

Mediators and Moderators of Treatment Effects in Randomized Clinical Trials

Helena Chmura Kraemer, PhD; G. Terence Wilson, PhD;
Christopher G. Fairburn, DM, MPhil, FRCPsych; W. Stewart Agras, MD

Randomized clinical trials (RCTs) not only are the gold standard for evaluating the efficacy and effectiveness of psychiatric treatments but also can be valuable in revealing moderators and mediators of therapeutic change. Conceptually, moderators identify on whom and under what circumstances treatments have different effects. Mediators identify why and how treatments have effects. We describe an analytic framework to identify and distinguish between moderators and mediators in RCTs when outcomes are measured dimensionally. Rapid progress in identifying the most effective treatments and understanding on whom treatments work and do not work and why treatments work or do not work depends on efforts to identify moderators and mediators of treatment outcome. We recommend that RCTs routinely include and report such analyses.

Arch Gen Psychiatry. 2002;59:877-883

Considerable progress has been made in the development and evaluation of treatments, both pharmacologic and psychological, for a variety of different psychiatric disorders. This research has emphasized the use of the randomized clinical trial (RCT), which is widely regarded as the gold standard of evaluation of efficacy and effectiveness in medicine. The characteristics of a well-performed RCT are well established.¹ They include the following features:

1. A well-defined and justified population, with a representative sample of sufficient size, to yield power to detect clinically significant differences between treatments and to provide accurate estimates of the effect sizes² in that population on which to base considerations of clinical or policy significance.^{3,4}
2. One or more control or comparison groups, with protocols for treatment in each group specified well enough to permit replication in the clinic or another research project.

3. Randomization to treatment and control or comparison groups to avoid confusing selection effects with treatment effects.

4. A few a priori, well-chosen, and justified outcome measures, selected in advance of the trial, obtained either blinded to treatment group or otherwise with measurement bias controlled to avoid confusing the opinions or expectations of patients or researchers with treatment effects.

5. Analysis performed by intention to treat (ie, all randomized subjects are included in the analysis of outcome). Only those subgroups specified and justified in the a priori hypotheses (eg, baseline severity) or in the design (eg, sites in a multisite study) are addressed in the primary analysis.

6. A valid test for statistical significance and estimates of effect sizes informative enough to guide consideration of clinical and policy significance.

The knowledge derived from such RCTs is of direct relevance to health care system reform and the growing demands for accountability. However, there is much more that can be learned from a successfully completed RCT than is currently learned. Ideally, RCTs should also provide

From the Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, Calif (Drs Kraemer and Agras); Department of Psychology, Rutgers University, New Brunswick, NJ (Dr Wilson); and Department of Psychiatry, Oxford University, Oxford, England (Dr Fairburn).

information on possible moderators and mediators of treatment outcomes to guide the next generation of studies and inform clinical applications.

MODERATORS AND MEDIATORS OF TREATMENT OUTCOMES

Treatment moderators specify for whom or under what conditions the treatment works.⁵ Consequently, they help clarify to investigators the best choice of inclusion and exclusion criteria or the best choice of stratification to maximize power in subsequent RCTs. They also suggest to clinicians which of their patients might be most responsive to the treatment and for which patients other, more appropriate, treatments might be sought. Moderators may identify subpopulations with possibly different causal mechanisms or course of illness. Thus, moderators may also provide unique new and valuable information to guide future restructuring of diagnostic classification and treatment decision making.

There has been considerable interest in identifying moderators of outcome, albeit with modest success.⁶ This is perhaps best exemplified by the enthusiasm for matching patients to specific treatments, as illustrated by the huge and largely uninformative Project MATCH (Matching Alcoholism Treatment to Client Heterogeneity), the most expensive controlled study of psychological treatment yet undertaken.⁷ Matching treatment to individual patients is a daunting task because the potentially relevant patient and treatment attributes are so numerous and their possible interactions often complex.⁸

Treatment mediators identify possible mechanisms through which a treatment might achieve its effects. These mechanisms are causal links between treatment and outcome. Just as all causal factors are risk factors but not all risk factors are causal factors,⁹ all mechanisms are mediators but not all mediators are mechanisms. However, demonstrating causality is much more difficult than establishing risk factor or mediator status. Thus, the invest-

ment of time and effort to narrow the search for causal factors by focusing first on a search for risk factors or mediators is worthwhile. Once mediators are identified, a subsequent RCT in which a treatment enhanced in those components associated with the mediator is shown to be more effective than the treatment in the original RCT would establish that the mediator identified in the original RCT is indeed a mechanism.

