Rationale and Design of the Cocaine Alternative Treatments Study (CATS): A Randomized, Controlled Trial of Acupuncture

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ABSTRACT

Acupuncture has been incorporated as a treatment component in numerous addiction treatment programs in the United States; however, its efficacy has not been demonstrated in large-scale, controlled clinical trials. In this article we discuss the background and design of the Cocaine Alternative Treatments Study (CATS), a randomized, controlled, multisite study of acupuncture that will enroll 500 cocaine-dependent individuals at 6 sites across the country, and that constitutes the largest controlled trial for the treatment of cocaine addiction undertaken to date. After presenting the background of the study, we discuss the approach taken to address several critical issues, including the choice of appropriate control conditions, point location for needle insertion, degree of blinding, and bias checks. Complementary therapies are used by a significant number of individuals, and the need to evaluate them in controlled clinical trials is an ongoing and urgent issue.

INTRODUCTION

Although widespread use has declined since the height of the cocaine “epidemic” in the mid-1980s, data from the most recent National Household Survey on Drug Abuse (NHSDA), conducted in 1996, suggest that a considerable number of Americans continue to abuse cocaine (Substance Abuse and Mental Health Services Administration, 1997). The NHSDA report estimates that 0.8% of the population, 1.7 million Americans, aged 12 and older use cocaine at least once a month. Frequent cocaine users—more than 51 occasions of use per year—comprise 0.3% of the population, a percentage that has remained fairly constant since 1985, the first NHSDA survey year. In addition to adverse effects at the level of the individual user, for example, on the cardiovascular (Kloner et al., 1992) and central nervous systems (Kosten et al., 1996), illicit cocaine use has important public health consequences. Cocaine use and drugs for sex transactions contribute to the spread of human immunodeficiency virus (HIV) and other infectious diseases, particularly among poorly served, inner-city populations (Edlin et al., 1994). This latter point is underscored by data from the yearly Drug Abuse Warning Network (DAWN) survey showing that in 1995, 27% of all drug-related emergency room visits were cocaine-related, with the highest increase

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(81%), since 1990, among African Americans (Substance Abuse and Mental Health Services Administration, 1996).

The search for an effective pharmacological treatment for cocaine addiction has not, to date, been successful. A large number of agents have been evaluated; although several have shown promise in small-scale pilot studies, none has demonstrated overall efficacy in randomized clinical trials (Institute of Medicine, 1995). The lack of an effective pharmacological treatment for cocaine addiction has created interest in formally investigating noncanonical, “complementary” forms of treatment such as acupuncture for their potential to address this unmet treatment need.

The use of auricular acupuncture for the treatment of addiction has grown substantially in the past decade. Presently, more than 300 clinics in the United States offer acupuncture as part of addiction treatment programs (Culliton and Kiresuk, 1996). Acupuncture is also used as a treatment component in approximately one-third of the “Drug Court” programs across the country (Cooper et al., 1997). Auricular acupuncture possesses a number of characteristics that are potentially advantageous in the treatment of addictions. It is a “low-tech” therapy—the standard treatment protocol is typically administered by addiction counselors after a relatively short, 70-hour, training period. It is relatively inexpensive to administer; the primary supply cost is for the disposable acupuncture needles. Many patients can be treated simultaneously, seated together in a large room. Because it is a nonverbal therapy, it may be particularly useful for patients who are new to treatment and reluctant to engage in psychotherapy. Clinical reports suggest that it is a treatment that patients seem to enjoy, with few side effects (Smith et al., 1997).

Despite its increasingly extensive use for the treatment of addiction, auricular acupuncture has been evaluated in only a few well-controlled clinical trials. Consequently, there is a gap between its widespread use in clinical practice and the demonstration of its effectiveness on which such use should, in principle, be founded (Woolf et al., 1997). In view of this divergence, there was a perceived need to evaluate auricular acupuncture in a well-controlled study, using a sufficiently large sample to ensure adequate power to detect treatment effects (McLellan et al., 1993). Pursuant to this end, funding was obtained from the Conrad N. Hilton Foundation to the Center on Addiction and Substance Abuse at Columbia University (New York, NY), with matching funds from the Office of National Drug Control Policy, the National Institute of Justice, and a National Institute on Drug Abuse grant to Yale University, New Haven, Connecticut, to conduct a multisite clinical trial—The Cocaine Alternative Treatments Study (CATS). To the best of our knowledge, CATS is the largest controlled clinical trial to date evaluating a treatment for cocaine addiction, as well as the largest clinical trial of acupuncture undertaken in the United States.

