

Mediators and Mechanisms of Change in Psychotherapy Research

Alan E. Kazdin

Department of Psychology, Yale University, New Haven, Connecticut 06520-8205;
email: alan.kazdin@yale.edu

Annu. Rev. Clin. Psychol. 2007. 3:1–27

First published online as a Review in
Advance on October 11, 2006

The *Annual Review of Clinical Psychology* is
online at <http://clinpsy.annualreviews.org>

This article's doi:
10.1146/annurev.clinpsy.3.022806.091432

Copyright © 2007 by Annual Reviews.
All rights reserved

1548-5943/07/0427-0001\$20.00

Key Words

mediators, moderators, mechanisms of psychotherapy, processes and outcomes of therapy, randomized controlled trials, mediation analyses, treatment evaluation

Abstract

There has been enormous progress in psychotherapy research. This has culminated in recognition of several treatments that have strong evidence in their behalf. Even so, after decades of psychotherapy research, we cannot provide an evidence-based explanation for how or why even our most well studied interventions produce change, that is, the mechanism(s) through which treatments operate. This chapter presents central requirements for demonstrating mediators and mechanisms of change and reviews current data-analytic and designs approaches and why they fall short of meeting these requirements. The role of the therapeutic alliance in psychotherapy and cognitive changes in cognitive therapy for depression are highlighted to illustrate key issues. Promising lines of work to identify mediators and mechanisms, ways of bringing to bear multiple types of evidence, recommendations to make progress in understanding how therapy works, and conceptual and research challenges in evaluating mediators and mechanisms are also presented.

Contents

INTRODUCTION.....	2	Meticulous Description.....	12
CONCEPTUAL AND		Moderators as a Path to Identifying	
DEFINITIONAL ISSUES.....	3	Mediators and Mechanisms....	13
REASONS FOR STUDYING		Direct Intervention and	
MEDIATORS AND		Manipulation.....	14
MECHANISMS.....	3	Converging Lines of Work.....	15
REQUIREMENTS FOR		General Comments.....	16
DEMONSTRATING		RECOMMENDATIONS FOR	
MEDIATORS AND		RESEARCH.....	16
MECHANISMS OF CHANGE..	4	Use Theory as a Guide.....	16
Multiple Criteria.....	4	Include Measures of Potential	
General Comments.....	6	Mediators in Treatment	
CURRENT STATUS OF		Studies.....	17
RESEARCH ON MEDIATORS		Establish the Timeline of the	
AND MECHANISMS.....	6	Proposed Mediator or	
Examples Where Mediators and		Mechanism and Outcome.....	17
Mechanisms are Discussed But		Assess More than One Mediator or	
Not Well Established.....	6	Mechanism.....	17
General Comments.....	8	Use Designs that Can Evaluate	
OVERVIEW OF METHODS FOR		Mediators and Mechanisms....	18
STUDYING MEDIATORS AND		Examine Consistencies Across	
MECHANISMS IN		Different Types of Studies....	19
PSYCHOTHERAPY.....	8	Intervene to Change the Proposed	
Statistical Techniques.....	8	Mediator or Mechanism.....	20
Design Methods for Studying		SPECIAL CHALLENGES AND	
Mediators and Mechanisms....	10	OBSTACLES.....	21
General Comments.....	11	Mechanism-Outcome Relations...	21
PATHS TO IDENTIFYING AND		Everything in Moderation.....	22
ELABORATING MEDIATORS		Measurement Development.....	22
AND MECHANISMS.....	11	CONCLUSIONS.....	23

INTRODUCTION

Several forms of psychotherapy for children, adolescents, and adults produce therapeutic change, as demonstrated in scores of controlled treatment studies (Kazdin & Weisz 2003, Lambert 2004, Nathan & Gorman 2007). The changes can encompass social, emotional, cognitive, behavioral, educational, and physical spheres of functioning. We know well that therapy “works,” i.e., is responsible for change, but have little knowledge of why or how it works.

Discussions and theory about why psychotherapy changes people are plentiful, but supportive evidence is quite rare. The American humorist and writer, Mark Twain (1835–1910) noted that, “everybody talks about the weather but nobody does anything about it.”¹ Mechanism is the weather of psychotherapy research. The focus of this review is on why treatment works, through what processes, and

¹Mark Twain (Samuel L. Clemens) is credited with this quote but some suggest that his coauthor A. Charles Dudley Warner wrote the statement (Twain & Warner 1874).

how change comes about, or more succinctly, on the mechanism(s) of therapeutic change. This review also discusses the importance of studying mediators and mechanisms of therapy, examines the limitations of existing data evaluation and design strategies, and provides recommendations for changes needed in research.

CONCEPTUAL AND DEFINITIONAL ISSUES

Several related concepts are important to delineate in part because of their confusion but also because they are relevant to elaborating mechanisms (please see **Table 1**). It is useful to begin with cause or causal relation. A randomized controlled trial (RCT) may show that treatment compared to no treatment leads to therapeutic change. From the demonstration, we can say that the treatment *caused* the change, as the term “cause” is used in science.

Demonstrating a cause does not say *why* the intervention led to change or how the change came about. To evaluate how change comes about, research often looks at mediators. As noted in the table, mediator is a construct that shows important statistical relations between an intervention and outcome, but may not explain the precise process through which change comes about. The term “mechanism” refers to a greater level of specificity than does the term “mediator” and reflects the steps or processes through which

therapy (or some independent variable) actually unfolds and produces the change. Mechanism explains how the intervention translates into events that lead to the outcome. This is easily confused with the notion of mediation. For example, cognitions may be shown to mediate change in therapy, an important lead perhaps. However, this does not explain specifically how the change came about, i.e., what are the intervening steps between cognitive change and reduced stress or anxiety. In this review, the primary focus is on mediators and mechanisms. The goal is to understand the mechanisms of change; the study of mediators is often a first step, as is illustrated below.

Moderator refers to some characteristic that influences the direction or magnitude of the relation between the intervention and outcome. If treatment outcome varies as a function of characteristics of the patient or therapist (e.g., sex, ethnicity, temperament), treatment delivery (e.g., individual versus group treatment), or cohort (e.g., so-called generation X versus baby boomers), these latter variables are moderators. I return to moderators below because they have important bearing on mediators and mechanisms.

