Methodologic Recommendations for Cocaine Abuse Clinical Trials: A Clinician-Researcher's Perspective

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INTRODUCTION

Dozens of medications have been tested as treatments for cocaine abuse, but none has shown clear promise (Kosten 1992; O'Brien 1993). Intensive psychosocial treatments have shown some efficacy (Carroll et al. 1991; Higgins et al. 1991, 1993; Magura et al. 1994; McLellan et al. 1993; O'Brien 1993; Rawson et al. 1990, 1991), but even with these, dropout rates and failure rates remain significant, and powerful medication treatments for cocaine abuse are still needed.

This chapter develops the thesis that the medications development effort for cocaine abuse would be improved by focusing on two problems:

1. Viewing cocaine abuse as a unitary syndrome and testing drugs on unselected samples. Instead, cocaine abusers may be heterogenous and divisible into subgroups, which may respond to different treatment approaches. For example, depression, attention-deficit hyperactivity disorder, and alcohol abuse or dependence all co-occur frequently with cocaine abuse and are all amenable to pharmacotherapy.

2. Reliance upon simple open-label pilot trials in choosing promising medications for further testing. Open-pilot trials have tended to create false impressions of efficacy, which have not been borne out in large placebo-controlled trials. O'Brien (1993) has challenged the field to come up with alternatives to the open-pilot trial. Designs for small, controlled pilot trials will be discussed.

This chapter builds from a review of controlled trials of tricyclic antidepressants, mainly desipramine, for treatment of cocaine abuse. This is the most thoroughly studied medication to date for treating cocaine abuse and will serve as a case example, highlighting the difficulties in testing medications for cocaine and motivating subsequent methodologic recommendations.

CONTROLLED TRIALS OF TRICYCLIC ANTIDEPRESSANTS FOR COCAINE ABUSE

Prospective, parallel group, placebo-controlled trials were selected for review. In the following narrative, each trial is summarized, while the main outcomes are collated in table 1.

The ground-breaking placebo-controlled trial of desipramine was that by Gawin and colleagues (1989). Twenty-four patients completed at least 1 week of treatment in each of three groups: placebo, desipramine, and lithium were compared. Fifty percent of the sample were intranasal (IN) users. The patients received counseling once per week in addition to medication. Patients who dropped out during the first week after randomization were replaced. The overall dropout rate at 6 weeks of treatment, including those early dropouts, was about 45 percent. Desipramine patients remained in treatment significantly longer than the other groups. The proportion of patients with 3 or more consecutive cocaine-free weeks, urine confirmed, was significantly greater on desipramine (59 percent) than placebo (17 percent). Robust effects of desipramine, compared to placebo, were also found for quantity of cocaine use and for cocaine craving, both self-report measures. For all groups, there was a substantial reduction in both cocaine use and craving during the first week of treatment, suggesting a moderate-sized placebo effect on these self-report measures. Outcome of mood or psychological symptoms was not reported, and less than 20 percent of the sample had comorbid DSM-III mood or anxiety disorders. However, removal of the small subgroup with depressive disorders did not alter the favorable desipramine effects. In summary, this trial replicated previous open-label trials in suggesting substantial efficacy for desipramine in unselected cocaine abusers.

A small, early trial by Giannini and Billett (1987) is of interest because mood, instead of cocaine use, was the main outcome measure, and again desipramine was found superior to placebo. Neither cocaine use nor craving was measured in this trial. The trial is also muddied because the desipramine group also received bromocriptine, which was discontinued after the early weeks of treatment with patients remaining on desipramine.

	Percent Intranasal Users	Dropout Rate	Abstinence Measures DMI > PBO	Self-Report Cocaine Use DMI > PBO	Cocaine Craving DMI > PBO	Depression/ Psych Sxs DMI > PBO	Subgroups with G Medication Effect
Gawin et al. (1989)	50	45% @ 6 weeks	+	+ (p)	+ (p)		(removal of small depressed subgrou not change effects
Giannini et al. (1987)						+	
Weddington et al. (1991)	30	50% @ 4 weeks	+ (trend)	- (pp)	- (pp)	- (pp)	
Kosten et al. (1992)	11	25% @ 12 weeks	-	- (p)	- (p)	+	Patients with depression or with antisocial persona
Arndt et al. (1992)	(majority using IV)	20% @ 12 weeks	-	+ (weeks 2, 4) - (weeks 8, 12)	-		Patients without antisocial persona
Carroll et al. (1994)	29	21% @ 2 weeks 65% @ 12 weeks	- pp	- (p)	- (p)	- (p)	Patients with mild cocaine abuse
Nunes et al. (1995)	46	46% @ 4 weeks	+ (trend)	- (p)	+ (p)	+	Patients with depression or intr use

KEY: (p) = moderate placebo response; (pp) = large placebo response.