Randomized clinical trials (RCTs) of acupuncture have been sparse in the United States and in China, its country of origin. As a result, the methodological infrastructure that has developed over the years for the investigation of Western treatments, pertaining to such basic issues as the use of appropriate control conditions, and in general, the implementation of procedures and checks to insure internal validity, does not exist for acupuncture. One result of these lacunae is that foundational methodological research often needs to be conducted in order to determine basic issues of research design. In this article, we discuss how this was undertaken for CATS. It is intended that this discussion will not only provide the reader with information regarding CATS that is applicable to acupuncture research in general, but also illustrate some critically important issues involved in investigating “complementary” therapies. Few of these treatment modalities possess a well-developed methodological infrastructure that researchers can adopt when designing controlled studies, or that readers can use as a frame of reference when interpreting results of studies in this area.

**BACKGROUND AND RATIONALE FOR CATS**

*Why evaluate acupuncture for cocaine addiction?*

Although acupuncture, in conjunction with herbal medicine, has been used for 2500 years
in China for the treatment of many disorders, it was introduced in the treatment of addictions in the 20th century by a fortuitous discovery by Wen, a neurosurgeon in Hong Kong. In the course of his research into acupuncture analgesia, a number of subjects who were opiate-addicted spontaneously reported a reduction in withdrawal symptoms after acupuncture treatments (Smith et al., 1997). As a result of these reports, Wen initiated a series of studies of acupuncture for the treatment of opiate addiction, and reported positive findings for this research in numerous publications (Wen and Cheung, 1973). Although acupuncture has subsequently been investigated for the treatment of a number of addictive disorders, its fastest growing application in this area is for cocaine addiction. This is due, in part, to the lack of an effective agent for the treatment for cocaine addiction, while there exist a number of pharmacological agents with some degree of efficacy for the treatment of opiate (eg, naltrexone, methadone), alcohol (eg, disulfiram, naltrexone), and nicotine addiction (eg, nicotine patch, bupropion). Furthermore, even if a pharmacological agent for cocaine addiction did exist, it is unlikely that it could be safely administered to pregnant, cocaine-abusing women, for whom auricular acupuncture treatments are not contraindicated.

Auricular acupuncture specifically for the treatment of cocaine addiction originated, and has been used for the last decade at Lincoln Hospital’s Substance Abuse Division in the Bronx, New York. Over 10,000 cocaine-abusing outpatients have received acupuncture treatments in this facility during this time; currently, 250 cocaine-abusing patients are treated daily (Smith et al., 1997; Smith and Khan, 1988). Based on the reported success of the clinical acupuncture program at Lincoln Hospital, the National Acupuncture Detoxification Association was formed in 1985 (Mitchell, 1995). This organization codified an acupuncture protocol for the treatment of cocaine addiction, as well as procedures for training addiction counselors in the provision of these treatments (Brumbaugh, 1995), and has been largely responsible for the promulgation of this treatment modality in the addictions. Uncertainty concerning auricular acupuncture’s mechanism of action

Knowledge regarding the physiological mechanisms underlying acupuncture’s effects has resulted almost exclusively from investigations on acupuncture-induced analgesia, which has been hypothesized to be linked to the release of endogenous opioids (Pomeranz, 1987). Evidence for this hypothesis stems from studies suggesting that acupuncture’s analgesic effects are blocked by naloxone (eg, Mayer et al., 1977), and that acupuncture-analgesia is enhanced by enzyme blockers that protect endogenous peptides from degradation (Cheng and Pomeranz, 1980). Traditional Chinese theories of acupuncture (Kaptchuk, 1983), involving the rectification of chi deficiency or excess in various “organ” systems, have not been investigated within a Western biomedical framework.

It should be noted that evidence for mechanisms underlying acupuncture’s effects has primarily been deduced from studies on body acupuncture, not auricular acupuncture, which is the type of acupuncture typically provided in drug treatment facilities. Auricular acupuncture is a nontraditional form of acupuncture developed by a French physician, Paul Nogier, in the 1940s (Nogier, 1983). Theories concerning auricular acupuncture’s mechanism include modulation of neural circuits in the midbrain affected by drugs of abuse (Katims et al., 1992), stimulation of the vagus nerve in the auricle (Sytinski and Galebsakaya, 1979; Ulett, 1992), and release of endogenous opioids (Simmons and Oleson, 1993). However, to the best of our knowledge, no study has examined the biochemical correlates of auricular acupuncture without electrical stimulation, and it is not known, for example, that the endogenous opioid hypothesis would apply to this form of treatment. Hence, there is currently no accepted biochemical “marker” of an active auricular treatment, nor one that would differentiate an active from a control treatment—at the present time, these must be based on patient self-report, as will be described. Clinical reports on the subjective effects of auricular acupuncture in cocaine-dependent patients suggest that it induces a state of relaxation and
promotes psychological and physiological homeostasis, which in turn relieves withdrawal symptoms and reduces cocaine craving (Smith et al., 1997).

