough to ensure retention of enough patients to do the statistical analyses needed to demonstrate treatment effects.

The nature of the condition being studied must be considered so that the study is not so short in duration that it misses certain clinical events associated with the condition such as periodic binging, delayed recovery, or delayed relapse (Kosten 1989). Studies should not be so long as to increase the likelihood of dropout, which is a highly likely event in drug-dependent populations. Twelve weeks seems to provide sufficient time to assess both stabilization and the possibility of relapse while on the drug.

Another critical factor in designing trials is to consider the latency of onset of clinical effect, which may take far longer than the study is designed or patients are able to remain in the study (Blaine et al. 1994). In some studies it has taken as long as 6 weeks for improvement to begin on SSRIs, while it often takes from 12 to 16 weeks to provide maximum benefit. It is especially difficult to include subjects with cocaine dependence in trials this long.

It is important to anticipate the problems of dropouts and to try to exclude unmotivated patients as well as those who are being pressured by others to enter into the program. Too many dropouts reduce the power of the statistical analysis and may leave a sample of patients that is unrepresentative of the group being studied. Special attention must be paid to the characteristics of dropouts not only in terms of demographic and clinical characteristics but also in terms of any kind of subtle clinical events that may have influenced their responses to treatment.

PLACEBO-CONTROLLED STUDIES

There seem to be many open-label noncontrolled studies with positive results in the area of cocaine abuse. These results by and large are not substantiated when controlled studies are done (Satel and Kosten 1991). The state of the field, the urgency of finding a new drug, and

perhaps the lack of standardized instruments no doubt contribute to these unreliable results.

The use of placebo is essential in studying a medication whose effects are as yet undetermined. The use of such a design reduces the numbers of patients required to demonstrate statistical significance between medication placebo and a known standard medication. Distinguishing active drug from placebo is often difficult because of a significant placebo response caused by too great a reliance on the patient's responses to the symptom cues that are given to elicit ratings, without sufficient attention being paid to the subtleties of symptoms and observation of the patient's behavior. Too much support of the patient, or encouragement of the patient to remain in a trial or psychosocial or psychotherapeutic support programs (which seem common in psychopharmacological trials for cocaine dependence) may also produce positive responses in patients who are generally believed to be highly susceptible to environmental and behavioral cues.

These positive responses may be particularly difficult to differentiate from positive responses to the medication.

PSYCHOSOCIAL INTERVENTION

There is no doubt that cocaine dependence is a condition very much affected by nonmedical or social factors. This is perhaps what makes the condition responsive to psychosocial intervention, and as such the regular use of such methods to maintain compliance must be questioned in any clinical trial of a new medication for cocaine. While psychosocial intervention oftimes contributes to compliance and may clearly have beneficial effects on cocaine dependency, it is likely to confound the study of the efficacy of psychopharmacology and must be measured against the effectiveness of new medications rather than used to reinforce compliance with the program.

These interventions can mask drug effect. They can also enhance drug effect, as in methadone maintenance programs where psychotherapy has enhanced the efficacy of methadone treatment of heroin addicts while being essentially ineffective when used alone (Woody et al. 1983). The use of such approaches to ensure patient compliance needs to be weighed carefully and utilized only when the addition of such interventions is likely to bring out the beneficial effects of a less potent pharmacological treatment. However, there are

problems in the use of such treatments especially in establishing a standardized method of treatment that can be uniform over time and among different therapists and multiple sites.

Given the sensitivity of the patient population and the fact that psychosocial interventions are often required to maintain patients in studies, it is important to keep asking the question of how various staff interactions with patients contributed to the patient's behavior and not simply assume that this is an area that does not need to be examined and that it can be assumed that there are no negative effects of staff attitudes and interactions on the patients.

SUMMARY

Clinical trials require a quite distinct shift in attitudes and procedures from ordinary clinical practice insofar as they require a proactive approach to patient recruitment, enrollment, and followthrough as well as significant attention paid to issues of documentation, regulatory compliance, and error prevention. Take documentation, for example: Today's requirement to have an independent record of clinical events that are recorded on the case report forms was until 5 or 7 years ago not addressed in as much detail as it is today. This is one of the first adjustments that the new investigator must address. The researcher must keep looking to see what is missing from the location and procedures as a study takes place in order to create the necessary patient base for doing the study and ensuring that all needs necessary to produce the result are in place and that procedures are done with as few errors as possible. Everything must be done in conformance with good clinical practice and the standards set by the protocol. The researcher must be willing to deal with a world of breakdowns such as missing data, and the failure of the patient to revisit the office within the appropriate time dictated by the protocol and within the window of time or grace period allowed by the study. The researcher must ensure that the patients comply with the dosing schedule and that they are trained to return medications for accurate pill counts. And so on.

This means creating new procedures that are motivated by a commitment to producing a specific enrollment result defined by specific criteria and increasingly because of the press of time enrolled in a specific time period and put through a well-defined protocol process. Clinical research is dependent on a willingness to commit to a specific end result and do all that is necessary on a day-by-day basis to produce that result in terms of specific numbers, clean and accurate

case report forms that are backed up by corroborating source documents in line with a specific timeline in which to accomplish the task, and an outreach effort to recruit and enlist patients, which may involve advertising and promotion of the program, all of which may contrast significantly with customary practice.

Clinical research involves reliance on additional dedicated personnel who are critical parts of the research team, including the telephone screening person who must be trained to follow a script and at the same time to be aware of the nuances of enrolling appropriate and compliant patients. The entire staff must be made part of the process and must work in concert to recruit and maintain the patient in a study while being aware of the effect these efforts may have on the placebo effect. It also requires considerable training, review, and constant communication among the staff to ensure that the complex coordination of numerous patients and procedures works smoothly.

There needs to be a willingness among the staff and the investigators to take correction from monitors who visit the site periodically and whose focus is on the quality of the data and not so much on the qualifications of the staff. This is not an action that people in nonresearch environments are trained to take.

Failure to appreciate the complexity of conducting clinical trials can contribute to much frustration to everyone involved. When there is understanding of all the variables that influence the ultimate results, there is a willingness to anticipate breakdowns and to turn breakdowns into opportunities to create new structures and develop new procedures that will ultimately facilitate a successful outcome.

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