The benefits of uncovering mechanisms of change would be considerable. Even the most potent of the available treatments are limited in their effects, helping many, but not all, patients, regardless of clinical disorder. Understanding the mechanisms through which treatments operate is likely to facilitate the development of innovative treatments that will yield larger effect sizes or the same effect sizes at lower cost or risk. Active therapeutic components could be intensified and refined, whereas inactive or redundant elements could be discarded.¹⁰ The result is likely to be both more potent and more efficient therapy. Therefore, not surprisingly, Hyman¹¹ presents as one of the central questions psychiatry must address in the new millennium, "How do our treatments, including psychotherapy, work?"

Combining procedurally different treatments (eg, cognitive behavioral therapy [CBT] and pharmacotherapy) has become commonplace in the treatment of a variety of psychiatric disorders. If the treatments combined operate via different mechanisms,¹² knowing what the mechanisms of change are not only would make for better, more synergistic combined treatment programs but also would forestall combining different treatments with potentially incompatible or mutually antagonistic mechanisms.¹³

Identifying mediators may not only enhance treatment structure but also advance our understanding of the nature of clinical disorders. If a treatment has its effects by influencing a particular process, this finding establishes the importance of this process in the maintenance of the disorder. For example, there is evidence that CBT for panic disorder

succeeds by eliminating catastrophic cognitions concerning the bodily changes. This finding lends strong support to the cognitive theory of panic.¹⁴

METHODS FOR DETERMINING MEDIATORS AND MODERATORS OF TREATMENT ON OUTCOME

The issue of mediators and moderators in a general framework has long been discussed in the psychology literature, particularly stimulated by the seminal work of Baron and Kenny,⁵ but the applications have had serious problems. As discussed by Kraemer et al,¹⁵ there is ambiguity between a moderator and a mediator and in the directionality of moderation and mediation. Kraemer and colleagues reconsidered these issues in the specific context of risk research and proposed operational definitions consistent with Baron and Kenny's conceptual definitions, which resolved many of the problems of applications. Although the concepts they propose apply in general, because the context was risk research, the effect sizes that were the basis of demonstration of moderation and mediation were those related to "potency" to detect a binary outcome. This reflected the clinical and policy impact of using the risk factor to identify high- and low-risk subjects for the purposes of prevention.¹⁶ In RCT applications, the effect sizes are usually different from those in risk factor research, largely because the outcome is often dimensional rather than categorical. The most common effect sizes used are the standardized mean difference between groups (often called Cohen's d^{17}) resulting from the use of linear models.^{18,19}

The particular linear model to be used for both moderator and mediator analysis comparing a treatment group (T) vs a control or comparison group (C) is exactly the same: the independent variables are T, M (the possible moderator or mediator), and the $T \times M$ interaction. Users of linear models often forget that how independent variables are coded can change the definition of the effects that are estimated and tested by the model. For clarity, the treatment effect is coded herein as

+1/2 for those in T and -1/2 for those in C. The mean of M for those randomly assigned to T is M_T and for those randomly assigned to C is M_C . The midpoint of these two is M_0 . The values of M for the analysis are centered at M_0 (ie, one uses as the covariate not the observed value M, but $M - M_0$). The linear model posits that the expected response in T and C for subjects with different levels of M are 2 straight lines (Figure 1). Also shown is a reference line halfway between the T and C lines. Terms such as *intercept*, *main effect of treatment*, *main effect of M*, *interactive effect of M and treatment*, *overall* (or *unadjusted*) *effect of treatment*, and *effect of treatment for the subset of subjects with $M=m$* are shown in Figure 1.

Moderators of Treatment

To show that M is a moderator of treatment, M must be a baseline or prerandomization characteristic (hence, by definition in an RCT uncorrelated with treatment: $M_T = M_C = M_0$) that can be shown to have an interactive effect with treatment on the outcome. Since $M_T = M_C = M_0$, the overall effect of treatment is identical with the main effect of treatment. Thus, the putative moderator does not help to explain the overall effect of treatment. However, an interactive effect means that the effect of treatment on individual subjects depends on their value of M. Thus, the moderator does help explain individual differences in the effect of treatment. If M is a characteristic of the individual (eg, age, sex, initial severity, comorbidity), then M indicates on whom the treatment may have the most clinically significant effects. If M characterizes the circumstances under which the treatment is delivered (eg, inpatients vs outpatients), then M indicates under what circumstances the treatment may have the most clinically significant effects.