REASONS FOR STUDYING MEDIATORS AND MECHANISMS

Evaluating mediators and mechanisms of therapeutic change is important for several reasons. First, there is an embarrassing

Table 1 Key terms and concepts

Cause: a variable or intervention that leads to and is responsible for the outcome or change.
Mediator: an intervening variable that may account (statistically) for the relationship between the independent and dependent variable. Something that mediates change may not necessarily explain the processes of how change came about. Also, the mediator could be a proxy for one or more other variables or be a general construct that is not necessarily intended to explain the mechanisms of change. A mediator may be a guide that points to possible mechanisms but is not necessarily a mechanism.
Mechanism: the basis for the effect, i.e., the processes or events that are responsible for the change; the reasons why change occurred or how change came about.
Moderator: a characteristic that influences the direction or magnitude of the relationship between independent and dependent variable. If the relationship between variable <i>x</i> and <i>y</i> varies is different for males and females, sex is a moderator of the relation. Moderators are related to mediators and mechanisms because they suggest that different processes might be involved (e.g., for males or females).

wealth of treatments in use. For example, in the context of child and adolescent therapy alone, 550+ psychotherapies can be delineated (Kazdin 2000). Some of these are known to produce change; it is not likely that the different treatments produce change for different reasons. Understanding the mechanisms of change can bring order and parsimony to the current status of multiple interventions.

Second, therapy can have quite broad outcome effects, beyond the familiar benefits of reducing social, emotional, and behavioral problems (e.g., suicidal ideation, depression, and panic attacks). Therapy also alters physical conditions (e.g., pain, blood pressure), improves recovery from surgery or illness, and increases the quality of life (see Kazdin 2000). How do these effects come about? Elaborating mechanisms of therapy will clarify the connections between what is done (treatment) and the diverse outcomes.

Third, by understanding the processes that account for therapeutic change one ought to be better able to optimize therapeutic change. Indeed, without understanding what is critical to treatment and how it operates, we are at a bit of a loss. Should we focus on more practice, catharsis, chatting, homework—what leads to change and why? If we know how changes come about, perhaps we can direct better, stronger, different, or more strategies that trigger the critical change process(es).

Fourth, extending treatments from research to clinic or “real world” settings will be difficult without understanding how treatment works. We enter the clinical arena with one hand tied beyond our back if we apply an unspecified and possibly low dose of some treatment that we do not understand. To optimize the generality of treatment effects from research to practice we want to know what is needed to make treatment work, what are the optimal conditions, and what components must not be diluted to achieve change.

Fifth, understanding how therapy works can help identify moderators of treatment, i.e., variables on which the effectiveness of a given treatment may depend. Understand-

ing the processes through which treatment operates can help sort through those facets that might be particularly influential in treatment outcome and permit better selection of suitable patients. For example, if changes in cognitive processes account for therapeutic change, this finding might draw attention to the pretreatment status of related processes (abstract reasoning, problem-solving, attributions) that might moderate who responds or fails to respond to treatment.

Finally, understanding the mechanisms through which change takes place is important beyond the context of psychotherapy. Many interventions or experiences in everyday life improve adjustment and adaptive functioning, ameliorate problems of mental and physical health, help people manage and cope with stress and crises, and more generally navigate the shoals of life. As examples, participating in religion, chatting with friends, exercising, undergoing hypnosis, and writing about sources of stress all have evidence in their behalf. Mechanisms that elaborate how therapy works might have generality for understanding human functioning beyond the context of therapy. The other side is also true. Mechanisms that explain how other change methods work might well inform therapy. Basic psychological processes (e.g., learning, memory, perception, persuasion, social interaction) and their biological pathways (e.g., changes in neurotransmitters) may be common to many types of interventions, including psychotherapy.

REQUIREMENTS FOR DEMONSTRATING MEDIATORS AND MECHANISMS OF CHANGE

Multiple Criteria

Establishing a mediator or mechanism has several requirements. The requirements are highlighted because they provide the background for why changes are needed in research. I focus on mediation because this is an important interim step between

demonstrating a causal relation and understanding concretely the mechanism of action through which the effect occurs. Also, mediation is the primary focus of contemporary research.

Strong association. Demonstration of a strong association between the psychotherapeutic (A) intervention and the hypothesized mediator of change (B) is an initial requirement. Then of course, there ought to be an association between the proposed mediator (B) and therapeutic change (C). Indeed, if these three variables are not related, the case for the operation of a mediator is greatly weakened, if not eliminated.

Specificity. The second criterion refers to the demonstration of the specificity of the association between the intervention, proposed mediator, and outcome. We would not want multiple mediators to account for the change, but rather show a more specific connection. A demonstration that many plausible constructs do not account for therapeutic change, with the exception of one, strengthens the argument that the proposed construct mediates change.

Consistency. Replication of an observed result across studies, samples, and conditions, i.e., consistency in the relation, contributes to inferences about mediators. We expect the relations among A, B, and C not to be sample specific. Inconsistency across two or more demonstrations does not necessarily mean that the proposed mediator is not involved. The relation between a proposed mediator and outcome might be perfectly consistent but moderated by a variable we have not yet identified. Yet, when consistency across studies is obtained, this greatly facilitates drawing inferences about whether a particular mediator may be involved.

Experimental manipulation. Direct manipulation through an experiment obviously makes a strong case between therapy and out-

come (A and C). This type of demonstration (e.g., RCT) is common and demonstrates cause. However, uncommon are experiments that manipulate the proposed mediator or mechanism (B) and show the impact on outcome (C). Experimental evidence strengthens the case that a proposed mediator is responsible for a change in the outcome of interest.

Timeline. A timeline must be established to infer a causal relation or mediator of change. Causes and mediators must temporally precede the effects and outcomes. Demonstrating a timeline between cause and an effect, albeit obvious, is the Achilles' heel of treatment studies, as I elaborate below.

Gradient. Showing a gradient in which stronger doses or greater activation of the proposed mediator is associated with greater change in the outcome can help make the case for a particular mediator. A common analysis in medicine, epidemiology, and public health is showing a dose-response relation. For example, there is a dose-response (and linear) relation between passive cigarette smoke (i.e., exposure to secondhand smoke) and coronary heart disease (He et al. 1999). Demonstrating a dose-response relation increases the plausibility of an agent being causally involved and may point to likely mechanisms as well. Of course, it is possible that there is no dose-response relation (e.g., a qualitative or on-off gradient) or that the relation is not linear. Such relations do not mean a particular construct is not causally related, but may make inferences more difficult or require supplementary information.

Plausibility or coherence. Plausibility or coherence of an explanation of how a mediator or mechanism operates and integration of findings with the broader scientific knowledge base contribute to the inferences. In medicine, pathophysiology often is invoked to meet this criterion. That is, in light of the findings, is there a plausible, coherent, and reasonable process (e.g., buildup of plaque)

through which the disorder (e.g., atherosclerosis and heart attack) might be explained? An explanation is plausible because it invokes other information and steps in some process-outcome relation that are reasonable or supported by other research.

