Outcome Measurement Considerations: Pharmacological Treatments for Substance Abuse

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INTRODUCTION

An extensive literature exists on outcome measurement for trials of treatments for psychiatric disorders. Less has been written specifically on outcome measurement for treatments for substance-related disorders; even less specifically for trials of pharmacological agents for substance disorders.

OVERVIEW

Six questions are presented to systematically guide investigators' decisions on outcome assessment for randomized clinical trials of pharmacological agents for substance-related disorders (American Psychiatric Association 1994). Use of the questions is illustrated by applying them to cocaine dependence. The questions were distilled from four sources: the author's experience conducting psychiatric treatment outcome research, the extensive literature on treatment outcome methodology (Kazdin 1994), a recent comprehensive text on the clinical evaluation of psychotropic drugs (Prien and Robinson 1994), and Kraemer and Telch's (1992) paper on outcome measurement for clinical trials.

Because of the breadth of the existing relevant literature, a discussion of outcome measurement considerations for trials of pharmacological agents for substance-related disorders could result in a lengthy treatise. Instead, a strategy was adopted for this chapter to make it maximally useful with minimal length. The strategy is to articulate a conceptual framework (actually, a set of six questions) to guide investigators' decisions on outcome measure selection and related assessment issues for clinical trials of pharmacological agents for substance-related disorders. Along the way, a few pertinent, comprehensive references are provided.

FRAME OF REFERENCE

The focus of this chapter is considerations relevant to answering the basic treatment outcome question: Does a pharmacological treatment have intended and clinically important effects on substance-related disorder(s) of interest? The discussion assumes that: (a) the measurement is to be done in the context of a randomized clinical trial (RCT), (b) the goal of the trial is to evaluate the efficacy of a pharmacological intervention for a substance-related disorder (e.g., as defined in the Diagnostic and Statistical Nomenclature of the DSM-IV, American Psychiatric Association 1994), and (c) a pharmacotherapy for adult outpatients is being examined. It is also assumed that the goal of the trial is explanatory rather than pragmatic (Lavori 1992). That is, the goal of the RCT is to draw conclusions about a treatment's causal effects on targeted outcomes.

Blaine and colleagues (1994) extensively discuss considerations relevant to designing clinical trials of pharmacological agents for substance-related disorders, including some of the particular problems (such as high attrition rates) associated with treatment efficacy trials for substance-related disorders. Moras (1993) discusses some of the outcome measurement problems that are unique to treatment trials for substance-related disorders, compared to trials for other common psychiatric disorders.

GUIDING QUESTIONS FOR OUTCOME ASSESSMENT

Six basic questions can be used to guide investigators' decisions on outcome measures and related methodological issues for RCTs of pharmacological agents for substance-related disorders (see table 1). The questions apply equally to RCTs of other psychiatric disorders, but they are discussed and elaborated here for RCTs of substance-related disorders. The six questions were distilled mainly from four sources: the author's experience conducting psychiatric treatment outcome research, the extensive literature on treatment outcome methodology (e.g., Kazdin 1994; Kraemer et al. 1987; Lambert 1990; Lavori 1992; Rush et al. 1994), a recent comprehensive text on the clinical evaluation of psychotropic drugs (Prien and Robinson 1994), and an excellent paper by Kraemer and Telch (1992) on outcome measurement in clinical trials. Selected issues that pertain to answering each of the six questions are considered in the sections that follow.

TABLE 1. *The basic questions.*

1. What problems do cocaine-dependent individuals have?
2. Which of the problems is the treatment intended to address?
3. What outcomes associated with the treatment are of primary interest?
4. Which of the outcomes of primary interest can be measured *reliably* and *validly*?
5. How can investigators be sure that the pharmacological treatment of interest contributed substantially to the outcomes obtained?
6. How can researchers be sure not to miss outcomes associated with pharmacological treatments of interest?

NOTE: Questions 1 through 3 are adapted from Kraemer and Telch (1992).