Weddington and colleagues (1991) compared cocaine abusers who completed at least 2 weeks of treatment on desipramine (N = 17), placebo (N = 21), and amantadine (N = 16) over a 12-week trial. The sample consisted of only 30 percent IN cocaine users. In addition to medication, patients received twice-weekly psychotherapy. The dropout rate was about 50 percent by week 4, if those who dropped out prior to week 2 are included. The number of weeks of consecutive, urine-confirmed cocaine-free weeks was analyzed as a continuous measure. The report shows a one-way ANOVA comparing the three groups, which was not significant. However, a test of the difference between the desipramine and placebo means would be a more appropriate gauge of the desipramine effect. Comparing the means (Å standard error of mean) reported for the desipramine (6.2Å1.1) and placebo (3.6Å0.8) groups yields a *t*-statistic of 1.96 with 36 degrees of freedom, which is a trend ($p <$ 0.10) for a two-tailed test. An argument could even be made for a one-tailed test (which would be significant here at the 0.05 level), since consecutive cocaine-free weeks was a primary outcome measure in the previous trial (Gawin et al. 1989), and this trial was a replication

attempt. For self-report cocaine use and craving, there were even greater reductions across groups during the first week than those observed by Gawin and colleagues (1989), again suggestive of a substantial early placebo effect. With such large placebo effects, demonstration of medication-placebo differences would be very difficult, and in fact none were observed on these measures. Mood outcome in the form of weekly Beck Depression Inventory scores was reported in this trial. There was no desipramine-placebo difference on the Beck, although the mean baseline score was less than 10, suggesting the sample was at most mildly depressed to begin with, leaving little room to demonstrate improvement from an antidepressant. This trial has generally been presented as a negative study and a failure to replicate. However, substantial placebo effects on most measures, as well as relatively small sample sizes, severely limit statistical power. Interestingly, on consecutive cocaine-free weeks there is a less pronounced placebo effect and a marginally significant desipramine-placebo difference.

A pair of studies were subsequently published evaluating desipramine for cocaine abuse in methadone maintenance patients. Arndt and colleagues (1992) randomized 79 patients to desipramine or placebo: 83 percent were intravenous (IV) users and only 11 percent were IN users. The dropout rate was only 25 percent at 12 weeks, substantially less than in the previous studies, likely reflecting the power of methadone in a well-run, multimodality clinic. Side effects and the dropout rate were greater on desipramine than placebo. No desipramine-placebo differences were detected on self-reported cocaine use or cocaine craving, and scores for these were about 40 percent reduced between baseline and end-study in the placebo group, suggesting modest placebo effects. In contrast, the proportion of drug-positive urines remained high throughout the trial, ranging from 60 percent to 90 percent, with no significant desipramine-placebo difference, and little trend toward reduction in the placebo group over time. Thus, similar to the pattern noted for other studies, abstinence rates were relatively low with little placebo effect. A number of Addiction Severity Index (ASI) factor scores and measures were analyzed, and none showed significant desipramine-placebo differences except for measures of psychiatric problems, where desipramine demonstrated a significant beneficial effect. A secondary analysis has subsequently suggested that medication effects were greater when patients with antisocial personality are removed (Arndt et al. 1994).