The use of plausibility and coherence to elaborate mechanisms is poignantly illustrated in child abuse. Occasionally, parents bring their very injured and pained child to an emergency room for treatment and tell the physician that the child has been injured. Three examples from my own experience include a child who allegedly fell off a bicycle, another who fell down the five front stairs of a cement porch at home, and a child who got into a fistfight with a seven-year-old sibling. In each case, the physician (a different person for each case) was suspicious because the injuries consisted of large and deep bruise marks across the back (with lines resembling a belt) and a mark that could resemble a belt buckle on the upper shoulder (child 1); three or possibly four round burn marks on the child's back in the size of the end of a cigarette (child 2); and a black eye and open scalp wound under the hair (child 3). The physician in each case was suspicious primarily based on the criterion of plausibility and coherence of the "mechanisms" or process involved leading to these outcomes. In light of how a child is likely to fall off a bicycle or down the stairs or to be hit by young sibling, respectively, the injuries were not very likely (plausible, coherent). However, the injuries were very plausible by invoking another process or mechanism, namely, parent abuse of their children. (One could use the term "parsimonious" here, but I use "plausible" and "coherent" to focus on a greater level of specificity, namely, looking at the operation of a mechanism and how it unfolds to produce an outcome.)

In relation to psychotherapy, plausibility and coherence convey the importance of theoretically based investigation of mediators and mechanisms of change. Here we need more than a global construct that can be used to explain onset of a clinical problem or therapeutic

change. We need a plausible account of how the construct works and leads (in a testable way) to the outcomes.

General Comments

Drawing inferences about a mediator of change requires convergence of multiple criteria because they act in concert. Interpretation of what accounts for or explains a particular relation (mediator, mechanism) is not likely to come from a single investigation. By the very nature of one of the criteria (consistency), replication is required. Yet, apart from that criterion, the case for a mediator is built by a sequence of studies that may vary in the set of criteria they address and the clarity of the demonstration. After several studies, and when all or most of the criteria are met, one can state that some intervening process accounts for change.

CURRENT STATUS OF RESEARCH ON MEDIATORS AND MECHANISMS

Mechanisms of treatment are increasingly discussed, a likely precursor to more empirical work on the topic (e.g., Brent & Kolko 1998, Grawe 2004, Hofmann 2000, Kazdin 2006, Kazdin & Nock 2003, Weersing & Weisz 2002). I believe this has fostered the view that we know about key processes leading to change and are using suitable methodological, statistical, and design tools. Few empirical studies are available that meet even two or three of the criteria mentioned previously. Consider briefly two therapy areas where mediators and mechanisms of action are often discussed.

Examples Where Mediators and Mechanisms are Discussed But Not Well Established

Therapeutic alliance and treatment outcome. The therapeutic alliance refers to the collaborative nature of the patient-therapist

interaction, their agreement on goals, and the personal bond that emerges in treatment. A consistent finding is that the stronger the alliance the greater the therapeutic change (Horvath & Bedi 2002, Orlinsky et al. 2004). Studies that evaluate alliance during (e.g., early, middle) treatment often show that alliance predicts improvement in symptoms at the end of treatment. Showing that alliance predicts later symptom change by itself does not show that alliance plays a causal role, leaving aside the more specific matter of reflecting a potential mediator. Merely because symptoms are not assessed in the middle of treatment, does not mean they have not already changed. Perhaps very early in treatment clients get a little better (some symptom improvement) and *as a result* form a positive alliance with the therapist.

For example, a study of psychodynamically oriented supportive therapy showed that changes in alliance early in treatment predicted symptom change at the end of treatment, in keeping with a large body of evidence (Barber et al. 2000). However, a critical addition was included. Both symptom change and alliance were assessed at multiple points. Symptom changes early in treatment predicted alliance and that alliance also predicted further symptom change. Thus, the familiar alliance-outcome correlation in part reflects the relation of early and later symptom change, and the timeline is symptom change to alliance as well as the reverse. Assessment of both symptom change and alliance were completed at multiple points during the course of treatment to identify these interesting relations. Other studies with assessments at multiple points have shown that a positive alliance may follow improvements in symptoms (DeRubeis & Feeley 1990, Tang & DeRubeis 1999).

From these examples, I do not wish to assert that alliance is invariably the effect rather than a cause. Indeed, the correlational evidence does not permit statements about cause or mediation. The reciprocal or bidirectional relations of symptoms and alliance are inter-

esting to pursue. The broader point is more pertinent here, to wit, in the vast majority of studies the timeline between alliance and symptom change has not been established.

Cognitions in cognitive therapy for depression. There are very few forms of psychotherapy as well established as cognitive therapy (CT) for unipolar depression among adults (American Psychiatric Association 2000, Hollon & Beck 2004). This treatment is evidence based, and then some, in light of the range of trials. But why does CT work, i.e., through what mediators or mechanisms? In fact, little can be stated as to why treatment works. In the development of this treatment, the basis of therapeutic change was thought to be changes in key cognitive processes (negative triad) that characterize many depressed patients. CT is designed to change these cognitions and in the process change depression. The relation of cognitions and cognitive change in treatment to therapeutic change has been studied in different ways by assessing symptom change and cognitive change at the end of treatment and showing that one shares variance with the other, or by evaluating whether cognitions assessed early or in the middle of treatment correlate with subsequent therapeutic change (e.g., DeRubeis et al. 1990, Kwon & Oei 2003). In both of these methods, the timeline problem is unresolved, i.e., we do not know the ordering of cognitive change and symptom change. This issue is similar to the concern raised in relation to alliance, namely, in the vast majority of studies, symptom change may have preceded or occurred concurrently with cognitive changes. From research as currently designed and discussed, it is not possible to say that cognitive processes serve as the mediators of therapeutic change.

Actually, unlike the research on alliance, perhaps one can say a bit more about mediators and mechanisms of cognitive therapy. The research permits one to say more about what is *not* a likely mediator of the effects of CT. Tests of mediation and evaluation of

therapeutic changes quite early in the course of treatment suggest that improvements can readily occur without changes in cognitions or in advance of implementing cognitive-change strategies in treatment (e.g., Burns & Spangler 2001, Tang & DeRubeis 1999). Challenges to the cognitive bases of change in CT for depression are not new (Ilardi & Craighead 1994, Whisman 1999). Perhaps we can state more confidently now than before that whatever may be the basis of changes with CT, it does not seem to be the cognitions as originally proposed.

General Comments

I have highlighted two areas that are often discussed as if we know the basis for the effect, i.e., the mechanism involved. In both alliance and cognitive therapy literatures, the timeline problem is a methodological shroud that covers most studies. Without clearly establishing that the putative basis for the effect invariably comes before symptom change, conclusions about mediation are in question. Of course, it follows that more specific statements about mechanisms are premature.