Step I: Identification of the Outcomes of Interest

Kraemer and Telch (1992) provide an exceptionally clear, yet sophisticated and comprehensive reference on outcome measurement for RCTs of psychiatric disorders. A systematic conceptual framework, in the form of three questions, is presented to guide investigators' selection of outcome measures. The questions are the first three in table 1. Kraemer and Telch (1992) illustrate and discuss the questions by applying them to mood disorders. However, the questions are appropriate for RCTs of other psychiatric disorders, including substance-related disorders. Once the three initial questions are answered, the investigator must evaluate and select (or develop, if necessary) measures to assess the outcomes of interest. "Outcomes" (see question 3, table 1) are features of a patient, such as frequency of drug use or frequency of associated high-risk activities such as use of dirty needles. Kraemer and Telch (1992) define an "outcome measure" as a procedure used "to obtain a number or classification from or about the patient that is indicative of the 'outcome' [of interest]" (p. 86).

The three questions are interdependent. As Kraemer and Telch (1992) point out, an "isomorphism" must exist between the disorder, the treatment that is being tested for the disorder, and the outcome assessment

procedures that will provide an index of the usefulness of the treatment for the disorder. Moreover, the three questions logically precede other central decisions for RCTs (e.g., design, assessment intervals, analysis).

The initial three questions might seem straightforward. However, answering them is not necessarily straightforward, particularly when substance-related disorders are to be examined. Some considerations pertinent to answering the first basic question will be illustrated by applying it to cocaine dependence.

Question 1. What problems do cocaine-dependent individuals have?
The perspective subquestion. Answering the first question requires answering the subquestion, "From whose perspective?" Obviously relevant perspectives, using the criterion of parties with a vested interest in treatment outcomes, are: the cocaine abuser, the cocaine abuser's family and others with whom he or she has close personal ties, society, and the clinical investigator.

Answering the first basic question from different perspectives will yield different answers. Table 2 provides illustrative answers for cocaine dependence from three perspectives: cocaine abuser, society, and clinical investigator. The lists are not intended to be comprehensive. Their purpose is to illustrate the fact that different problems will be identified as central to a disorder, depending on the perspective from which the problems question is addressed. One obvious implication is that the outcome measures chosen will depend, at least partially, on an investigator's view of which perspectives are important.

A key variable: Low subjective distress. Problems 1 and 2 from the cocaine abuser's perspective (table 2) point to a key variable that must be considered when designing RCTs of substance-related disorders, in contrast to most other DSM-IV (American Psychiatric Association 1994) Axis I psychiatric disorders. The variable can be labeled in a variety of ways, e.g., "minimal subjective distress" or "low motivation to change." The point is that the symptoms that constitute DSM-IV diagnostic criteria for substance-related disorders often are not experienced as problematic by the person who meets the criteria for the disorder. In

TABLE 2. *Perspectives: What problems do cocaine abusers have?*

1. Cocaine user
    a. None.
    b. Feelings of euphoria, mastery, well-being, interest in life aren't frequent enough without use of cocaine.
    c. Loss of energy needed to sustain use pattern.
    d. Social reproach; dissatisfaction of family and others.
    e. Loss of life satisfactions.
    f. Fear of health effects.
2. Society
    a. If intravenous user, can transmit HIV.
    b. Poor performance in social roles (parenting, work).
    c. Criminal behaviors.
    d. Service overutilization (medical, incarceration, public assistance, foster care).
3. Clinical investigator
    a. Features of cocaine use "syndrome."
        - Binges: repeated self-administration with larger and larger doses.
        - Withdrawal symptoms.
        - Craving.
        - Relapse.
    b. Clinical depression.
    c. HIV risk.
    d. Poor quality of life even if stops drug use.
    e. Activity of reward centers in brain.
    f. Drug use maintained by operant and classical conditioning.

contrast to most other common DSM-IV Axis I disorders of adulthood, substance-related disorders often are not associated with subjective distress. In fact, the subjective experiences associated with drug use often

are very positive: The experience typically is not just a neutral one of lack of subjective distress. The pleasure-producing or reinforcing effects of the "symptom" of substance use can be expected to compete with any associated negative effects or problems that could provide motivation for treatment.