Kosten and colleagues (1992*b*) randomized 94 methadone maintenance patients abusing cocaine to desipramine (N = 30), amantadine (N = 33), or placebo (N = 31) for a 12-week trial. The majority of patients were IV users. Dropout rates were again relatively low at 27 percent on desipramine and 13 percent on placebo. Interpretation of outcome is hampered by the fact that desipramine and amantadine effects are not separated. For self-report cocaine use there was a significant advantage for medication over placebo in the second and fourth weeks of the trial, but no differences later in the trial. Again, abstinence rates were low, with little improvement over time (i.e., little placebo effect), and no medication-placebo differences. In contrast to the other trials, there was also little improvement in self-report cocaine use or craving over time. A secondary analysis (Ziedonis and Kosten 1991) suggested the subgroup with depression may have done better on medication than on placebo. Another secondary analysis suggested medication effects were enhanced by removing the subgroup with antisocial personality (Leal et al. 1994).

Carroll and colleagues (1994*a*, 1994*b*) randomized outpatient cocaine abusers (not on methadone) to two levels of psychotherapy (relapse prevention or case management) and two levels of medication (desipramine or placebo). There were 139 patients randomized; 110 completed two or more treatment sessions and 49 completed all 12 weeks, a large dropout rate consistent with that observed in the other outpatient studies. The majority (62 percent) were freebase users, while 29 percent were IN users. There were no effects of medication assignment on any major outcome measures. Self-report measures of cocaine abuse and for psychological problems (ASI composite scores) showed moderate reductions over time on placebo. In a departure from other trials, the proportion of abstinent days was high, around 70 percent in all groups. Analysis of interactions suggested a significant advantage for desipramine over placebo on consecutive-abstinent days in the subgroup with low-severity cocaine abuse at baseline.

The author and colleagues (Nunes et al., submitted) randomized 113 outpatient cocaine abusers to imipramine or placebo. All patients received once-per-week counseling. Slightly under half the sample (46 percent) were IN users. The attrition rate at 4 weeks was 46 percent (52/113). There were no medication-placebo differences in self-report cocaine use. Interestingly, for abstinence-based measures, there were at least trends favoring imipramine. Among 4-week completers, the proportion of patients with three consecutive cocaine-free weeks, urine- confirmed, was 11/34 (32 percent) on imipramine

versus 3/27 (11 percent) on placebo ($p < 0.10$). There were again moderate-sized reductions in self-report cocaine use and craving on placebo over time. Imipramine was superior to placebo on craving and on the Hamilton Rating Scale for Depression score. This study differed from the others in that it was stratified prospectively by route of cocaine use and by level of depression. Analysis of these subgroups suggested the imipramine effect on abstinence was occurring mainly among the IN and depressed patients.

Summary of the Controlled Tricyclic Trials

Considering these trials together, and inspecting table 1, several points become clear.

1. Dropout rates: Dropout rates are high, especially in the early weeks of treatment.

2. Placebo effects: Substantial placebo effects are evident for self-report measures of drug use and craving, although not for measures of urine-confirmed abstinence.

3. Efficacy: The overall impression of efficacy, based both on review of these trials and the author's experience treating patients in his own trial, suggests there is something there—some effect on craving, or mood, or on cocaine use early in the trial, or perhaps in some subgroup of patients. However, the effect is modest and certainly not a large effect such as that of methadone upon opiate dependence.

4. Subgroup hypotheses: Inspection of table 1 suggests tricyclic effects on cocaine use may increase with the proportion of IN users in the sample, suggesting that the subgroup of nasal users may be more responsive. Posthoc analyses of several trials have suggested other subgroup hypotheses—that depressed cocaine users (Ziedonis and Kosten 1991) and mild cocaine users (Carroll et al. 1994*a*, 1994*b*) may respond preferentially, and that cocaine users with antisocial personality do not respond (Arndt et al. 1994; Leal et al. 1994). In the author's trial, IN and depressed groups, identified prospectively, appeared to respond preferentially.

METHODOLOGIC ISSUES AND RECOMMENDATIONS

Sample Heterogeneity and Targeting Subgroups

Klein (1991) has argued that failure to recognize sample heterogeneity can easily doom a drug development effort. If response is restricted to a subgroup, and this is not recognized early in Phase II, subsequent large Phase II or Phase III trials may falter because study samples are diluted with unresponsive patients. As noted in this chapter, subgroups based on addiction severity, route of use, or depression may be relevant to cocaine abuse pharmacotherapy and should be considered when devising interventions and designing clinical trials, either in terms of restriction of inclusion criteria or stratification.