The two examples are intended to convey how a key criterion, establishing a timeline, is not met in otherwise well-studied areas where mechanisms are discussed. The examples were used to illustrate this single point rather than to review comprehensively the respective literatures. Although I focused on the timeline problem, other concerns in relation to these literatures could be illustrated by applying all of the criteria. Let me mention one to note that this is not a vacuous claim.

We do not have a clear picture or set of studies that test how the putative mechanism unfolds in such a way as to alter symptoms. In relation to plausibility and coherence of the mechanism-outcome relation, precisely what happens that leads to symptom change? For example, through what process or sequence of events along any dimensions (cognitive processes, neurotransmitters, stress) does alliance lead to reductions in depression, anxiety, or

feelings that life is meaningless? The time sequence problem is more basic, but how does one get from “my therapist and I are bonding” to “my marriage, anxiety, and tics are better”? This is a leap with the intervening steps unspecified or untested, at least to my knowledge. The steps are not academic. If we could identify the steps, there may be other ways to activate them than through alliance alone. Also, we might identify novel moderators related to the mechanisms that help us select individuals likely to vary in responsiveness to the intervention.

OVERVIEW OF METHODS FOR STUDYING MEDIATORS AND MECHANISMS IN PSYCHOTHERAPY

Dominant methods of evaluating mediators in therapy research have limited what can be concluded in large part because critical conditions mentioned previously are not met. I highlight current methods and discuss why we have not been able to learn very much about mediators or mechanisms from them.

Statistical Techniques

Tests of mediation. Statistical evaluation can play a central role in addressing whether a particular construct accounts for change. Multiple regression techniques, path analysis, structural equation modeling, and bootstrap methods are prominent options (Baron & Kenny 1986, Holmbeck 2002, Hoyle & Smith 1994, Kenny et al. 1998, MacKinnon et al. 2002, Shrout & Bolger 2002). Multiple regression analyses have been the most commonly used techniques, and an overview of the logic conveys the benefits as well as the problems. Consider a hypothetical outcome study in which we evaluate the following components:

- A = an intervention (the treatment)
- B = a mediator or intervening variable
- C = an outcome (therapeutic change)

The interrelations of A, B, and C, as evaluated statistically, are used to infer whether B can explain why treatment works. In demonstrating mediation statistically, four conditions and tests are usually proposed:

- The treatment or intervention (A) must be related to therapeutic change (C);
- The treatment (A) must be related to the proposed mediator (B);
- The proposed mediator (B) must be related to therapeutic change (C); and
- The relation between the intervention (A) and therapeutic change (C) must be reduced after statistically controlling for the proposed mediator (B).

The logic seems compelling because the many conditions, if met, suggest that the impact of treatment (A) on therapeutic change (C) really depends on some intervening processes (B). My simple description ignores many nuances. For example, the extent to which the A-C relationship is reduced by controlling for B is a matter of degree, and there is no cut point (beyond statistical significance [e.g., Sobel test]) to decide whether there is or is not support for a particular mediational view. Also, the various statistical analyses are not free from controversy or challenge (e.g., Kraemer et al. 2001, 2002). I merely wish to convey that the statistical analyses highlighted here are used to evaluate mediators of change in therapy.

As is so often the case in statistical analyses, the concerns here are not about the statistics per se but about their use and interpretation. A key interpretive limitation is the fact that the timeline between the mediator and the outcome is not necessarily established. Most psychotherapy studies of mediation evaluate the mediator and symptoms at pre and post or evaluate the mediator but not the symptoms during treatment. Change in the mediator is shown to correlate, predict, and account for variance in relation to the outcome. The statistical analysis alone cannot establish that one influence preceded, and therefore possibly mediated, the other.

Even when the timeline is established, mediation does not necessarily suggest the mechanism of action. If, for example, some cognitions are shown to come before symptom change and statistically explain the intervention-outcome (A-C) relation that by itself does not show the construct is the mechanism. What precisely is the process of change, what are the steps from the construct to the change, and are other variables embedded in the measure? One might say that cognitions as a mediator might be a first step to move to more fine-grained analyses, a defensible position. But one must also say that cognitions might not be the variable at all or at least the cognitions of interest to the investigator. Cognitions might be a proxy variable for some other construct or be a global construct that includes multiple distinguishable components (Kraemer et al. 2001).

In cross-sectional studies, the language used to describe the data-analytic strategies and the findings lends itself to misconception in relation to the timeline. For instance, regression analyses identify variables as “predictors” or independent variables and others as “outcomes” or dependent variables. Yet, the timeline is only established by the experimental design. The distinction between antecedent (independent) and outcome (dependent) variables, from the standpoint of the steps of the statistical analyses (and printouts) is arbitrary. Similarly, the accompanying diagrams of the results with a flow chart of some kind to convey the authors’ views of mediation (e.g., a structural equation model with arrows pointing to the right) may lead the author or reader to conclude erroneously that there is a timeline.

Percentage of variance. Occasionally, researchers focus on the notion of percentage of variance accounted for, or “explained by,” a variable and consider this as proof that a critical process or the critical explanation has been identified. If two variables are correlated (r), then one can identify the proportion of common or shared influence (r^2). For example,

therapeutic processes (e.g., alliance) “predict” therapeutic change. Researchers often note that alliance accounts for a significant proportion of variance and sometimes even more variance than other influences (e.g., treatment technique). Further interpretation is often added to suggest this must mean that the alliance is why treatment leads to change or is the most significant/important influence in therapy.

Nothing in the measure of percentage of variance speaks to mediators or mechanisms. First, shared variance of alliance and outcome could be huge, but that could be due to symptom change occurring before alliance. Second, the therapeutic alliance can “account for” treatment outcome variance but itself be explained by one or more other variables, such as common method variance in the alliance outcome measures or even characteristics of the patients before they came to treatment (e.g., Kazdin & Whitley 2006, Zigler & Glick 1986). In short, amount variance may or may not point toward mediators or mechanisms. Whether the relation (any correlation) provides meaningful leads will stem from the conditions required for establishing mediators, as enumerated above.

Biases in the data analysis. The way the data analyses are completed occasionally can foster the view that a critical influence or mediator has been identified. An example in psychotherapy research pertains to integrity or fidelity of treatment, that is, the notion that treatment was carried out as intended. Investigators evaluate whether clients who received the treatment as intended show greater change than those who did not (for a review see Pereplechikova & Kazdin 2005). Obviously, if critical procedures of treatment are responsible for change, adherence to these procedures ought to make a difference in outcome. A measure of treatment integrity may allow the investigator to delineate the extent to which clients received the full dose or proper implementation of treatment. (Related to this article, but not this section, many

studies that assess integrity do so at the end of treatment, at the same time that symptom change is evaluated, raising some timeline issues we can forego here.) The investigator may analyze the data with only those clients who received the intervention as intended or who received some minimal dose or by including all the data and showing a correlation between how well treatment was implemented and the degree of therapeutic change. Receiving the appropriate levels of treatment is not randomly distributed and may well be confounded with client or client \times therapist characteristics. For example, getting more, better, or more carefully implemented treatment may relate to the personality of the client (or therapist), severity of his or her problems, match of values and interests between the therapist and patient, and more.