For example, in the Infant Health and Development Program (IHDP),²⁰ an 8-site RCT testing a behavioral intervention for low-birth-weight, premature infants, with outcomes at 3 years of age, it was found²¹ that the intervention was effective primarily for children from disadvantaged families. Presumably the resources added to usual care by the intervention were those already avail-

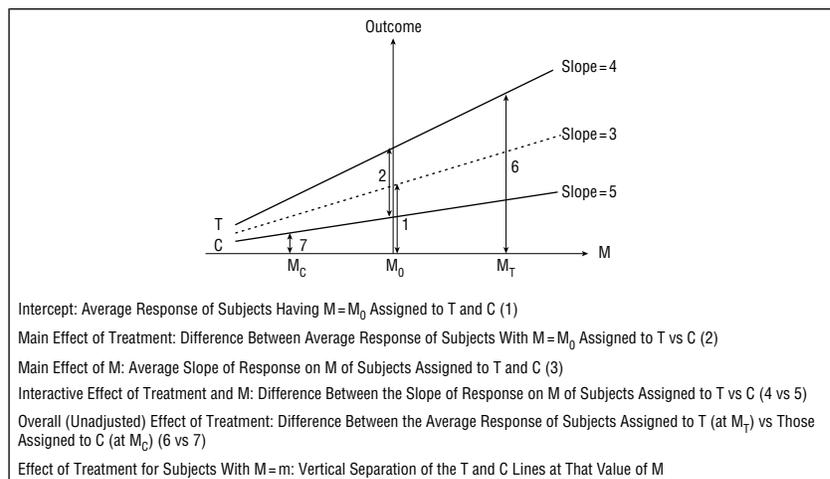


Figure 1. Definitions of terms used in the linear model, with treatment coded +1/2 for those in the treatment group (T) and -1/2 for those in the control or comparison group (C), with the moderator or mediator (M) centered at the mean of M in T (M_T), the mean of M in C (M_C), and the midpoint of these two (M_0).

able to advantaged families. In an RCT of the effects of fluvoxamine maleate alone vs fluvoxamine plus pindolol, a polymorphism within the promoter of the serotonin transporter gene was a moderator of antidepressant efficacy.²² This last example is particularly important, since genes may moderate the effect of environmental manipulation (eg, drug administration) on outcome. The effect of genes on outcome may only be understood once the factors they moderate are identified.

Mediators of Treatment

To show that M is a mediator of treatment, M would have to measure an event or change occurring during treatment, and then it must correlate with treatment choice, hence possibly be a result of treatment, and have either a main or interactive effect on the outcome.

In this case (Figure 1), the typical subject in the population, if assigned to T, will average M_T and, if assigned to C, will average M_C , which are not equal (since M is correlated with treatment choice). Then the overall effect of treatment is not usually equal to the main effect of treatment. Part of the overall effect of treatment arises from the fact that treatment shifts the value of M. If there is a main effect of M on the outcome, this would automatically shift the response in T relative to C, even in absence of a main effect of treatment. In fact, the overall effect of

treatment differs from the main effect of treatment by the quantity (main effect of M) \times ($M_T - M_C$). For this reason, some methodologists would recommend that a main effect of M coupled with a correlation between treatment and M ($M_T - M_C$) should be both necessary and sufficient to define a mediator. However, this recommendation would ignore a situation such as that shown in Figure 2, where there is no main effect of treatment, no main effect of M, and no overall effect of treatment, but clearly M is explaining individual differences in response to treatment (interactive effect of treatment and M). In such a situation, treatment may not merely change the level of M (inducing the difference between M_T and M_C) but may change the nature of M, thus changing the relationship of M to the outcome in the 2 groups. If this is so, this effect may also suggest a mechanism that influences the effect of treatment that should not be ignored. For this reason, we propose that both main and interactive effects of M be included in the definition of a mediator.

In a 6-site RCT for children with attention-deficit/hyperactivity disorder (ADHD) comparing a medical management intervention, a behavioral intervention, and a combination of the two vs treatment as usual, it was shown that compliance with treatment protocol, according to standards set a priori, was a mediator of treatment

effects.²³ As a result, in the intention-to-treat analysis that examined the overall effect of treatment, the effect of medical management may have been understated.