A relatively unexplored strategy is treatment of comorbid psychopathology among cocaine abusers. Comorbid psychopathology is more prevalent among substance abusers than in the general population (Regier et al. 1990) and has consistently been associated with poor prognosis (Carroll et al. 1993; Kosten et al. 1986; Rounsaville et al. 1982, 1986). To the extent that psychopathology may contribute to the etiology of substance abuse in an individual, treatment of the psychopathology should improve outcome.

Treatment of depression with tricyclics in alcoholics and opiate addicts has received some study. The author (Nunes and Quitkin, in press) has recently reviewed this literature. The consensus from these is encouraging in that depression appears identifiable and treatable. Such treatment may improve substance abuse, although the evidence for this is weaker. It seems likely that this strategy will prove to be a useful adjunct to substance abuse treatment, but will not yield a large-sized effect akin to methadone for opiate dependence. Nevertheless, in the absence of powerful and globally effective anticocaine agents, such subgroup strategies are probably worth pursuing.

Further, among cocaine abusers, there has been little study of the treatment of subgroups with comorbid psychopathology. In addition to depression, alcoholism, antisocial personality, attention-deficit disorder, and schizophrenia are all associated with cocaine abuse. All but antisocial personality can be effectively treated with pharmacotherapy. Thus, a series of studies suggest themselves to determine the extent to which targeting comorbid psychopathology is useful in cocaine abuse.

The Placebo Effect and Open-Pilot Trials for Cocaine Abuse

Reflection on the placebo groups in the controlled tricyclic trials suggests why open-pilot trials are likely to yield false-positive results and reinforces the notion (Kosten 1992; O'Brien 1993) that this design may be fundamentally flawed as a medications development tool for cocaine abuse. In most of the trials, clear reductions over time in self-report quantity of cocaine use and "craving" were observed, especially over the first 1 to 3 weeks of the trial. Were these uncontrolled pilot trials of new agents, most would have been interpreted as indicating efficacy.

These "placebo" effects are probably created, in part, by the psychosocial interventions that accompanied pharmacotherapy. All the trials provided at least once-weekly counseling visits, and some provided more (Carroll et al. 1994*a*, 1994*b*; Weddington et al. 1991). Another contributor may be a reporting bias in which patients, perhaps wishing to please their clinicians or significant others, report less cocaine use over time when there had in fact been little real change. This would be consistent with the observation that placebo effects were more prominent for self-report measures, whereas for more objective measures, urine-confirmed abstinence, and retention, there was less placebo effect and dropout, and nonabstinence rates remained high. A tendency of sicker patients to drop out, leaving the sample progressively enriched with less severe cases, could also help create the impression of improvement over time.

Placebo effects varied in strength across trials. This may simply represent fluctuations due to sampling or differences between local populations. However, it may also be that the psychosocial interventions differed in their efficacy. This promoted the argument that an overly effective psychosocial intervention might overwhelm medication effects and that medications should therefore be tested in the setting of minimal psychosocial interventions. On the contrary, the relatively high rates of dropout and of failure to achieve abstinence suggest there would still be plenty of room for a medication to demonstrate an effect in such trials. An argument can be made that medication trials should be superimposed on a strong psychosocial intervention, so that the trial is informative in terms of what medication has to add to good standard treatment. Anything less may lack clinical credibility with the control group becoming a "straw man" receiving poor care. The field can look to the experience with methadone, which shows that this highly efficacious medication is best applied in an adequate psychotherapeutic setting (McLellan et al. 1993).

Recommendations

The above features of "placebo response" in cocaine abusers suggest the following design features for preliminary trials:

1. A single-blind placebo lead-in phase: A 2-week, single-blind placebo lead-in would "wash out" the early placebo effect and early dropouts and provide a more stable baseline. The one disadvantage of this feature would be loss of the opportunity to see a medication effect on early attrition. On the other hand, much early attrition may relate to insufficient motivation and occur before a minimum adequate exposure to medication has occurred.