The example is on treatment integrity but the broader point is critical. In studying any intervening process or construct of therapy, the investigator may wish to include in the data analyses only those individuals for whom the putative mediator was invoked or occurred. After random assignment of cases to different groups, keeping or using only cases where the mediator was effectively manipulated changes the equality of the sample and introduces other constructs that are likely to be confounded with the variable (mediator) of interest.

Design Methods for Studying Mediators and Mechanisms

Randomized controlled trials. RCTs remain the primary method of demonstrating a causal relation between treatment and therapeutic change. The most common limitation of RCTs pertinent to this discussion is the failure to establish a timeline between a proposed mediator or mechanism and outcome, as I illustrated above. Assessing the proposed mediator during treatment is necessary but not sufficient to show the timeline between the mediator and outcome. The assessment of symptom change is required during treatment

as well. Changes in assessment and design of treatment trials, noted later in the chapter, can address this concern.

Component analyses of treatment techniques. One way that investigators attempt to get at mediators and mechanisms is by analyzing a treatment that is known to be effective. In this context, treatment is considered a “package,” i.e., several distinguishable ingredients or components (e.g., x , y , and z). Dismantling studies provide all the components of the package to one group and variations without all of the components to one or more other groups. The complementary approach is the constructive strategy in which one begins with one component and adds others (to other groups or individuals in a crossover design) (see Kazdin 2003). The idea behind each strategy is to identify necessary, sufficient, and facilitative ingredients for treatment to achieve change. Under ideal circumstances there is a theory underlying the package with a more specific statement that some ingredient (e.g., focus on specific activities or exercises) is essential for therapeutic change. If a component is shown to contribute greatly to change and little or no change occurs without that component, investigators often interpret this as evidence for a mediator or mechanism.

Identifying a critical component of treatment, while valuable for many reasons (e.g., for extending abbreviated versions of treatment to clinical work), does not provide direct support for a mediator or mechanism. A component might achieve its effects for all sorts of reasons (processes) that must be assessed. Investigators might note that dismantling is a first step—true in principle. In practice, there are scores of very informative dismantling studies that have not moved to the next steps to understand why a component might be important.

General Comments

In demonstrating causal relations and identifying candidates that might be mediators or

mechanisms of change, one ought to begin with the criteria or requirements mentioned above. Statistical analyses and experimental designs (arrangements) are tools to address these requirements. One completes the statistical analysis and then reverts to one of the criteria to ask, “Was this criterion met?” Whether the timeline of a supposed mediator or mechanism of change or whether a construct is a plausible and coherent explanation of therapeutic change are not questions about statistical analyses per se but about interpretation of those analyses.

PATHS TO IDENTIFYING AND ELABORATING MEDIATORS AND MECHANISMS

Understanding mediators and then mechanisms is not a matter of one study but is a matter of creeping up on the process that draws on a series of projects often seemingly unrelated or from different disciplines or types of research. It is useful to think of the search for mechanisms as a chess game. Even though there might be a final winning move (checkmate), the game is won on multiple fronts, an integrated sequence of actions, and converging moves that make checkmate possible. Critical to a chess game is that there is movement toward a goal; whether psychotherapy research shows this movement, at least in relation to understanding mechanisms, is not so clear. By movement, I refer to a progression that reflects depth or type of understanding of the factors that produce therapeutic change.

Consider the progression in understanding based on the concepts of correlate, risk factor, and cause (Kraemer et al. 1997) in relation to the familiar example of cigarette smoking and lung cancer. The connection between the characteristic and outcome began as a correlate (e.g., cross-sectional study findings that people with lung cancer reported a higher rate of smoking) and moved to a risk factor or a correlate where one characteristic clearly precedes another (e.g., longitudinal study findings that those who smoked had higher

mortality rates for lung cancer). Then the connection moved to being identified as a causal factor. Both quasi experiments with humans and true experiments with animals showed that the amount of smoking altered the outcome. The dose-response relation of the findings as well as direct experimentation supported the causal role of smoking and disease. Once a causal role is demonstrated, one can ask more analytically how, or through what mechanism, does the cause operate?

Much of research on treatment, but also on psychiatric disorders, identifies correlates and risk factors (predictors) of the outcome. A difficulty is that the work rarely progresses to the next step that would provide a more in-depth evaluation of how the factor operates. Research on heart disease and cholesterol illustrates the progress and more in-depth evaluation. Cholesterol has been known to be a risk factor and predictor of heart disease. Research progressed to evaluate whether cholesterol is causally involved, and indeed, it is. Changing (reducing) cholesterol, in fact, alters the subsequent risk for heart disease.

Psychological research often moves from risk factor to causal risk factor casually and without actual tests. In the usual instance, a study identifies, let us say, two risk factors for some deleterious outcome. The investigator then suggests that we ought to change, address, or in some way attend to these risk factors to make people better. This is a non sequitur. We do not know that the risk factors bear any causal relation to the outcome. The practice of identifying a risk factor and then discussing an intervention to alter that risk factor is so common that one looks for system issues that might foster it (e.g., journals or funding agencies that insist on clinical implications on what might [merely] be a basic critical finding).

Psychological research rarely moves the evaluation from correlate, to risk factor, to causal agent. A usual reason given is that one cannot experimentally manipulate critical variables in humans (e.g., child-rearing practices, attachment style), and therefore we

are confined to correlation. The problem is elsewhere, namely, little theory about key constructs (mediators) and how they could be studied, little effort to identify steps or processes (mechanisms) by which the construct leads to an outcome, and little use of convergent lines of inquiry that could strengthen inferences about causes, mediators, and mechanisms. One does not need true experiment necessarily. One needs to build the case by meeting the requirements outlined above. There are many strategies to understand mechanisms or at least to move the ball forward significantly beyond correlation, as I address below.

Meticulous Description

Understanding mechanisms is readily framed as an explanation of some phenomenon of interest. In research (and life) one can readily distinguish description (what is happening) from explanation (why it is happening or through what forces, processes, or mechanisms). This is a helpful distinction to learn and to teach but for this discussion to blur. In many instances in science, one can conceive of description and explanation as related and as opposite ends of a continuum. Depending on the detail, level of analysis, and sequence of moving from one to the other, description can become explanation. Let us continue the example of cigarette smoking and lung cancer.