Previous research findings

To date, eight published studies have investigated the efficacy of acupuncture in samples wholly or partly composed of cocaine-abusing subjects (Brewington et al., 1994). Two uncontrolled studies reported positive findings, one in a population of methadone-maintained patients (Margolin et al., 1993a), the other in an inpatient dual-diagnosis unit (Gurevich et al., 1996). Several controlled studies, using a nonacupuncture treatment or some form of nonaddiction-specific needle insertion as a control, have found either no differences between active and control groups on cocaine-use outcomes (Avants et al., 1995; Richard et al., 1993; Wells et al., 1995), or small differences favoring acupuncture (Konefal et al., 1994, 1995; Lipton et al., 1994). Typically, patients in both active and control groups have shown improvement. Because the infrastructure of acupuncture research is not well developed, the validity of studies in this area may be considered problematic in certain respects (McLellan et al., 1993; ter Riet et al., 1990; Whitehead, 1978). Problems that we hoped to address in the design of CATS included use of possibly inappropriate control conditions, failure to provide checks on staff bias, high drop-out rates, and lack of checks on the credibility of the control treatments. After providing an overview of CATS, we discuss how these issues were addressed.

CATS DESIGN OVERVIEW

CATS is a multisite, randomized controlled clinical trial the primary objective of which is to determine the efficacy of auricular acupuncture for the treatment of cocaine addiction, with secondary objectives of examining differential changes in psychosocial functioning among active and control groups. CATS plans to enroll a total of 500 patients at 6 participating research sites: Hennepin County Medical Center, Minneapolis, Minnesota, University of California at Los Angeles; University of California at San Francisco; University of Miami, Florida; University of Washington, Seattle, Washington; and Yale University, New Haven, Connecticut (see Appendix for a list of investigators and other personnel involved in CATS). In order to enhance the generalizability of the study, CATS' subject are drawn from two subpopulations: cocaine-dependent methadone-maintained patients (n = 205), and primary cocaine-dependent (nonopioid-dependent) patients (n = 345). In the original design, a third group was intended—pregnant cocaine-addicted women. However, when it became apparent that recruitment of this group would be problematic, the total n of the primary cocaine group was increased by an equivalent number.

Criteria for entry into the study include diagnosis of cocaine dependence by Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria, and either provision of a cocaine-positive urine screen or self-reported cocaine use within the past week. Patients are excluded if they are dependent on any substance other than cocaine or nicotine (or opiates, if not a member of the methadone-maintained population). Pregnant women are admitted only if they are between 12 and 28 weeks gestation, to avoid the potential for miscarriage in the first trimester and in order to be available for the full duration of the study.

Patients enrolled in CATS undergo a psychosocial assessment at baseline, post-treatment, and at 4- and 6-month follow-up. The primary outcome measure, change in illicit drug use, is assessed by an objective laboratory measure, three times weekly urine toxicology screens for cocaine metabolite, and once weekly urine screens for opiates and benzodiazepines, as well as by weekly self-reports of amount and frequency of use.

SELECTION OF TREATMENT PROTOCOL AND APPROPRIATE CONTROLS

Currently, the National Acupuncture Detoxification Association (NADA) protocol is the de facto standard acupuncture treatment that is
used worldwide in the treatment of addictions, and it therefore formed the basis of the acupuncture treatment to be tested in CATS. Its development was mainly guided by clinical observations that suggested that the auricular sites are more effective than body points in the treatment of the addictions, and that adding body points to the auricular sites does not improve treatment outcome (Smith et al., 1997). Consideration of the control conditions to be used in CATS began with aspects of this auricular protocol. This treatment has one obvious and salient characteristic—it involves inserting needles into the outer ear. Piercing the skin may elicit a powerful placebo response, affecting treatment outcome independent of presumably acupuncture-specific effects. For this reason, it was decided that one of the groups in CATS would control for needle insertion as well as other nonspecific factors that attend the acupuncture procedure. Because the acupuncture treatment context also contains a number of nonacupuncture-related, incidental factors that may influence outcome, it was decided that CATS would also use a no-needle insertion control—a relaxation group. CATS participants are therefore randomized to one of three treatment conditions: needle insertion in hypothesized "active" sites; needle insertion in hypothesized "inactive" sites; and a no-needle insertion, relaxation control condition. Because the choice of treatment and control conditions was regarded as a critical issue in the design of CATS, we will discuss the rationale for each of these groups in some detail.