The central relevance of this fact for outpatient RCTs of treatments for substance-related disorders is suggested by the high attrition rates in such studies (typically greater than 50 percent dropout in the initial phase of treatment). In fact, high attrition is one of the most robust findings from substance abuse treatment research to date. The fundamental problems posed by attrition to the interpretation of findings from RCTs are described by Howard and colleagues (1990).

Attrition in RCTs of substance-related disorders typically is substantially higher than in RCTs of other common disorders, such as mood and anxiety disorders. Attrition rates ranging from 20 percent to 40 percent generally are found in RCTs of mood and anxiety disorders (e.g., Elkin et al. 1989). Even attrition in the placebo control conditions of outpatient treatment studies of such disorders tends to be 40 percent or lower. The difference in attrition rates in RCTs of substance-related disorders and other psychiatric disorders typically is attributed to the relative lack of subjective distress and pleasurable effects associated with substance use which, in turn, reduces motivation for treatment.

What are the implications of the foregoing points for outcome measurement in RCTs of pharmacological treatments for substance-related disorders? One implication is that investigators should try to identify *problems* associated with the targeted substance-related disorder from the patient's perspective. The more able investigators are to find some source(s) of subjective distress associated with the disorder and the more effectively the pharmacological treatment, or the "treatment package" within which the pharmacological treatment is embedded, affects problems that are associated with subjective distress, the more likely that interpretable efficacy findings will be obtained (i.e., from a study with low attrition rates). A second implication of the low subjective distress feature is that society's perspective on the problems associated with a disorder is likely to exert more influence on outcome measure selection for substance-related disorders than for disorders in which the treated individual identifies the primary problems to be treated.

A consideration: Outcomes assessed from different perspectives are likely to yield different findings. The perspective subquestion is relevant to outcome assessment of pharmacological treatments in yet another way. A

basic methodological conclusion from psychotherapy outcome research over the years is that outcomes typically differ depending upon the perspective from which outcome data are obtained, e.g., the patient, the therapist, an independent clinical evaluator, or a significant other (Strupp and Hadley 1977). The observation has led investigators to include outcome measures from multiple perspectives in studies, based on the premise that several perspectives typically must be recognized as valid when evaluating the state of a disorder. In other words, reasonably complete information on a treatment's efficacy requires outcome data from the perspectives that are most affected by, can provide expert opinions on, and/or can provide judgments that are less affected by the subjective biases inherent in the other important perspectives on the state of the disorder being examined.

Other considerations: Necessary and sufficient conditions for defining a substance-related disorder, and the central role of society's perspective in evaluating outcomes. The disorder of cocaine dependence also illustrates a point that is infrequently discussed when designing RCTs for substance-related disorders. The first basic question, "What problems do patients with the disorder have?" can confront investigators with the prominent role played by social values in the identification of substance use "disorders." For example, in a literature review prepared for the DSM-IV Substance-Related Disorders Workgroup, Irwin (1994) noted that "prior to the 1980's cocaine was considered to be a relatively safe, nonaddictive, euphoriant agent" (p. 169).

What are the scientific implications of the fact that society's opinions can change about what is and what is not problematic substance use? First, as already mentioned, society's perspective is a central one in identifying the problems associated with a substance-related disorder. Second, as recognized in the diagnostic criteria for substance-related disorders in the DSM-IV (American Psychiatric Association 1994), use of an illicit substance in itself does not merit being labeled a "disorder." Rather, certain patterns of use, i.e., patterns that are associated with functional impairment and/or high risk to oneself or others (in the absence of subjective distress), are required to be designated as a disorder.
The principle that the primary problems of substance users are *patterns* of use that are associated with functional impairment and/or types of risk to oneself or others is an important one for investigators to consider when choosing outcomes for pharmacological treatments for substance-related disorders. Conceptualizing the problem to be treated as a pattern of behavior (or use) will doubtless lead to different decisions about the most appropriate outcome measures and measurement strategies. Furthermore, the principle could affect investigators' decisions about which treatments

or treatment packages merit testing in RCTs. For example, if a particular pharmacological agent targets only an isolated feature of use of a substance, such as craving or withdrawal symptoms, embedding the agent in a treatment package that consists of psychosocial interventions and, perhaps, other sequentially administered pharmacological agents, might be considered. For pharmacological agents that target narrow outcomes, a modular treatment package is likely to be needed to produce clinically significant outcomes in substance-related disorders, especially the outcomes of most interest from society's perspective.