Spanning decades, cross-sectional and longitudinal studies and research with humans and animals have established a causal role between cigarette smoking and lung cancer, which is where we left off in the comments above. Establishing a causal relation does not automatically explain the mechanisms, i.e., the process(es) through which lung cancer comes about. The mechanism has been uncovered by describing what happens in a sequence from smoking to mutation of cells into cancer (Denissenko et al. 1996). A chemical (benzo[*a*]pyrene) found in cigarette smoke induces genetic mutation at specific regions of the gene's DNA that is identical to the damage

evident in lung cancer cells. This finding is considered to convey precisely how cigarette smoking leads to cancer at the molecular level. This is an example of where the “what” (description) can be sufficiently fine grained to convey the “how.”

In therapy, proposed mechanisms might encompass such constructs as the therapeutic relationship. Research needs to go beyond the demonstrated correlation and even the predictive portion (i.e., on the assumption that the timeline can be firmly established). One way to move closer to understanding mechanisms would be to describe social interaction outside of the context of therapy in relation to neurological or other biological indices (e.g., Adolphs 2003, Meyer-Lindenberg et al. 2005). What changes take place in social interaction? There is still a huge leap between these descriptions and explaining how a relation in therapy leads to symptom change, but this is a start and moves beyond where we are today in the therapy literature.

Moderators as a Path to Identifying Mediators and Mechanisms

Moderators refer to characteristics that influence the direction or strength of the relation between an intervention and outcome. For example, we know that childhood signs of antisocial behavior predict later delinquency in adolescence for boys but not for girls, i.e., sex moderates the relationship (Tremblay et al. 1992). This suggests that different mediators and mechanisms are likely to be involved in the onset of delinquency for boys and girls. The finding is very useful indeed, because any search for mediators that combined boys and girls might not find an effect; a clear effect for boys might be diluted or nullified by the absence of any effect among girls.

Moderators can play a more direct role in elaborating mediators and mechanisms of action, and these have yet to be exploited. Consider an example of the effect of experience during childhood on subsequent criminal behavior, where a genetic characteristic is a mod-

erator. As is well known, children with a history of physical abuse are at risk for later antisocial behavior. Most people who are abused as children do not engage in antisocial behavior. A genetic characteristic moderates the relationship. Abused children with a genetic polymorphism (related to the metabolism of serotonin) have much higher rates of antisocial behaviors than those without this polymorphism (Caspi et al. 2002). Among boys with the allele and maltreatment, 85% developed some form of antisocial behavior (diagnosis of conduct disorder, personality assessment of aggression, symptoms of adult personality disorder, or court conviction of violent crime) by the age of 26. Individuals with the combined allele and maltreatment constituted only 12% of the sample, but accounted for 44% of the cohort's violent convictions. Further research has replicated and extended the finding by noting that parent neglect as well as abuse in conjunction with the polymorphism increase risk for conduct problems and violence (Foley et al. 2004, Jaffee et al. 2005).

So far, this is a fascinating illustration of moderation. However, closer scrutiny is helpful here because it hints at mechanism. Caspi and colleagues (2002) looked at the allele for monoamine oxidase A (MAO-A) because:

- The gene that encodes the MAO-A enzyme that metabolizes neurotransmitters is linked with maltreatment victimization and aggressive behavior;
- A rare mutation causing a null allele at the MAO-A locus in human males is associated with increased aggression;
- Animal gene knockout studies show that deleting this gene increases aggression; and
- Restoring this gene expression decreases aggression.

In one sense we have identified a moderator—the influence of an independent variable (abuse in the home) and outcome (antisocial behavior years later) is influenced by some other characteristic or variable (MAO-A allele). Clearly, we have much more

because the work and the results it generated are beginning to point to the genetic and molecular underpinnings. We do not know how the allele and abuse traverse specific steps from *a* to *z* in which aggression emerges, but we are getting close. For example, recent findings show the neural mechanisms through which the genetic influence is likely to operate (Meyer-Lindenberg et al. 2006). The MAO-A allele is associated with diminished brain circuitry related to impulse control that would promote aggression.

The type of moderator work illustrated here has some characteristics uncommon in the usual moderator research in relation to therapy. In the illustration, the moderator was identified based on considering mechanisms that might be involved. Theory about potential mechanisms, prior correlational evidence (abuse and victimization), and other studies indirectly related served as background. In much of treatment research and moderator research in clinical psychology more generally, moderators of convenience are used, such as information routinely obtained and global indices (e.g., socioeconomic class, ethnicity, comorbidity). There is little sound theory behind the research or predictions that derive from proposing precisely what facets of the moderator might be important in explaining the relation. Thus, there is a vast literature with analyses showing boys and girls, younger versus older, and this ethnic group versus that ethnic group differ. This is fine as a start, but much of the research never gets past the "start." Moderation can lead to insights about mediation, as the example of aggression shows, but it requires tests of ideas about what the mechanisms are or could be.

Direct Intervention and Manipulation

Direct manipulation of a proposed mechanism is of course a powerful way to move our understanding forward. Consider the work on fear conditioning and psychotherapy. There have been decades of research on Pavlovian

conditioning of fear in humans and animals. Conditioning as an explanation of fear acquisition and extinction as an explanation of fear reduction or elimination are useful paradigms for the processes that might be involved in treatment. Research has suggested that extinction is not merely unlearning (elimination of a previously established connection) because the connection is not erased or lost, but rather is actively suppressed through relearning of an acquired inhibition (Myers & Davis 2002).

Understanding the neurological underpinnings of extinction has moved to intervention research. Conditioning and extinction of fear depend on a particular receptor in the amygdala (N-methyl-D-aspartate) (see Davis et al. 2006). Chemically blocking the receptor shortly before extinction training blocks extinction in animal research, a finding that shows a dose-response relation. Blocking the receptor after extinction training also blocks extinction, which suggests that the consolidation process can be interrupted. A compound (D-cycloserine) binds to the receptor and makes the receptor work better, i.e., enhances extinction when given before or soon after extinction training.

The laboratory research has moved to therapy trials where exposure therapy, based on an extinction model, was evaluated to test whether enhancing a mechanism of extinction would improve treatment outcome. An initial controlled trial was completed with individuals who suffered acrophobia (fear of heights) (Ressler et al. 2004). Exposure therapy, one of the most well demonstrated treatments for anxiety, was used as the treatment. The goal was to extinguish fear; exposure to heights was provided in presentations via virtual reality. Presumably, activation of the critical receptor (with D-cycloserine) would improve the effects of exposure therapy (i.e., augment extinction). Indeed, that was found. Participants who received the drug (oral administration two to four hours before each session) showed greater improvements than those who received a placebo. The results were reflected

on several measures of avoidance, anxiety, global improvement, and self-exposures to real-world heights as well as skin conductance, as a measure of anxiety during and after treatment. The effects were evident one week and three months after treatment. The enhanced outcome effects (with D-cycloserine) have been replicated for the treatment of social anxiety (Hofmann et al. 2006).