   The utility of the initial placebo lead-in phase has recently been challenged in the setting of medication trials for outpatient depression, based on analyses showing that it reduces ultimate response rates about equally across groups and therefore does not sharpen the discrimination between placebo and medication (Trivedi and Rush 1994). On the other hand, Quitkin and colleagues have shown, again in the setting of depression trials, that removal of early responses (Quitkin et al. 1993) or covariation by degree of early response (Quitkin et al., submitted), does enhance power, although the advantage may be slight (Quitkin et al., submitted). In cocaine abuse trials the advantage is likely to be greater, since early placebo effects, and early attrition, are more pronounced.

2. Some form of concurrent placebo control: Given the evident variation in placebo effects in cocaine abuse trials, some estimate of the placebo effect within the sample of a pilot study is needed, even if the sample size is small.

3. A standardized and potent psychosocial intervention: The goals of this would be to reduce attrition and reduce variation contributed by nonpharmacologic factors. This would best be manual driven, so that all patients receive approximately the same "dose" of psycho-social/behavioral therapy. For example, relapse prevention (Carroll et al. 1991, 1994*b*) has demonstrated efficacy and is a reasonable choice. Simple once-per-week counseling is probably not adequate treatment for outpatient cocaine abusers (Kang et al. 1991), and trials may need to provide more than this, particularly in the early weeks.

Providing positive incentives, contingent on clean urines, has proved a powerful intervention (Higgins et al. 1991, 1993), and this might indeed overpower medication effects. However, not all patients respond. Medication might be tested as an adjunct in the incentive-refractory group, and this could be viewed as another example of the strategy of restricting the inclusion criteria to target a specific subgroup and reduce sample heterogeneity. Incentives might also be applied, contingent on attendance, to improve retention in medication trials.

Measurement of Outcome in Cocaine Abuse Pilot Trials

A second set of problems reflected in the controlled tricyclic trials has to do with measurement of outcome. Reduced quantity of cocaine use by self-report may not be all that meaningful clinically. Patients wishing to please clinician-investigators may report less use over time, giving the appearance of improvement in within-subjects comparisons (i.e., an expectancy effect). The same problems may apply to retrospective self-reports of craving. Objective outcomes may be more likely meaningful. Urines remain the "gold standard" for documenting abstinence, ultimately the most desirable outcome. Quantitative urine cocaine metabolites from at least two samples per week may provide more objective documentation of reduced use short of abstinence (Batki et al. 1993). Several chapters in this monograph present promising new methods for analyzing quantitative urines (Preston et al., this volume). Response to cocaine-related cues in the laboratory also deserves consideration. Cue response has been associated with relapse (Ehrman et al. 1993) and includes objective physiologic measures (Childress et al. 1992; Ehrman et al. 1992).

Nevertheless, Klein (1991) argues that in preliminary Phase II trials, experienced clinicians should follow the patients because they may observe important improvements not detected by the planned primary outcome measures, or conversely they may judge improvement in some primary outcome measure to be of little clinical significance. The author found that direct clinical involvement with patients in his own trial was helpful in interpreting the numerical outcomes.

Quitkin and colleagues (1984) and Klein (1991) also argue for the importance of observing patients on a medication beyond an initial 6-week acute trial in a "maintained improver" design. An effect slow to develop could be missed in a 6-week trial. More importantly, acute improvements will be more clinically meaningful if sustained over time, whereas transient improvements and "placebo effects" will wash

out. For example, in Gawin and colleagues' (1989) original 6-week desipramine trial, the response criterion of three or more consecutive, urine-confirmed, cocaine-free weeks would be more impressive if supplemented by a second 6 weeks of observation on medication as opposed to long-term naturalistic followup during which treatment is no longer controlled by design (Kosten 1992*b*).

Quitkin and Rabkin (1981) and Klein (1991) argue that it is useful to study the medication withdrawal process systematically. For patients who have improved on a medication, tapering back to placebo can increase the information yield, since true medication responders should relapse on placebo. This placebo-controlled discontinuation design is discussed further below.

Recommendations for Design and Measurement

1. Emphasize "objective" outcome measures, including urine-confirmed abstinence, quantitative urine-cocaine metabolites, and possibly response to cocaine-related cues.

2. Retain a role for the experienced clinician in judging whether a clinically significant improvement has occurred and identifying responsive subgroups.
3. Consider the "maintained improver" design (Quitkin et al. 1984), in which patients remain on medication for a total of 12 weeks, a 6-week acute trial followed by a 6-week maintenance phase.