Selection of the auricular acupuncture protocol

The experimental acupuncture treatment protocol. The acupuncture treatment protocol used in CATS calls for one needle to be inserted bilaterally in each of four anatomically defined regions in or near the concha of the auricle. In acupuncture nomenclature these four regions are known as "lung," "liver," "shen men," and "sympathetic." The experimental protocol represents a modification of the five-needle, NADA protocol, which uses one additional point ("kidney"); however, there is some variability in the number of needles used in the NADA protocol in actual clinical practice. After consultation with study and nonstudy acupuncturists experienced in treating addicted patients, it was concluded that the benefits to the overall research design, particularly with respect to achieving relatively lower "activity" of the control condition by inserting four rather than five needles, as will be discussed below, outweighed any possible diminution of treatment intensity resulting from using one fewer needle in the experimental condition. The acupuncture needles used in CATS are small, 0.20 X 15 mm, stainless steel, disposable needles (Seirin Co., Shimizu, Japan) individually packaged and sterilized in ethylene oxide gas. The needles are left in place for 40 minutes, at which time they are removed, and disposed of by the acupuncturist.

Ensuring adequate treatment "dose." For all three groups, the treatment duration is 8 weeks, with treatments offered daily (Monday through Friday). In clinical settings acupuncture is usually offered on an "as-needed" basis. However, this may result in wide variation across patients in treatment frequency and duration; thus, the systematic evaluation of acupuncture's efficacy required specifying minimum and maximum treatment levels. The maximum treatment intensity is defined as patients attending all five treatment sessions each week of the study; the minimum level is defined as patients attending at least three treatments in the first 8 days, and a minimum of one session per week thereafter. Patients who do not meet the minimum criterion level are discharged and coded as drop-outs. To encourage participation and attendance in the study, financial incentives are offered. Patients may earn a total of $160.00 for participating in CATS. Patients receive $10.00 at the end of each week if they attend at least 2 days of treatment, provide all three urine samples, and complete all of the required paperwork. To cover bus or other transportation expenses, patients also receive $2.00 for each treatment session they attend. Because previous research in the addictions suggests that ancillary psychosocial treatments enhance treatment retention and adherence to treatment, as well as outcomes (Carroll, 1997), all CATS patients participate in drug counseling sessions. Methadone patients receive standard drug counseling provided by
their methadone maintenance program; the primary cocaine patients receive a weekly intervention, based on the Group Drug Counseling Manual developed at the University of Pennsylvania (Philadelphia; Mercer et al., unpublished manual).

**Issues to consider in the selection of a needle insertion control condition**

In order to function as a comprehensive control for acupuncture treatment, the needle insertion control condition should include all of the elements of the experimental acupuncture condition, with the important exception that the points chosen are not hypothesized to be effective for the treatment of cocaine addiction. However, determining in advance which points in the ear satisfy these criteria is by no means straightforward. Traditional Chinese medicine sheds little light on this issue—it does not include the concept of a "placebo," and the organismic model that underlies acupuncture theory does not embody a concept of a systematically "inert" treatment (Wiseman and Ellis, 1985). There is also little guidance from extant Western research. No acupuncture trial of which we are aware presented evidence, prior to starting the study, that the control points used were in fact relatively "inactive" (Liao et al., 1994). From a Western biomedical perspective, some acupuncture researchers have proposed (eg, Ulett, 1992) that auricular acupuncture's effects are due to stimulation of the vagus nerve, which innervates the ear concha, and therefore that needles placed anywhere in the concha, regardless of their alignment with points claimed by acupuncture theory to be ailment-specific, should produce the same effects. This suggests that relative and unknown levels of activity within and between active and control conditions constitutes a potentially serious impediment to the interpretation of findings (Lewith and Machin, 1983).

Designing a suitable control for auricular acupuncture is a complex task that would by itself necessitate a major research project. In the planning stages for a controlled trial of auricular acupuncture, it was therefore necessary to strike a balance between the need to validate the control conditions and the need for a timely evaluation of this widely used intervention. Among the many possible issues that pertain to conducting controlled research in this area, it was decided that three were of critical importance and should be addressed before the design of CATS was formalized: (1) the control condition should be comparable to the active treatment with regard to any adverse effects of needle insertion; (2) the control condition should possess less therapeutic activity than the "active" treatment; (3) an objective method for the reliable location of points for needle insertion that could be used by acupuncturists across treatment sites should be investigated.