The model of the research program, i.e., movement from moderators and mediators to mechanisms and from basic to applied research, more than two outcome studies needs to be replicated. Understanding mechanisms of learning and extinction, but also memory, belief, persuasion, control, stress alleviation, anticipation, and so on are within empirical reach in a similar way. Once such mechanisms are studied, potential targets can be identified, with a similar paradigm of manipulating the mechanisms. Manipulation might be through psychological interventions as well as biological ones.

Converging Lines of Work

The prior examples emphasize key elements of the demonstrations such as studying moderators or intervening directly on an intended mechanism. Actually, the emphases are useful but the examples are part of a broader strategy. Multiple lines of evidence are likely to be needed to converge on precisely what the mechanism is. The examples I have provided focus on moderators and mechanisms and underpinnings that are biological. This is not a coincidence; the technological advances for studying biological processes are astounding and in some cases, processes (e.g., neurotransmitter or synapse activity) can be observed in real time. Studying mediators and mechanisms and key theses of this review have nothing inherently to do with biology. The focus on mechanisms and the convergence of multiple lines of work can be gleaned from studying psychological processes and human interaction, as illustrated in research on parenting practices in the homes of young children.

In the 1960s, Patterson and his colleagues began an extensive research program designed to understand the emergence and maintenance of aggressive child behavior (Patterson 1982, Patterson et al. 1992). The studies included directly observing child and parent interaction in the home in a detailed fashion (29 different behaviors and interactions occurring from moment to moment including such behaviors as attending to and unwittingly reinforcing child deviant behavior, using commands, delivering harsh punishment, and failing to attend to appropriate child behavior). Among the many interaction patterns, those involving coercion have received the greatest attention (Patterson et al. 1992, Snyder & Stoolmiller 2002). Coercion refers to a sequence of parent and child actions and reactions that increase the frequency and amplitude of angry, hostile, and aggressive behaviors. The sequence may begin with an argument over some action that has or has not been performed. This intensifies through verbal statements (e.g., yelling, screaming) to more intensive actions (e.g., hitting, shoving). Ultimately, a high-intensity action of one person (usually the child) ends the aversive behavior of the other person (usually the parent). Thus through negative reinforcement (increase in likelihood of a behavior that terminates an aversive condition), children are inadvertently rewarded for their aggressive interactions. Their escalation of coercive behavior is increased in the process, and children are likely to be more aggressive (more often, higher intensity) in the future. The parent behaviors are part of the discipline practices that sustain aggressive behavior. The interaction does not place a single-unidirectional causal relation between the parent and child. Rather, a dynamic interaction exists in which aversive behavior on the part of both parties escalates and does so in a way that systematically programs, fosters, and develops greater deviance in the child.

The parent-child interaction does not necessarily determine the next behavior but increases the probability that the behavior

would move in one direction and toward some end rather than another. Given x (behavior of the parent), y (behavior of the child) is much more likely to occur and so on in the sequence. Conditional probabilities of behaviors were used to describe the interactions leading to aggression. I mentioned previously that there is a way in which meticulous description can blend with and become an explanation. Much of the sequence of interactions was of this type, namely, showing that the interactions fostered aggression and that the timeline was clear.

The studies showing that specific inept child-rearing practices contributed to aggressive behavior served as a model for intervention (Reid et al. 2002). Several studies have shown that changing parent-child interactions (via parent management training) significantly reduces aggressive behavior and related conduct problems (see Kazdin 2005, Reid et al. 2002 for reviews). Thus, a converging set of studies showed a sequence of coercive parent-child interactions leading to escalation, support for a model that explains the interaction (coercion theory and reinforcement leading to escalated aggression), and an intervention that changes putatively critical parenting processes that controvert aggressive child behavior. The unfolding of coercive behavior and effective intervention go very far to suggest the mechanisms involved in onset and elimination of aggression in the home, at least for some children.

General Comments

The discussion highlights examples of treatment-related research that moves from

causal relations toward understanding mediators and mechanisms. I have omitted studies on mediation, which have become relatively common. The reason for omitting these was explained in the discussion of statistical tests of mediation, namely, the studies rarely establish the critical conditions for establishing a timeline and a mediator is not necessarily a mechanism. When the timeline is not established, it is even too much of a leap to imply there is a mediation relation beyond a statistical connection in which the mediator and outcome could be reversed.

RECOMMENDATIONS FOR RESEARCH

Psychotherapy research has a long history of discussing processes of therapy, but little research has addressed the conditions necessary to establish mediators or mechanisms. In general, the investigation of mediators and mechanisms of therapy can be improved in several ways. **Table 2** lists recommendations to enhance our understanding of therapeutic change.

Use Theory as a Guide

The guiding question for treatment research is how does treatment achieve change? The answer may involve basic psychological processes (e.g., memory, learning, information processing) or a broader theory (e.g., motivation). It is no longer sufficient to provide global conceptual views (e.g., psychodynamic, cognitive, or familial) that foster a treatment approach or orientation toward what to do in the sessions. Rather, to ensure progress, specific conceptual models are needed to explain those processes that are responsible for therapeutic change. What is needed further is greater specificity in conceptualizing not only the critical construct but also how that operates to produce symptom change. We need more than tests of mediation to understand mechanisms. Mediation tests of plausible

Table 2 Recommendations for research

1. Use theory as a guide
2. Include measures of potential mediators in treatment studies
3. Establish the timeline of the proposed mediator or mechanism and outcome
4. Assess more than one mediator or mechanism
5. Use designs that can evaluate mediators and mechanisms
6. Examine consistencies across different types of studies
7. Intervene to change the proposed mediator or mechanism

constructs can provide a screening device of sorts to identify potential avenues to be pursued in a fine-grained fashion.

It would be helpful for intervention research to identify “candidate mediators” and mechanisms or plausible constructs that would explain or account for (statistically) therapeutic change, manipulate the proposed mechanism, assess to ensure it has been manipulated, and then evaluate change. For example, in relation to tobacco use among teenagers, several mediators that may serve as useful targets have been identified, including coping skills of the youth, peer influences, and availability of tobacco, among others (MacKinnon et al. 2002). The targets can be the focus of intervention. If one of these targets leads to change in tobacco use, this would serve as an excellent basis for further work to understand exactly how the influence produces change. We need next-step research that begins with theory but tests directly how the proposed mediator operates.