4. Consider the placebo-controlled discontinuation design (Quitkin and Rabkin 1981), in which patients are systematically tapered from medication back to placebo.

POTENTIAL EARLY PHASE II DESIGNS

Drawing together the methodologic issues discussed earlier, several designs are considered as likely improvements over the open-pilot trial. Again, the goal for "early Phase II" is to test drugs for preliminary indications of safety and efficacy in small samples before moving on to larger, more costly controlled trials. Each of the following designs incorporates some form of placebo control and has features that enhance power, allowing smaller samples to be utilized. In keeping with the recommendations mentioned previously, all these designs can include an initial placebo washout phase and a manualized psychosocial intervention, received by all subjects, to

enhance retention and teach skills of abstinence initiation and relapse prevention.

The Two-Period Crossover Design

This is a classic design aimed at extracting the maximum information from a small sample. Power is in theory enhanced by the fact that each patient serves as his or her own control. This design is best for detecting effects with rapid onset, rapid offset, and few withdrawal or "carryover" effects, in samples with low dropout rates (Fleiss 1986). Unfortunately, it is not clear what offset or "carryover" effects might occur with a cocaine abuse medication, and further, despite best efforts at providing a psychotherapeutic foundation, dropouts will occur. Batki and colleagues (1994) employed this design to test fenfluramine in cocaine-abusing methadone patients. Interpretation of the results was clouded both by dropouts and also by an effect of time, such that patients in both groups who were retained into the second period had reduced cocaine use compared to the first period. Both the dropout and time effects are consistent with the results of the desipramine trials reviewed earlier and are likely to hamper efforts to employ this design. However, it might still be considered in stable samples under highly controlled conditions such as inpatient or intensive residential or day-treatment settings.

The Placebo-Controlled Discontinuation Trial

In this design, patients are at first treated in an open-label trial, and responders are then randomly assigned to either remain on medication or taper to placebo under a double-blind. This has the advantage of an open-label trial that a larger number of patients get initial exposure to the candidate medication. The open-label phase can be analyzed for predictors of response. Only the relatively homogenous sample of treatment responders enters the placebo-controlled phase, reducing heterogeneity and in theory enhancing power (Klein 1991; Quitkin and Rabkin 1981). This would seem a particular advantage, given the suggestions from the tricyclic trials that subgroups (antisocial personality, mild severity, route of use, depression) may be relevant to response. Of course, the randomized experiment in this design bears more on maintenance of response or relapse prevention, whereas a prospective randomized trial bears on induction of initial response. These are different questions, both relevant to cocaine abuse medications development.

The author and colleagues have successfully applied this design to a study of imipramine treatment for depressed alcoholics (Nunes et al.

1993). However, a large number of patients had to be entered initially (N = 85) in order to randomize a small number (N = 26), so that the effort was ultimately larger and more labor intensive than one might like for an initial pilot trial. This is partly due to dropouts and nonresponders in the open phase, and partly to the problem that patients who are doing well on open-label medication are often reluctant to be randomized with a risk of coming off medication.

The Multiple Baselines Design

In a simple form of this design, patients are randomly assigned to two groups, one of which receives the candidate medication and the other placebo. At a later timepoint, the placebo group is crossed over to medication. This provides an initial prospective, parallel-group, placebo-controlled trial, yielding an estimate of the placebo effect against which the effect of the candidate can be judged. At the same time, this design affords advantage of the open-label trial that most patients (i.e., those who do not drop out) can be observed on medication. Such designs have yet to be implemented in clinical trials of medications for substance abuse.

A Proposed Hybrid Design

Table 2 describes a hybrid design that combines features of the multiple-baseline, crossover, and discontinuation designs. Treatment-seeking cocaine abusers enter a 2-week, single-blind, placebo baseline phase, after which they are randomly assigned to one of two groups as summarized in table 2, below.