The **Table** summarizes these definitions, but also fills in other possible relationships among target measure, treatment choice, and outcome. For example, if a posttreatment variable (not a moderator of treatment) is not correlated with treatment choice (also not a mediator of treatment) but has an interactive effect with treatment on the outcome, then treatment is a moderator of that measure (not vice versa). Thus, for example, in a program designed to treat depression, the effect of the death of a relative or friend during the treatment (presumably not related to which treatment was assigned) on outcome may be moderated by treatment. This would be the case if those in T are better able to cope with such an event than those in C. The directionality of mediation and moderation is important to note. Moderators always precede what they moderate, which in turn precedes

outcome; mediators always come between what they mediate and the outcome.

A baseline measure (not a mediator) that has a main effect on outcome but no interactive effect (not a moderator) might be called a nonspecific predictor of outcome. Such a target measure predicts response in both treatment groups, but the effect size of treatment is the same regardless of the value of the target measure. Thus, for example, in the multisite ADHD study, there were major site differences in almost all outcomes, but few site-by-treatment interactive effects.²⁴ Similar results were obtained in a multisite RCT that tested the relative effectiveness of CBT and interpersonal psychotherapy (IPT) for bulimia nervosa.²⁵ In both cases, site was a nonspecific predictor of outcome, but not a moderator (ie, the effect size of treatment did not differ over sites, even though the response to treatment did).

A posttreatment measure (not a moderator) uncorrelated with treatment (not a mediator) that has a main effect but no interaction might also be called a nonspecific predictor of

outcome. Unlike the ADHD result, compliance with treatment might nondifferentially enhance treatment response to all treatments. If so, compliance with treatment would be a nonspecific predictor of outcome. The message would be that improvement of compliance would enhance outcomes whatever the treatment.

A posttreatment measure (not a moderator) that is correlated with treatment, which has neither a main nor an interactive effect with treatment on outcome, is an independent outcome of treatment. For example, a cardiovascular risk reduction program may reduce weight and increase activity level, but it may be that the decrease in weight does not relate to the increase in activity level or vice versa. In such a case, weight decrease and activity increase are 2 independent outcomes of the treatment.

Finally, a target variable, either before or after baseline uncorrelated with treatment, that has neither a main nor an interactive effect on an outcome is not demonstrated to be relevant to the treatment outcome. In a sample from the population, this may, of course, be a matter of inadequate power owing to small sample size or unreliable measurement.

COMMENT

The Role of Theory

Clearly, there should be some theoretical basis for the choice of measures to be considered as possible mediators and moderators. For example, a measure that is simply part of the definition of one of the treatments should not be considered as either a mediator or a moderator. When one considers comparing the effects of a medication treatment vs a psychotherapy treatment, one

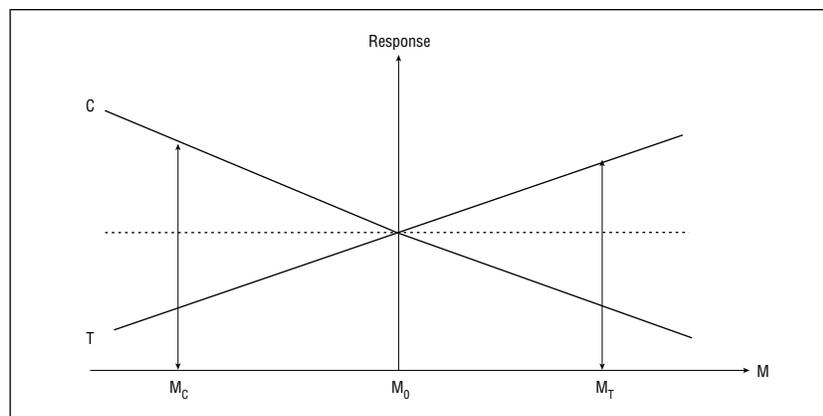


Figure 2. A special case in which there is no main effect of treatment, no main effect of moderator or mediator (M), and no overall effect of treatment, but in which treatment may change not only the level but also the action of M on the outcome, a mediating effect. T indicates treatment group; C, control or comparison group; M_c , the mean of M in C; M_t , the mean of M in T; and M_0 , the midpoint of these two.

Summary of Population Definitions Relating Target Measure to Treatment and Outcome

Target Measure	Correlation With Treatment	Relationship to Outcome in Linear Model	Classification of Target Measure
Pretreatment	No (by definition)	Interaction with or without main effect	Moderator of treatment outcome
Pretreatment	No (by definition)	Main effect only	Nonspecific predictor of treatment outcome
Posttreatment	Yes	Main effect or interaction	Mediator of treatment outcome
Posttreatment	Yes	Neither main effect nor interaction	Independent outcome of treatment
Posttreatment	No	Interaction with or without main effect	Treatment moderates target variable
Posttreatment	No	Main effect only	Nonspecific predictor of treatment outcome
Pretreatment or posttreatment	No	Neither main effect nor interaction	Target measure irrelevant to treatment outcome

would not consider blood level of the medication or attendance at therapy sessions as possible mediators. To “prove” that drug level mediates a drug effect vs therapy or that therapy exposure mediates a therapy effect vs drug seems a trivial finding.