**Preliminary studies investigating needle-insertion controls**

Study No. 1: Comparison of acute effects of active and proximate insertion sites. This study investigated a control for needle insertion that had previously been used in acupuncture research in the addictions (Bullock et al., 1989)—needle insertion into points relatively close (ie, within 2–3 mm) to active sites. On theoretical grounds, it was supposed that these proximate sites, sometimes referred to as "sham" acupuncture points, are less active and no more painful than the treatment sites. However, to the best of our knowledge, there were no data to support this assertion. Pain is an important characteristic to consider because greater pain in one of the treatment conditions may produce differential drop-out rates. In order to address the issue of relative degree of pain and other acute sensations in active and proximate control sites, a study was conducted utilizing a single-session, within-subjects design, in which needles were inserted concurrently into "active" sites in one ear, and into loci 2–3 mm from these sites in the other ear and left in place for 45 minutes (Margolin et al., 1993b). After the needles were withdrawn, subjects rated a number of acute effects for each ear, including pain, warmth, and fullness. Findings suggested few differences between the active and proximate sites; neither site was rated as very painful. Subject's ability to guess which ear had received which form of needling did not rise above the level of chance. Although this study suggested that needle insertion into proximate and active sites elicit equivalent pain ratings,
the relative degree of activity of these sites remained to be determined.

Study No. 2: Comparison of short- and long-term effects of active and proximate needle site insertion on treatment outcome. This study investigated the relative therapeutic activity of the proximate control and active sites. A parallel-arm study was conducted in which 40 cocaine-abusing patients were assigned to receive either addiction-specific or proximate needle insertion for 6 weeks (Avants et al., 1995). Outcomes included acute sensations as well as cocaine use. Results showed that both groups reduced cocaine use equivalently. There were no significant differences in the acute effect ratings of the two types of needle insertion, nor in subject ratings of treatment credibility. These results were in accord with findings from a study by Wells et al. (1995) that also used a proximate needle puncture control, and reported positive outcomes for methadone-maintained patients in both needle insertion groups. Findings from this study could be interpreted as implying that either the proximate control points are relatively active compared to the active sites, and hence are not suitable controls, or both sites are inactive and equivalently evoke a placebo response. Given the uncertainties surrounding the control condition, it was considered premature to conclude the latter; hence, it was decided that further studies were needed to evaluate the relative degree of activity in various putative control configurations.

Study No. 3: A comparison of acute and systemic effects of four needle insertion configurations. In order to address the issue of relative degree of activity among a number of candidate control needle insertion sites, a study was conducted that assessed four different needle-insertion conditions utilizing a within-subjects design (Margolin et al., 1995). Ten cocaine-abusing, methadone-maintained patients received four sets of needle insertion conditions, in random order: (1) "addiction specific"—sites used for the treatment of cocaine addiction; (2) "proximate control"—needle insertion into points within 2–3 mm of addiction specific points; (3) "nonspecific control"—needle insertion into active sites outside of the concha, not indicated for the treatment of cocaine addiction (eg, "knee," "sciatic," "elbow," "shoulder"); and (4) "helix control"—needle insertion into regions on the ear rim, or helix. After each treatment session, subjects completed acute effects ratings covering a range of possible local and systemic effects of needle insertion. At the end of the last session, subjects rated overall preferences, and ranked the four treatments from most to least preferred. Results showed that needle insertion into proximate control sites had the highest systemic effect ratings, and was rated second most preferred, after "addiction-specific," by a majority of patients, suggesting that needling of the proximate sites was not a suitable control. The condition with the lowest overall mean ratings of systemic effects was needling of the helix sites. Subjects were least confident in these sites as a treatment for addiction. The helix sites had a number of other characteristics that further suggested their appropriateness as a control condition: they were not ranked as more painful than the other sites; needles inserted into the helix are maximally distant from the experimental sites within the compass of the auricle; the helix regions are not vagally innervated; lastly, they are never used in the treatment of the addictions. Based on these characteristics, results from the preliminary study, and the findings from studies using proximate controls showing no differences between groups, it was decided to adopt needle insertion into the helix regions as a control condition for CATS. However, in order to further decrease the chances that this control condition would be too active, the number of needles was reduced by one to avoid overstimulation of the auricle, and for this reason in CATS four needles are inserted bilaterally in both active and control groups. Figure 1 shows the locations of the "active" and "control" sites.