TABLE 2. *Proposed design for pilot clinical trials for cocaine medications.*

	Schedule				
	2-Week Baseline	Weeks 1-6	Weeks 7-12	Weeks 13-18	Weeks 19-24
Group 1	Placebo	Candidate	Candidate	Placebo	Placebo
Group 2	Placebo	Placebo	Candidate	Candidate	Placebo

The extended single-blind placebo phase at the front end is designed to wash out early dropouts and early placebo effects. The first two 6-

week phases (weeks 1 through 6 and weeks 7 through 12) form a multiple-baselines design, as discussed earlier. Finally, patients remaining in treatment during weeks 13 through 24 are systematically tapered back to placebo (double-blind), affording the opportunity to observe whether symptoms of cocaine abuse recrudesce off medication, as in a crossover or discontinuation design. For subjects who complete the entire trial, the design may be viewed as an ABA design, or a series of single-subject experiments. Ultimately, the results of the initial between-groups comparison (weeks 1 through 6) would be synthesized with the crossover discontinuations and within-subjects comparisons, over several outcomes, and with clinicians' impressions, to arrive at a preliminary impression of efficacy, safety, and tolerability.

Data Analysis, Sample Size, and Power Considerations

Early Phase II clinical trials, such as the designs described previously, are preliminary, exploratory studies with the purpose of suggesting whether a candidate medication warrants consideration for larger, more definitive trials. As such, investigators should be more concerned about missing a true effect (Type II error) and more tolerant of a Type I error, than in a larger, more definitive study.

The author would also argue that investigators should be interested mainly in detecting medium to large effects. While small effects might be of some theoretical interest, they are unlikely to have much clinical impact on cocaine abuse.

Power will be discussed mainly with respect to a between-groups medication versus placebo comparison, such as at the 6-week endpoint in the hybrid design presented earlier. Power of within-subjects comparisons (baseline versus endpoint on medication or ABA designs) or of crossovers may be greater, although potentially more clouded, by effects of time in treatment and attrition.

On an abstinence-based, dichotomous response measure, a low placebo response rate could be anticipated based on the desipramine-placebo trials reviewed earlier. Assuming a placebo response rate of 10 percent, a sample size of 30 patients (15 per group) is sufficient to detect large effects (10 percent response on placebo versus 65 percent on medication), given the usual assumptions of beta = 0.20 and two-tailed alpha = 0.05. Relaxing alpha to = 0.20 will begin to permit detection of medium-sized effects (10 percent response versus 50 percent), at the expense of a greater Type I error rate (Fleiss 1981).

Likewise, for continuous measures such as self-report cocaine use, proportion of positive urines across the weeks of a trial, or quantitative urine cocaine metabolites, setting beta at 0.20 and two-tailed alpha ranging from 0.05 to 0.20, 15 per group is sufficient to detect large (1.1) to medium-large (0.80) effect sizes (Cohen and Cohen 1983). These power estimates are based on simple two-group comparisons. Power may be enhanced by stratifying the randomization on baseline severity of cocaine use, and by entering baseline levels of outcome measures as covariates in the data analysis. To the extent that baseline correlates with outcome, power is increased (Fleiss 1986; Klein and Ross 1993). The single-blind placebo lead-in, by reducing variance contributed by early placebo effects, should protect power.

These power calculations assume two-tailed alphas. It can be argued that interest is only in the one-tailed hypothesis that medication is superior to placebo. Again, the goal is to determine whether a positive effect is likely and whether further investigation with the candidate medication is warranted. Failure to find an effect and finding medication worse than placebo would have similar implications, namely to discourage further research with that agent.

At N = 30, the designs proposed herein would not be highly powered to detect statistical significance, particularly for small- to medium-sized effects. However, Cohen and Cohen (1983) argued that clinical investigators should be more concerned with the sizes of effects than with statistical significance per se. A useful alternative approach, then, for early Phase II trials would be to place confidence limits on the effect size. Investigators can then judge whether the likely range of effect sizes warrants further trials. For example, it can be shown that with a sample size of 15 per group, an observed effect size less than or equal to zero virtually rules out a true effect in the medium to large range. The more the observed effect exceeds zero, the greater the probability of a medium to large effect.