For example, in a comparison of CBT and IPT for bulimia nervosa, it might be hypothesized that self-monitoring of daily eating habits is a mediator of treatment effect. However, self-monitoring occurs only in CBT and not at all in IPT. Since it is part of CBT, it would be totally collinear with treatment and thus could not be shown to be a mediator. On the other hand, in the IHDP, day care was one component of a multicomponent behavioral treatment. Not all the subjects randomly assigned to T received the same exposure to day care, whereas some subjects randomly assigned to C availed themselves of day care in the community. Thus, although the use and quality of day care were clearly higher in T than in C (correlated with treatment choice), it was possible to show that day care was a mediator of the IHDP treatment response.²⁶

In the same way, one should be wary of proposing M that merely reflects the outcome of interest as a possible mediator of response. For example, if the outcome of an evaluation of a smoking cessation program were smoking cessation at 1 year, proposing smoking cessation at 1 month, 2 months, 3 months, and so on as possible mediators would undoubtedly lead to the trivial conclusion that smoking cessation is a mediator of treatment on smoking cessation. There should be some clear distinction between the constructs measured by the proposed mediators and both the definitions of the treatments and outcome of interest. In short, there should be some rationale and justification, some biological and psychological plausibility, in the selection of variables to be considered as possible moderators and mediators and attention to their validity and reliability.

Comparisons With Other Approaches

Although the conceptual basis here is the same as that of Baron and

Kenny,⁵ the operational framework differs in several important ways from their analytic approach. Demonstration of precedence is required. A moderator precedes treatment; a mediator occurs during treatment. In absence of such a criterion, what mediates (or moderates) what is often arbitrarily decided and may reflect investigators' biases. Similarly, demonstration of correlation is required. A moderator is not correlated with treatment; a mediator is. In absence of such criteria, the interpretation of whether a relationship is mediating or moderating is often arbitrary. The analytic model, in contrast to the several linear models proposed by Baron and Kenny, is exactly the same for moderators and mediators. The difference lies in how M is defined in terms of time relation to treatment onset and correlation with treatment choice.

For example, in his article on mediators and moderators in cognitive therapy for depression, Whisman²⁷ points out that some researchers have proposed as moderators the therapeutic alliance and adherence to cognitive therapy procedures. By the definition used herein, neither can be a moderator, since both occur during, not before, treatment. However, Whisman warns that “a particular variable may assume the roles of both mediator and moderator,”^{27(p260)} again referring to the therapeutic alliance, which confuses the issue.

Problems stem from the proposal by Baron and Kenny⁵ that a mediator directly influences the outcome (main effect only), whereas a moderator affects the relationship between the treatment and the outcome (interactive effect only). As shown in Figure 2, when treatment changes M, it may change not only the level but also the impact of M on the outcome. The latter is an interactive effect that may be important in understanding the mechanism by which treatment affects outcome.

More important, under the present definition, the same variable cannot be both a moderator and a mediator of treatment, and the directionality of moderation and mediation is unambiguous. Although some methodologists may disagree, we believe that this theory forces

clearer thinking about possible moderators and mediators and their consequences. For example, lack of social support before treatment may or may not be a moderator of treatment outcome. Change in social support during treatment may or may not be a mediator of treatment outcome. However, lack of social support before treatment is not the same variable as change of social support during treatment. Whether one is a moderator has nothing to do with whether the other is a mediator. Currently, because both measures involve social support, these are often mistakenly treated as 2 measures of the same construct and reported as both mediating and moderating the treatment outcome.

The emphasis in this approach is on the effect size of treatments in the population and what influences the effect size for a particular choice of M. This is important, because it is easy to show that any nonlinear rescaling will produce an interaction effect for any outcome measure with no interaction effect. In many, but not all, cases it can be shown that for an outcome measure with a strong interaction effect, one can remove the interaction effect by suitable transformation. Such transformations (eg, log, square root, or arcsine) are often used to bring the data in line with the linearity and equal variance assumptions of these linear models. Once those assumptions are satisfied, conclusions regarding moderator or mediator status relate to that particular M and will be invariant for all linear transformations of that M.