Study No. 4: Is there an objective method for locating points within zones for needle insertion? This study examined a method by which acupuncturists across sites would locate the precise point for needle insertion within the active auricular zones. Because these zones range from approximately 2 to 5 mm in diameter, they contain a multiplicity of possible points
for needle insertion, and it is possible that some of these points may elicit more of a therapeutic response than others. Therefore, a reliable and objective method for locating the optimal points for needle insertion in the active zones could potentially reduce treatment variability. One method that has been used in previous acupuncture studies entails the use of electrical "point finders," predicated on observations that acupuncture points characteristically exhibit low electrical resistance readings (e.g., Hyvarinen and Karlsson, 1977). However, a preliminary examination at the Yale site of several commercially available devices suggested a number of problems in the design and implementation of the circuitry (Falk et al., 1996). Consequently, an electrical resistance measuring device that obviated some of these circuit design problems was specifically designed and constructed for use in our preliminary research. A study was then conducted in which the active and control zones were divided into quadrants, and the electrical resistance as well as three characteristics traditionally associated with "active" sites—skin discoloration, skin topography, and tenderness—was compared within and across these zones (Margolin et al., 1996). Findings showed that zones did not possess significant variability, that is, a "defining" point for needle insertion, along any of the assessed dimensions. However, comparisons across type of zone showed that active zones possessed lower overall electrical resistance than the control zones, suggesting that a needle placed anywhere within an active zone was likely to be inserted into a point of relatively low electrical resistance compared to a needle inserted into a control zone. In view of this finding, and because a relatively elaborate procedure involving the use of gel and a spring-loaded probe must be used in order to avoid pressure artifacts—a potentially serious confound in determining skin resistance readings (Noordergraaff and Silage, 1973)—the use of electrical "point finders" was not recommended for CATS. The study acupuncturists therefore use clinical judgment in selecting the optimal points for needle insertion within the prescribed zones. The exact location of these zones within the auricle was defined in training sessions with the study's acupuncturists prior to the beginning of CATS; the acupuncturist's accurate location of these zones is verified to prevent "drift" during twice-yearly site visits by the study's master acupuncturists. Although an objective method for point location would have been desirable, the CATS procedure, based on clinical judgment, does in fact accord with the way in which the NADA treatments are delivered in clinical settings, in which point finders are rarely, if ever, used.

Controlling for relaxation and nonspecific effects: use of a no-needle-puncture control condition

The needle insertion control does not, by itself, address the issue of whether incidental aspects of the acupuncture treatments not related to needle insertion may affect outcome. Because a number of clinical reports suggest that acupuncture induces a state of relaxation, which may, in turn, reduce craving for cocaine (Smith and Khan, 1988), we concluded that a possible relaxation effect, induced by sitting in a quiet, darkened room in a comfortable chair for 40 minutes, was an important confound to control for. In considering a non-needle insertion control, we drew on concepts of control conditions developed for psychotherapy research, an area, similar to acupuncture, in which the choice of an appropriate "placebo" is a controversial topic (Parloff, 1986). Considerations for designing controls in psychotherapy research have included the presentation of a credible rationale for treatment, the provision...
of a comparable patient/therapist relationship and attention, and the involvement of a comparable level of desirability or, conversely, patient burden (Parloff, 1986). The adoption of relaxation training as the second control group promised to address all of these factors simultaneously. Relaxation training does not possess the active element specific to acupuncture (ie, needle insertion) but does possess most of the nonspecific elements, including credible rationale, equivalent time demands, patient-staff contact, and relaxation-promoting conditions. The credibility of relaxation training is further enhanced by the fact that it has been used, with varying degrees of success, as a treatment for drug addiction (eg, Chaney and Roswell, 1983; Klajner et al., 1984). Hence, it serves both as a treatment comparison group and as a control condition.

In CATS, the relaxation control condition consists of having subjects watch and listen to prerecorded commercially produced videotapes of pleasant nature scenes, which have quiet music in the background. Five different tapes are used, one for each day of the week. Because the two needle insertion conditions are ostensibly different, and are both, of course, different from the relaxation control condition, we attempted to ensure that the treatments would be presented to the patients as being equivalently credible by developing a script describing the rationale for each treatment, which is communicated to each patient after randomization. Before the first treatment, patients assigned to the relaxation control receive an introduction to relaxation-training techniques and an explanation of why this treatment might be expected to be beneficial for cocaine addiction. All three treatment conditions are of the same duration, are provided at approximately the same time each day, and in the same group setting.