IMPORTANCE OF LABORATORY MODELS

Medications development for many mental disorders enjoys the advantage of prototype-effective medications. Examples include methadone for opiate dependence or various medications effective against depression. These prototypes can be used to validate laboratory models, which then serve to screen and identify new agents with potential efficacy. The prototype can also guide initial clinical observations, serving as a model for how an effective agent should

perform clinically and what outcome measures are most appropriate. An overarching problem with medications development for cocaine abuse is that no such anticocaine prototype exists (O'Brien 1993). Nevertheless, animal and human laboratory models with face validity and at least limited predictive validity exist, and clinical investigations need to be informed by them. Animal models will serve as a source of hypotheses for candidate medications. Cocaine choice (Fischman et al. 1990) and cue response (Childress et al. 1992; Ehrman et al. 1992) procedures are human laboratory models that can be used to test potential medications. Early Phase II trials might be enhanced by coordinated efforts between clinical trials and human laboratory studies. Testing the same medication in both the clinic and the laboratory would broaden the available data on safety and efficacy and perhaps provide a clearer recommendation as to whether a medication is promising for further Phase II or Phase III testing.

THE ROLE OF THE CLINICIAN-INVESTIGATOR

As discussed previously, Klein (1991) emphasizes the involvement of clinician-investigators during early Phase II, arguing that their depth of clinical experience can help to judge clinical significance when statistical significance is detected on some measures, or to perceive responsive or unresponsive subgroups. Direct work with patients can also yield hypotheses, and the history of psychopharmacology includes many advances that began with serendipity and clinical observation.

Not surprisingly, then, many of the most senior principal investigators and center directors at the National Institute on Drug Abuse (NIDA) have strong clinical roots. At the author's own institution, the role of research-psychiatrist has always involved substantial clinical work. However, the balance of priorities needed to flourish in the traditional research-physician or research-clinician role is becoming more difficult to achieve. Increased sophistication and complexity of methodologies, regulatory burdens, and funding requirements, among other issues, will perforce tend to draw principal investigators away from regular contact with patients. A clinician-investigator who spends substantial time with patients runs the risk of producing too few papers, grants, and new initiatives to keep a research operation going. Some balance needs to be struck. Furthermore, a steady supply of new clinician-investigators is needed. NIDA is, therefore, to be encouraged in its commitment to the funding of fellowships and other early career mechanisms that afford research training to clinicians and clinical experience to researchers.

SUMMARY AND CONCLUSIONS

This chapter reviewed the controlled tricyclic trials for cocaine abuse with both a clinician's and a researcher's eye in order to develop methodologic recommendations for future medications development efforts. The review is summarized in table 2. The main points are that attrition is high, particularly early in the trials; placebo effects are high, particularly early and in subjective or self-report measures; and the samples may be heterogeneous with responsive (depressed, mild severity) and unresponsive (antisocial personality) subgroups.

Methodologic recommendations are summarized in table 3.

Emphasis is placed upon the potential heterogeneity of cocaine abusers and targeting

TABLE 3. *Summary of methodologic recommendations for early Phase II clinical trials of medications for cocaine abuse.*

Methodologic Problem	Proposed Solutions
Sample heterogeneity	• Target subgroups (based, for example, on comorbid psychopathology, route, or severity) either by restricting inclusion or stratification.
Large placebo effects (especially on self-report and subjective measures)	• Emphasize objective measures (e.g., urine-confirmed abstinence). • Single-blind placebo lead-in to wash out early placebo effects and provide more stable baseline. • Discard the uncontrolled, open-label pilot trial in favor of small controlled pilot trials with concurrent randomized placebo control. • Standardized psychosocial intervention.
High attrition	• Single-blind placebo lead-in to wash out early dropouts. • Increase intensity of psychosocial intervention.
Measurement issues	• Emphasize objective measures, mainly urine-based measures; consider also cue response. • Weigh the observations of experienced clinicians.

treatments to subgroups on the one hand, and various methodologic recommendations to tighten up the design of early, small-scale pilot trials on the other. These include use of potent, standardized interventions to reduce attrition; a prolonged, single-blind placebo lead-in to wash out early dropouts and placebo effects; discarding the uncontrolled pilot trial in favor of crossover, discontinuation, or multiple-baselines designs; and considering the impressions of experienced clinicians as well as objective, urine-based measures when judging efficacy. These recommendations are all arguable in that they have disadvantages as well as advantages and that they all depart to some extent from current practice and wisdom. It is hoped that

they will promote discussion and stimulate methodologic innovation in the search for effective medications for cocaine abuse.

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Click here to go to page 96