Moreover, the definitions are couched in terms of population parameters, not in terms of test statistics and *P* values. Although statistical hypothesis testing based on linear models will often be the tool used to test certain hypotheses about the population effect sizes, the definitions themselves are not based on statistical significance. By increasing sample size one can generate more statistically significant results.¹⁵ For that reason, *P* values are not and should not be used to define moderators and mediators of treatment, because then moderator or mediator status would change with sample size.

The present approach must also be differentiated from that of finding variables that predict (baseline) or correlate with (events or changes during treatment) response in T or C separately. It is a basic tenet of RCT methods that one cannot estimate the treatment effect except in relation to another treatment (the control or comparison treatment). This is because when one evaluates one treatment alone, even the most inert placebo, one may see what appears to be change in the response due to artifacts such as statistical regression to the mean,²⁸⁻³¹ expectation effects on the part of the subjects and the evaluators, naturally occurring secular trends, and drift in measurement. When one evaluates how variables correlate with response within any single treatment group, any variables identified may be moderators or mediators or nonspecific predictors of response, but they may also be merely correlates of such artifactual effects. In any case, by these definitions, one could not, in absence of C, distinguish between moderators and mediators of treatment response and nonspecific predictors. It is necessary, as it is in RCTs, to have C.

The approach of Kraemer et al¹⁵ to moderators and mediators in risk research is basically the same as the one proposed herein. However, it differs in 2 respects. One difference is in the effect sizes used in RCTs vs those used in risk research. Another important difference is that all the factors considered in the risk context were assumed to be risk factors and thus correlated with the outcome. There is no need for any similar a priori requirement that the treatment first be shown effective overall in changing the outcome (Figure 2). There may be zero overall effectiveness, but there may still be important moderator or mediator effects. In short, moderator and mediator analyses may be just as important for what seems an overall noneffective treatment. It would preclude discarding a treatment that only appears ineffective because of overly generous inclusion criteria.

Impediments to Application

Although mediator and moderator analysis for treatment effects has

been strongly advocated^{10,32} and often attempted, there has been little formal emphasis on such analyses following an RCT. Clearly, such analyses are hypothesis-generating rather than hypothesis-testing. In absence of such formal, careful hypothesis-generating activities, the hypotheses tested in hypothesis-testing studies are often weak and the designs underlying such studies frequently based on flawed assumptions rather than empirically based ones, often lacking power to detect treatment effects. Even when such studies do detect treatment effects, they are likely to produce attenuated effect sizes. One then is left wondering whether, statistically significant or not, these effects have any clinical or policy significance.

In the evaluation of proposals and research papers, so much emphasis has traditionally been placed on hypothesis-testing activities that reviewers often dismiss hypothesis-generating as “data dredging” or “fishing expeditions.” There has recently been growing recognition among methodologists that carefully and expertly performed hypothesis-generating activities are necessary to foster stronger hypotheses for the next generation of hypothesis-testing studies and to provide the background information necessary to design such powerful studies.

In hypothesis-generating studies, conventional interpretations of significance tests no longer hold, and each finding considered to be important should be validated in the next generation of hypothesis-testing studies before being considered conclusive.³³ Any strong moderator should be considered as a stratification variable in the next RCT, and a formal test should be performed on the now a priori hypothesis of a moderator-by-treatment interaction. Any strong mediator should be considered in restructuring treatments to be evaluated in the next RCT, and a formal test should be performed on the now a priori hypothesis that the treatment effect would be increased by appropriate manipulation of mediators. To do so not only validates the moderator and mediator hypotheses generated in earlier studies, but also increases the

effect sizes and power in the subsequent RCTs. In the meantime, moderator and mediator analysis does not substantially increase the time or cost of performing RCTs, since such analyses are typically covered under secondary hypotheses and current funding would cover such activities. Everyone wins.

However, currently, to disseminate the results of such activities, authors often misreport their hypothesis-generating activities as hypothesis-testing. Even when authors carefully avoid doing so, reviewers and editors often demand inappropriate tests and *P* values. Information valuable to developing clinical and policy insights into present treatments, developing optimal treatment for different subpopulations (moderators), and maximizing the effects of treatments (mediators) may be simply misreported or not reported at all. Everyone loses.

Although moderator and mediator analysis is post hoc, the decision to perform such an analysis must be a priori. Considerable thought should be given in the design of the RCT to selection of a comprehensive set of high-quality and timely measures, which theory or experience might suggest as possible moderators or mediators without overburdening the subjects. Otherwise, the measures one needs are simply not available when the RCT is finished.