Single-blind versus double-blind design issues

Blindness, or masking of the active and control treatments to participants, is a critical issue in research design because it protects against multiple sources of bias. Although designs using double-blind conditions constitute the "gold standard" for clinical trials, it was decided that conducting CATS under double-blind conditions was not practicable (cf. Vincent and Richardson, 1986). There were several reasons for this. In order for an acupuncture study to be conducted double-blind, the acupuncturists would, of necessity, have to be inexperienced in delivering acupuncture treatments, because they would have to be unaware which is the hypothesized "active" or "nonactive" treatment for addiction. However, in order to assure the fidelity of the NADA acupuncture protocol being tested, the acupuncturists providing treatments in CATS are experienced practitioners, licensed in their respective states. Although we know of no study comparing treatment effectiveness of acupuncture delivered by inexperienced and experienced acupuncturists, it is possible that acupuncture treatments provided by inexperienced acupuncturists are not as effective or are more painful than those provided by experienced acupuncturists. It would also be difficult to verify that an initially inexperienced acupuncturist had not read any literature, over the course of a multiyear trial, that identified the sites commonly used for the treatment of cocaine addiction. Furthermore, unlike conditions in a pharmacotherapy study, in which the active medication and the placebo are matched in appearance so that they cannot be differentiated by treatment providers or by patients receiving the treatment, in clinical trials of acupuncture the control and active treatments are perceptibly different to the treatment providers, undermining any attempted blind.

For the above reasons, it was decided that rather than adopt a double-blind condition that would be unsustainable, CATS would be conducted unmasked with multiple checks on bias.

Guarding against and checking on bias. Although it is recognized that not all interventions can be assessed under double-blind conditions (Kramer and Shapiro, 1984), to the best of our knowledge there are no generally accepted set of guidelines for protecting against bias in unmasked studies. This is an important concern, borne out by meta-analyses suggesting that even single-blind studies that are masked tend to overestimate treatment effects (Schulz et al., 1995). Given that CATS is un-
masked, careful attention was given to addressing two important domains of potential bias: treatment allocation bias (Schulz et al., 1995), and, in general, participant bias (Pocock, 1983).

**Treatment allocation bias.** In order to assure unbiased allocation to the three treatment groups, CATS uses a computer-based randomization program. This program, written specifically for CATS, stratifies by gender and provision of positive or negative urine sample at screening, with the six sites and the two patient groups randomized independently. After administration of the psychosocial assessments, the appropriate information for each patient is entered into the program, which then specifies that patient’s group assignment. This system effectively conceals the treatment allocation schedule and precludes staff influencing treatment assignment.

**Participant bias.** One way in which participant bias can affect findings from a single-blind study is by enhancing the placebo power of the hypothesized active treatment and diminishing that of the controls. Following suggestions in the acupuncture research literature (Vincent and Richardson, 1995), placebo power in CATS was conceptualized as a function of two primary factors—treatment provider/patient relationship, and treatment credibility. These factors are assessed using two instruments originally developed for psychotherapy studies, which are also conducted under unmasked conditions—the Working Alliance Inventory (WAI), and the Treatment Credibility Scale (TCS). The WAI was developed to evaluate the relationship between the patient and the treatment provider concerning the bond developed, and agreement on goals and tasks (Horvath and Greenberg, 1989). CATS uses a modified version of the WAI, emphasizing the trust and confidence that the patient has in the treatment provider. Patients in CATS complete the WAI at the end of the first week of treatment, and at the beginning of weeks 4 and 8. We expect any preferential treatment given to patients in the active group to be detected by comparing the scores across the three groups on this instrument. The TCS was originally developed to evaluate the relative credibility of different psychotherapies (Borkovec and Nau, 1972). CATS uses a modification of the TCS developed for acupuncture research (Vincent, 1990). Patients complete the TCS during intake, after introduction to the assigned treatment, and at post-treatment, in order to detect differences between the credibility of the active and control treatments before and after the patients have experienced them.

**Additional procedural steps taken to decrease and monitor bias.** In order to diminish the possibility that the acupuncturists might knowingly or unknowingly attempt to influence outcome in favor of the active treatment, consideration was given to placing constraints on the interactions between acupuncturists and patients. We should mention why one seemingly straightforward strategy, the proscription of any verbal exchanges between the acupuncturist and patients, was not adopted. Although seemingly plausible, there were several problems with this procedure: (1) it was thought that a uniformly mute acupuncturists might result in this individual being perceived as cold and uncaring by patients, which could negatively impact their participation in the study; (2) the acupuncturists should be able to answer questions concerning the acupuncture procedure, especially because some individuals are somewhat apprehensive before receiving their first acupuncture treatment; (3) as discussed above, one check on acupuncturist bias is by having patients complete the WAI; given that the acupuncturists must provide the acupuncture treatments, it was decided that they should also introduce the patients to the relaxation sessions as well, permitting evaluation of the acupuncturist/patient relationship across all three groups.