Question 2. Which of the problems is the treatment intended to address? Possible answers to the second question, using the example of cocaine dependence, are shown in table 3. The answers there are based on a review of recent treatment studies for cocaine dependence and the discussion by Weiss and Mirin (1990). The table illustrates the kinds of problems and outcomes that currently tend to be examined in RCTs of cocaine dependence.

Question 3. What outcomes associated with the treatment are of primary interest? Table 4 presents examples of how the third basic question might be answered by investigators who want to examine a pharmacological treatment for cocaine dependence, based on current conventions in treatment research on cocaine use.

Step II: Identification of Measures and Methodological Considerations

Once the first three questions have been answered, three more questions must be addressed to answer the basic treatment outcome question: Does pharmacological treatment X affect the desired outcomes for substance-related disorder Y? The next three questions are 4, 5, and 6 in table 1.

TABLE 3. *Question 2: Which of the problems is the treatment intended to address?*

1. Binge use (compulsive self-administration).
2. All use.
3. Withdrawal symptoms.
4. Craving.
5. Relapse.
6. Reward centers in brain.
7. Possible use-maintaining symptoms (e.g., depression).

TABLE 4. *Question 3: What outcomes associated with the problems are of primary interest*?

1. Reduced frequency of use.
2. Reduced amount of use.
3. Initial abstinence period (e.g., > 1 month).
4. Long-term abstinence.
5. Relapse prevention after a period of abstinence.
6. Less impairing or dangerous use pattern.
7. Less dangerous route of ingestion.

Question 4. Which of the outcomes of primary interest can be measured *reliably* and *validly?* Answers to the first three basic questions rely mainly on an investigator's conceptual skills, understanding of the disorder to be treated, knowledge of the potential effects of the treatment of interest, and value judgments. The next question requires psychometric expertise to answer. Reliability and validity (e.g., Guilford

1954; Kraemer and Telch 1992; Nunnally 1978) are the fundamental psychometric features of any measure that could be used to assess outcomes in RCTs. Simply defined, reliability refers to the repeatability of scores obtained on a measure. For scientific purposes, researchers want to know that the score or value assigned to a respondent based on a measure is a replicable index of his/her status on the measure at the time when the measurement was made. Psychometric methods for determining the reliability of a measure are designed to estimate the "true score variance" (e.g., compared to either random or nonrandom error variance) in a score on the measure. Alternatively stated, reliability statistics are estimates of the signal-to-noise ratio contained in scores on a measure. More reliable measures have more signal, less noise (error). Validity is the extent to which scores on a measure do, in fact, reflect the construct or variable that researchers think they do. An outcome measure's reliability and validity credentials are the fundamental determinants of the potential strength of the evidence (e.g., effect sizes) (Leon et al. 1995) and the accuracy of the conclusions (interpretation of the findings) obtained from an RTC.

Despite the linchpin importance of a measure's reliability and validity statistics, both tend either to be ignored or acknowledged only in superficial ways in psychiatric clinical outcome research. Well-established methodologies exist for the evaluation of a measure's reliability and validity (Nunnally 1978). Familiarity with the methods and knowledge of how to interpret reliability and validity statistics are required to choose between alternative measures to examine an outcome of interest. If an investigator does not have the required expertise, consultation on this aspect of measure selection should be sought.