For example, there is increasing evidence that a rapid response to CBT occurs in a number of disorders.³⁴ Ilardi and Craighead³⁵ have shown that as much as 60% to 70% of total improvement in CBT for depression occurs in the first 4 weeks of therapy. Yet in RCTs, investigators have often assessed possible mediators at midtreatment with a view to explaining posttreatment effects. Exemplifying this convention, DeRubeis et al³⁶ measured proposed cognitive mediators of cognitive therapy for depression at midtreatment. This assessment point occurred after 6 weeks (10 sessions) of therapy. As the analysis by Ilardi and Craighead reveals, however, by this time point, much of the therapy effect would have already occurred. Similarly, in a recent com-

parative study of CBT and IPT for bulimia nervosa,^{25,37} the differential effects of the 2 treatments were apparent by week 6, well before the planned midpoint (10 weeks) assessment of most of the proposed mediators. Fortunately, the study design included an earlier measure of dietary restraint (covering weeks 3 and 4) that could then be shown to be a mediator of the treatment response. Such a rapid initial response suggests that considerable thought must be given to mediators that might operate very early and intensively. These would have to be measured early in the treatment, perhaps in the case of psychotherapy, on a session-by-session basis.

In summary, rapid progress in identifying the most effective treatments and understanding on whom treatments work and do not work and why treatments work or do not work depends on efforts such as those described herein to identify moderators and mediators of treatment outcome. In addition, RCTs should routinely include and report such analyses. Subsequent experimental studies should then consider these results in their design, thus systematically testing the hypotheses previous RCTs generate.

Submitted for publication May 16, 2001; final revision received September 7, 2001; accepted October 1, 2001.

The theoretical basis of this work was supported by the John D. and Catherine T. MacArthur Foundation (Chicago, Ill) Research Network on Psychopathology and Development (Dr Kraemer). This application was conceived while Drs Wilson, Fairburn, and Agras were fellows at the Center for the Advanced Study in the Behavioral Sciences at Stanford University. This fellowship was supported by the Henry J. Kaiser Family Foundation (Menlo Park, Calif) (84R-2459-HPE) and the Fund for Research in Psychiatry. The particular study in which the ideas were developed was supported by grant R10MH49877 from the National In-

stitute of Mental Health, Bethesda, Md. In addition, Dr Fairburn holds a Wellcome Trust (London) Principal Research Fellowship (046386).

Corresponding author: Helena Chmura Kraemer, PhD, Stanford University Medical Center, Department of Psychiatry, 401 Quarry Rd, Room C305, Stanford, CA 94305-5717.