Therefore, in order to balance the need to create an appropriate therapeutic milieu, the capacity to compare patient/treatment provider relationships across treatments, and the advantages of constraining acupuncturist/patient interactions, the following guidelines were adopted. Acupuncturists answer patients’ questions concerning the treatments in a clear and succinct manner, with no additional information volunteered beyond what is needed to address the specific question. However,
acupuncturists do not initiate exchanges and do not engage patients in conversation. In order to assure compliance, on the part of both patients and acupuncturists, the treatment sessions are monitored by a staff member who records the interactions between the acupuncturist and patient in the study log, which is reviewed regularly by the site director with appropriate feedback given to the acupuncturist.

**Patient Bias.** One potentially important source of bias in an unmasked study such as CATS is patients’ appraisal of whether they are receiving the putative active treatment. This will be a function in part of the similarity between the active and control treatments, as well as patient’s foreknowledge as to the appearance of the “real” treatment. In auricular acupuncture the treatment region is relatively small, and the procedure is fairly unfamiliar, therefore, it is not obvious which configuration of needle insertions constitutes the “sham” treatment or the active treatment. In preliminary studies it was noted that patients did not scrutinize or remark on the placement of needles, and seemed willing to accept needle insertion in the helix as a plausible form of auricular acupuncture. This observation is consistent with findings that studies in which the active and control treatments are similar have less of a placebo effect (Turner et al., 1994). Prior to entry into the study, patients are told that the study involves treatment with two different types of acupuncture: needle insertion into points presently considered standard treatment for substance abuse (type I), or into points that have not yet been tested for the treatment of substance abuse (type II).

The relaxation group is, of course, conspicuously different from the two needle insertion groups. Because referring to the study as an “acupuncture” study could potentially bias patients against this group, the study is referred to, and presented to patients, as a study investigating a number of “alternative” treatments for cocaine addiction. Relaxation therapy has been used in the treatment of drug abuse with some success, and so it is legitimately presented to patients as a potentially useful treatment for their problem. The TCS constitutes a check on the credibility of this treatment. In order to obviate comparisons between the treatments, patients in the three groups do not receive treatments together in the same room.

In order to reduce patient-initiated interactions with the acupuncturist, patients are asked not to attempt to engage the acupuncturist in conversation, and are told before they begin treatment that the acupuncturist’s lack of interaction should not be interpreted as a sign that the acupuncturist is uncaring with respect to them or their recovery.

**Staff Bias.** In order to preclude staff bias from influencing self-reported change in the psychosocial measures, the pre- and post-treatment assessment interviews are conducted by staff members who are blind to group assignment. In order to militate against the creation of a context in which staff consider the control needle insertion condition to be inert, which may be, even unknowingly, communicated to patients, the active and control needle insertion groups are referred to by staff members as type I and type II acupuncture. After the introduction of the treatments to new patients after intake, staff members are instructed not to discuss the treatments with the patients, but to refer questions to the acupuncturist, whose interactions with patients are monitored.

**CONCLUSION**

Like most complementary therapies, acupuncture does not possess a well-founded research infrastructure that can be utilized in designing and implementing controlled studies. In the current article we discussed the approach taken to a number of critical issues in the design of CATS, with particular emphasis on the development of appropriate control conditions, and measures taken to minimize and check on bias. One of the implicit goals in the design of CATS was to advance the state of the art in acupuncture research. However, we are well aware that no methodology for protecting against bias in clinical trials is definitive, and that the procedures adopted in CATS are by no means foolproof. We hope that the state of the art represented by CATS will be superceded in the not too distant future.
We note that, based on several recent surveys, it has been estimated that between 25 and 60 million Americans make at least one yearly visit to a complementary or alternative (CAM) therapy treatment provider (Eisenberg et al., 1993; Paramore, 1997). Nontraditional treatments, including acupuncture, are now offered as paid benefits by Health Maintenance Organizations (Eisenberg, 1997; Weeks, 1997). Hence, there is an urgent need to evaluate these noncanonical treatments for efficacy as well as for adverse effects in well-controlled studies (Woolf et al., 1997). This goal will entail the ongoing development of a methodological infrastructure for CAM clinical research, currently in its infancy. Without such a generally accepted, empirically validated infrastructure, each study in this area will have the burden of providing evidence that its design is reasonably well-founded. Methodological endeavors such as validating control conditions—showing that something is relatively inert—are perhaps not the most appealing of scientific enterprises. However, it is not likely that CAM studies possessing high credibility within the general healthcare community will be routinely conducted before such basic methodological issues are empirically addressed.

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APPENDIX

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