A full discussion of reliability and validity evaluation of outcome measures is beyond the scope of this chapter. Only two additional points will be made here: One concerns a prominent error about reliability in psychiatric research and the other concerns the use of measures intended to circumvent self-report to evaluate drug use outcomes (e.g., urinalysis). Kraemer and Telch (1992), Leon and colleagues (1995), and Rush and colleagues (1994) provide additional discussion of reliability and validity of outcome measures, and of the critical need for psychometrically sound measure development for psychiatric treatment research.

Reliability of observer-judged measures. One of the most common investigator errors in published RCTs for psychiatric disorders is the belief that reliability inheres in observer-rated measures, such as the Hamilton Rating Scale for Depression (Hamilton 1960), the Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D, Williams

1988), and the Structured Clinical Interview for DSM-IV Disorders (SCID, First et al. 1996). This belief is reflected in statements like "the SCID has been shown to have adequate reliability for the diagnosis of X." Such statements are sometimes followed by a kappa coefficient and a citation of a study that reported the kappa.

The reliability of scores on observer-rated instruments is always a function of both the instrument and the specific observer/user. Reliability-relevant features of observer/users typically include their clinical experience, both general and with the specific patient population being studied, and the training they received to use the instrument. Because reliability is never inherent in observer-judged instruments, reliability must be evaluated for every study. Figures from other studies in which other observers provided the data give no information whatsoever on the reliability of the data from the measures in the current study.

Validity of self-report measures of drug use. A second highly relevant point for outcome measurement in RCTs of substance-related disorders concerns the validity of self-report measures. It is commonly assumed by both investigators and clinicians who work in substance use treatment that self-report data on drug use during treatment cannot be relied upon as accurate. This concern has led to the standard utilization of other measures to evaluate drug use, i.e., measures that can circumvent dissimulation. To date, urinalysis is the most commonly used alternate method in RCTs of substance-related disorders.

Technical complexities associated with using urinalysis results to measure the outcome of reduced drug use are well detailed in several other chapters in this monograph and in Blaine and associates (1994). Less often considered are the psychological impacts and possible impact on attrition associated with the requirement to provide urine samples as part of a treatment program. Investigators of substance use treatments must closely consider (a) the probable validity of self-report measures of drug use and possible ways to enhance their validity (see Moras 1993), and (b) the benefits and costs (including low reliability and validity, and technical complexity) associated with methods that are designed to circumvent self-report indices of drug use.

Question 5: How can an investigator be sure that the pharmacological treatment of interest contributed substantially to the outcomes obtained? Answering this question requires sophistication and expertise in experimental design in general, the design of RCTs in particular, and careful attention to the implications of each design decision for the internal validity of the study (Cook and Campbell 1979). Internal validity

refers to the extent to which a study's design, methods, and procedures allow the data obtained to be interpreted as evidence of the main hypothesis(es) being examined. The aforementioned edited volume by Prien and Robinson (1994) contains several chapters on relevant design and methodological issues, specifically for RCTs of pharmacological agents for substance-related disorders.

Table 5 presents an abbreviated list of pertinent design, methodological, and procedural questions that must be considered to plan an RCT that yields findings that can be interpreted as effects of a pharmacological agent on the outcomes of interest. All design considerations included in the list are discussed in chapters in Prien and Robinson (1994).

Problems posed by adjunctive treatments. Only one of the points listed in table 5, i.e., number 3, "Control and/or limit adjunctive psychosocial and pharmacological interventions," will be discussed here. The point concerns one of the most common sources of low internal validity in RCTs of treatments for substance-related disorders. The relevant principle is a simple one: Interpreting outcome findings as evidence for the efficacy of a treatment of interest requires, at minimum, that patients' receipt of other treatments is proscribed or somehow controlled.

Despite the logical necessity of the foregoing principle, patients in RCTs of treatments for substance abuse commonly receive many ancillary treatments and, even more problematic for the internal validity of a trial, often receive them on an as-needed (uncontrolled) basis. (Ancillary or adjunctive treatments are therapeutic or potentially therapeutic interventions that are not regarded by the investigators as part of the treatment[s] being examined.) Moreover, investigators often neglect to report any information on the ancillary treatments (e.g., what they were, what percentage of the patients in each treatment condition received each one, etc.). Failure to control ancillary treatments in an RCT will fundamentally compromise interpretation of any effects found as due to the pharmacological treatment of interest.