REFERENCES

- Meinert CL. *Clinical Trials: Design, Conduct, and Analysis*. New York, NY: Oxford University; 1986.
- Borenstein M. The case for confidence intervals in controlled clinical trials. *Control Clin Trials*. 1994; 15:411-428.
- Jacobson NS, Truax P. Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. *J Consult Clin Psychol*. 1991;59:12-19.
- Kraemer HC. Reporting the size of effects in research studies to facilitate assessment of practical or clinical significance. *Psychoneuroendocrinology*. 1993;17:527-536.
- Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol*. 1986;51:1173-1182.
- Roth A, Fonagy P. *What Works for Whom: A Critical Review of Psychotherapy Research*. New York, NY: Guilford Press; 1996.
- Group PMR. Matching alcoholism treatment to client heterogeneity: Project MATCH posttreatment drinking outcomes. *J Stud Alcohol*. 1997; 58:7-29.
- Longabaugh R, Wirtz PW, DiClemente CC, Litt M. Issues in the development of client-treatment matching hypotheses. *J Stud Alcohol*. 1994;12:46-59.
- Kraemer H, Kazdin A, Offord D, Kessler R, Jensen P, Kupfer D. Coming to terms with the terms of risk. *Arch Gen Psychiatry*. 1997;54:337-343.
- Kazdin AE, Weisz JR. Identifying and developing empirically supported child and adolescent treatments. *J Consult Clin Psychol*. 1998;66:19-36.
- Hyman SE. The millennium of mind, brain, and behavior. *Arch Gen Psychiatry*. 2000;57:88-89.
- Morganstern J, Longabaugh R. Cognitive behavioral treatment for alcohol dependence: a review of mediating mechanisms and effectiveness. *Addiction*. 2000;10:1475-1490.
- Craighood LW, Agras WS. Mechanisms of action in cognitive-behavioral and pharmacological interventions for obesity and bulimia nervosa. *J Consult Clin Psychol*. 1991;59:115-125.
- Clark DM. Panic disorder and social phobia. In: Clark DM, Fairburn CG, eds. *Science and Practice of Cognitive Behaviour Therapy*. New York, NY: Oxford University Press; 1997:119-153.
- Kraemer HC, Stice E, Kazdin A, Kupfer D. How do risk factors work together to produce an outcome? mediators, moderators, and independent, overlapping and proxy risk factors. *Am J Psychiatry*. 2001;158:848-856.
- Kraemer HC, Kazdin AE, Offord DR, Kessler RC, Jensen PS, Kupfer DJ. Measuring the potency of a risk factor for clinical or policy significance. *Psychol Methods*. 1999;4:257-271.
- Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. Hillsdale, NJ: Lawrence Erlbaum Associates; 1988.
- Hedges LV. Estimation and testing for differences in effect size: a comment on Hsu. *Psychol Bull*. 1982;91:691-693.
- Rosenthal R. Parametric measures of effect size. In: Cooper H, Hedges LV, eds. *The Handbook of Research Synthesis*. New York, NY: Russell Sage Foundation; 1994:231-244.
- Infant Health and Development Program. Enhancing the outcomes of low birth weight, premature infants: a multisite randomized trial. *JAMA*. 1990; 263:3035-3042.
- Brooks-Gunn J, McCarton CM, Casey PH, Brooks-Gunn J, McCarton CM, Casey PH, McCormick MC, Bauer CR, Bernbaum JC, Tyson J, Swanson M, Bennett FC, Scott DT. Early intervention in low-birth-weight premature infants. *JAMA*. 1994;272: 1257-1262.
- Smeraldi E, Zanardi R, Benedetti F, DiBella D, Perez J, Catalano M. Polymorphism within the promoter of the serotonin transporter gene and antidepressant efficacy of fluvoxamine. *Mol Psychiatry*. 1998;3:508-511.
- Moderators and mediators of treatment response for children with attention-deficit/hyperactivity disorder: the Multimodal Treatment Study of Children with Attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry*. 1999; 56:1088-1096.
- The MTA Cooperative Group. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder: Multimodal Treatment Study of Children With ADHD. *Arch Gen Psychiatry*. 1999;56:1073-1086.
- Agras WS, Walsh BT, Fairburn CG, Wilson GT, Kraemer HC. A multicenter comparison of cognitive-behavioral therapy and interpersonal psychotherapy for bulimia nervosa. *Arch Gen Psychiatry*. 2000;57:459-466.
- Ramey CT, Bryant DM, Wasik BH, Sparling JJ, Fendt KH, LaVange LM. Infant Health and Development Program for low birth weight, premature infants: program elements, family participation, and child intelligence. *Pediatrics*. 1992;89:454-465.
- Whisman M. Mediator and moderators of change in cognitive therapy of depression. *Psychol Bull*. 1993;114:248-265.
- Davis CE. The effect of regression to the mean in epidemiologic and clinical studies. *Am J Epidemiol*. 1976;104:493-498.
- Samuels ML. Statistical reversion toward the mean: more universal than regression toward the mean. *Am Stat*. 1991;45:344-346.
- Senn S. Regression to the mean. *Stat Methods Med Res*. 1997;6:99-102.
- Stigler SM. Regression towards the mean, historically considered. *Stat Methods Med Res*. 1997; 6:103-114.
- Holmbeck GN. Toward terminological, conceptual, and statistical clarity in the study of mediators and moderators: examples from the child-clinical and pediatric psychology literatures. *J Consult Clin Psychol*. 1997;65:599-610.
- Meinert CL. Toward more definitive clinical trials. *Control Clin Trials*. 1980;1:249-261.
- Wilson GT. Rapid response to cognitive behavior therapy. *Clin Psychol*. 1999;6:289-292.
- Ilardi SS, Craighead WE. The role of nonspecific factors in cognitive-behavior therapy for depression. *Clin Psychol*. 1994;1:138-156.
- DeRubeis RJ, Evans MD, Hollon SD, Garvey MJ, Grove WM, Tuason VB. How does cognitive therapy work? cognitive change and symptom change in cognitive therapy and pharmacotherapy for depression. *J Consult Clin Psychol*. 1990;58:862-869.
- Wilson GT, Loeb KL, Walsh BT, Labouvie E, Petkova E, Liu X, Wateraux C. Psychological versus pharmacological treatment of bulimia nervosa: predictors and processes of change. *J Consult Clin Psychol*. 1999;67:451-459.