TABLE 5. *Question 5: How can researchers be sure that the pharmacological agent contributed substantially to the outcomes?*

1. Pretrial "lead-in" placebo washout phase.

2. Placebo control condition in design.

3. Control and/or limit adjunctive psychosocial and pharmacological interventions.

4. Control use of substances.

5. Assess compliance with the pharmacological treatment.

Substance-related disorders are maintained by multiple variables. A common rationale for providing ancillary treatments to patients in substance disorder treatment studies is that the patients have multiple problems (Moras 1993). Furthermore, it is often argued that the treatment of interest is unlikely to be efficacious if the patients' other problems are not also addressed. Oddly, when the latter statement is made, it is not linked to the logical implication that the findings of the study cannot be interpreted as evidence for the treatment being examined alone: The efficacy data necessarily pertain to the entire treatment package within which the treatment of interest was (sometimes naturalistically) embedded.

The foregoing points are likely to be particularly relevant for RCTs of pharmacological agents for substance disorders. Many experienced substance abuse treatment investigators hypothesize that substance-related disorders are caused and/or maintained by a network of variables, with psychosocial factors playing a substantial role in maintaining, if not causing, patterns of substance abuse. Such hypotheses, plus the commonly acknowledged limitations in the efficacy of methadone, the most efficacious pharmacological intervention for a substance-related disorder to date, have obvious implications for the development of other pharmacological interventions. They suggest that efforts to develop other pharmacological agents for substance disorders will be limited unless the interventions are provided in the context of more comprehensive treatment packages or programs.

Need for multicomponent treatments. What do the preceding arguments suggest about the development of new pharmacological treatments for substance-related disorders? One implication is that investigators are well

advised to consider the range of problems associated with the disorder of interest, which aspects of the disorder the pharmacological agent can reasonably be expected to affect, and other interventions that might be needed in conjunction with the pharmacological agent to attain clinically significant outcomes. Another implication is that pharmaco-logical agents that are intended to have only narrow effects (e.g., on craving) might be most cost-effectively examined in basic research studies with human beings; then, if efficacious, included as a component of a more comprehensive treatment. The comprehensive treatment would then be examined in an RCT, not the pharmacological treatment alone. The National Institute on Drug Abuse's Behavioral Therapies Development Program (1994) provides an incentive for the development of such treatment packages.

Question 6. How can researchers be sure not to miss outcomes associated with a pharmacological treatment of interest? Similar to question 5, answering this question requires sophistication in experimental design. It also requires expertise in the conduct of pharmacological treatment trials, particularly knowledge of variables that affect the effects of pharmacological agents. Table 6 lists a few central considerations for answering this question. The points listed will be discussed briefly. The reader is referred again to the comprehensive edited text by Prien and Robinson (1994) with chapters on the relevant considerations.

The first two points in table 6 concern a topic previously discussed, the severe compromise posed by high attrition to obtaining interpretable efficacy findings from an RCT. Point 1 in table 6, matching the outcome goals of patients who have the substance disorder to be treated with the probable effects of the treatment, will reduce attrition as long as the treatment itself is not unduly noxious in some way. The second point, "stability of the patient's motivation for the goal," also relates to attrition concerns, but is focused on sample selection. Comorbid psychiatric disorders and comorbid substance-related disorders are examples of variables that can undermine the stability of patients' motivation for a treatment that they actually endorse. Therefore, the presence of such comorbid conditions can increase attrition. On the other hand, adding exclusion criteria to sample selection criteria can compromise a study's external validity, i.e., the generalizability of the results.

TABLE 6. *Question 6: How can researchers be sure not to miss outcomes associated with the pharmacological agent?*

1. Patient goal and treatment goal matching.

2. Stability of patient's motivation for goal.

    a. Polysubstance abuse

    b. Comorbid psychiatric diagnoses

3. Reliable measures.

4. Variables that affect pharmacokinetics and pharmacodynamics.

5. Optimal psychosocial treatment "context" for pharmacological agent.

6. Statistical analyses.

Point 3 highlights the role of reliable measures in obtaining scores that have minimal error variance which will, in turn, increase the probability of finding desired outcomes if they are, in fact, effected by a treatment. Point 4 highlights the fundamental importance of using knowledge of the pharmacokinetics and pharmacodynamics of a pharmacological agent (Greenblatt et al. 1994) in design and sampling decisions for an RCT. Needed knowledge of this type ideally will be generated in preparation for an RCT so that it can be used in designing the RCT. Such knowledge is a central determinant of the effects that will be found in an RCT of a pharmacological agent. The knowledge is equally as central to the findings as are the reliability and validity of the outcome measures. For example, knowledge of gender differences associated with pharmacokinetics, such as the impact of the menstrual cycle, is critical information for planning RCTs of agents intended to be used with both male and female substance users.

The earlier section of this chapter on basic question 5 (table 1) also is relevant to point 5 in table 6. A pharmacological intervention might be capable of potentiating a desired effect, but will do so only if other aspects of a patient's substance-related disorder also are treated in some way. Point 6 highlights the importance of using appropriate statistical techniques intelligently (Lavori et al. 1994). Also, new and sophisticated

statistical procedures are being identified that can be applied to RCTs. For example, random regression (Gibbons et al. 1993) might be productively applied to evaluate and compare the rates of change of various outcomes associated with different treatments when repeated measures of outcomes are obtained.

CONCLUDING REMARKS

This chapter was intended to be concise, despite the broadness and complexity of the topic. Thus, main points will not be summarized here. Rather, for a summary, refer to table 1, which contains six basic questions for planning outcome assessment for RCTs of pharmacological agents for substance-related disorders. As noted, the six questions are equally applicable to RCTs of other common psychiatric disorders. For more information on any of the questions, the reader should turn to the relevant section of the text.

One potentially controversial point made here is that investigators who are interested in developing and examining pharmacological agents for use in the treatment of substance-related disorders are encouraged to closely consider the requisite psychosocial treatment "context" for optimal delivery of the agent of interest, i.e., the context that is needed for the agent to be associated with clinically significant effects. This point was made based on the relative lack of highly efficacious treatments for substance-related disorders, either pharmacological or psychosocial, despite many years of research effort. The difficulty in developing treatments with the desired levels of efficacy has led many experienced substance abuse researchers to posit a complex network of maintaining variables that, even if not causative, make strong contributions to the continuation of substance-related disorders in adults. The preceding speculation, in turn, is associated with a clear current trend to recommend the development of comprehensive treatment packages for substance-related disorders, including treatments that combine psychosocial and pharmacological components.

A final point to be made is that a considerable amount of knowledge has been amassed over the years on the conduct of RCTs for psychiatric disorders. This knowledge is well illustrated in several references that were cited such as Kazdin (1994), Kraemer and Telch (1992), and the chapters in Prien and Robinson (1994). As alluded to by Kraemer and Telch (1992), one of the main problems now faced in generating interpretable findings from RCTs is the failure of many investigators to *implement* available knowledge (e.g., about the central importance of

selecting reliable and valid outcome measures). One contribution to this problem, perhaps, is the incentive system that affects investigators who work in university settings. Promotion typically is largely contingent on number of publications, rather than their quality. In addition, designing and conducting rigorous studies is more labor intensive than completing weaker studies. The time and effort involved in a rigorously done study also can be associated with longer time to publication and, perhaps, fewer publications. Investigators interested in pharmacological treatments for substance-related disorders who have been strongly influenced by standards applied in many pharmaceutical company-sponsored trials might be especially susceptible to design and methodological "shortcuts." In any event, the point to be made is that much sophistication now exists about the critical considerations for, and necessary elements of, interpretable RCTs. This sophistication is ready to be applied to pharmacological treatments for substance-related disorders.

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