In research training, there is often a strong demand of the investigator to begin with a theory or conceptual model. The study that follows is a test of that theory. However, the goal of research is to end up with an understanding of how therapy works. This goal can be achieved by research that generates hypotheses and theories in addition to research that tests hypotheses. There is far too little research that focuses on generating hypotheses from careful observation and on building theory that can be tested (Kazdin 2003, McGuire 1997).

Include Measures of Potential Mediators in Treatment Studies

The mediator or mechanism ought to be specified so it can be measured. Studies occasionally include such measures (Hofmann 2000, Weersing & Weisz 2002), although their administration has not allowed evaluation of timelines. Yet, measures are available. More fine-grained analyses will be needed to study the unfolding of processes over time and how

a change in some process results in symptom change. As a prerequisite to understanding, assessments of potential mediators ought to be included in treatment studies.

Establish the Timeline of the Proposed Mediator or Mechanism and Outcome

It is important to establish that the proposed mediator is changing before the outcome. The timeline has two requirements: (a) the proposed mediator must be assessed before the proposed outcome, and (b) the “outcome” must also be assessed early to ensure the mediator has in fact changed before the outcome. Even during the middle of treatment, long before the investigator may be interested in therapeutic change, it is quite possible that improvements occur in the client and these improvements come before change in the putative mediator.

Assessment is the main change needed in research. Assessment on multiple occasions during treatment can provide information on the timeline of mediators and mechanisms and outcomes and the possibility of bidirectional changes, i.e., each one influences the other in some way and at different points. Assessment on a session-by-session basis (i.e., every occasion over the course of treatment) permits evaluation of the mediator of change and symptom reduction and considers individual differences in the course of these changes.

Assess More than One Mediator or Mechanism

The accumulation of evidence would profit from the assessment of more than one mediator in a given study. It is rare that one mediator is studied, and hence there may be little value in raising the bar even higher by recommending the assessment of two or more mediators. Recommending the assessment of more than one mediator during treatment means that the assessment battery (e.g., how many measures) will increase as each mediator is added to the

design. In laboratory (efficacy) studies of therapy, the addition of one or two measures during the course of treatment may not be particularly onerous.

The assessment of multiple mediators in a given study has enormous benefits. If two or more mediators are studied, one can identify if one is more plausible or makes a greater contribution to the outcome. In addition, the assessment of multiple potential mediators within individual studies is economically efficient, given the tremendous amount of time and resources needed for any treatment investigation. Across many studies, some mediators may repeatedly emerge as possible contenders while others fall by the wayside.

Use Designs that Can Evaluate Mediators and Mechanisms

Table 3 lists five designs that vary in the assessment of potential mediators or mechanisms of change and treatment outcome. Assume all to be RCTs in which treatment is compared with no treatment. The first and most commonly used design variation omits assessment of potential mediators. RCTs are excellent in demonstrating a causal relation between the intervention and therapeutic change. Yet, the designs that resemble the first variation can say nothing about mediators or mechanisms, even though we as authors often do. In the second design variation, symptoms and possible mediators are assessed at the

same time at pre- and post-treatment. With this variation, conclusions cannot be reached about whether improvements in symptoms influenced the proposed mediator or vice versa, or whether both were altered by another variable.

The third design variation assesses symptoms at pre- and post-treatment, but during the course of treatment (on one or more occasions) the proposed mediator is assessed. The data analyses then evaluate whether the process during treatment contributes to (predicts, accounts for) treatment outcome. This research gives a strong but misleading impression that a timeline is established between some process (e.g., cognitions, alliance) and therapeutic change. The failure to measure symptoms at the same time or indeed before the mid-assessment of the supposed mediator precludes conclusions about whether the mediator comes before symptom change. Just because symptoms were not assessed in the middle of treatment does not mean they did not improve or indeed even improve before the putative process variable.

The fourth design variation improves on the prior designs by including assessment of the proposed mediator and the outcome (symptoms) during treatment. Ideally, there will be more than one assessment occasion during treatment. This variation can evaluate the time sequence, i.e., whether changes in the mediator preceded symptom change and whether symptom change preceded change in

Table 3 Outcome study designs and evaluation of mediators or mechanisms

Design variation	Mechanism assessment			Outcome assessment		
	Pre	During	Post	Pre	During	Post
1. Usual outcome design	N	N	N	Y	N	Y
2. Concurrent study of mechanisms and outcomes	Y	N	Y	Y	N	Y
3. Assessment of mechanism during treatment	N	Y	N	Y	N	Y
4. Assessment of mechanisms and outcomes during treatment	Y	Y	Y	Y	Y	Y
5. Assessment of mechanisms and outcomes all or most sessions	Y	Y, Y, Y, . . .	Y	Y	Y, Y, Y, . . .	Y

Y = yes, assessment is conducted; N = no assessment.

the putative mediator (which may make the mediator an effect rather than a cause). However, if the assessment is only on one occasion during treatment, it is possible that both the proposed mediator and symptom change occurred or appear to have occurred at the same time. Their relation might not be easy to discern and the possibility exists that a third variable led to both changes in the mediator and symptoms.

A disadvantage of the fourth design variation is that it presumes that the course of change for both the mediator and outcome is captured by measuring each of these at only one (or even two) fixed points during treatment. There could be great variation in when the change is made among patients receiving the same treatment. Both the mediator and symptoms may change at different points among a set of patients. The fifth design variation, an extension of the prior design, provides a more fine-grained analysis of change in mediator and symptoms and overcomes this concern. Assessments are made so that one can examine the course of change of the mediator and symptoms and can take into account individual differences in when the changes occur.

Examine Consistencies Across Different Types of Studies

Understanding mediators and mechanisms through which therapeutic change occurs could profit from different types of studies, beyond those that might be construed as therapy research. Conclusions from these studies may be consistent and converge in making a particular process plausible.

Animal laboratory research. Granted, many of proposed mediators of therapy may not be amenable to mouse or zebra fish models. Yet, some of the mediators and mechanisms of therapy might be studied in the lab, and we ought not to be shy about them or shy away from them. I mentioned above the work on fear conditioning and how

understanding key mechanisms of extinction has already improved the effectiveness of extinction-based treatment (Davis et al. 2005). Therapeutically relevant phenomena (e.g., attachment, separation, social support) can be studied in animal research to identify processes (e.g., changes in the structure or function of the brain) and their consequences in behavior. These in turn might direct research to plausible underpinnings to support a conceptual view of the mechanism of therapeutic change. Such tests, far removed from therapy settings, provide important tests of principle. For example, maternal caregiving behaviors (e.g., nursing, licking, grooming) among rats influence the responsiveness to stress in the offspring; the effects can be seen in behavioral as well as from the neurological and endocrine responses of the offspring (e.g., Champagne et al. 2003, Pruessner et al. 2004). This might well be pertinent to understanding stress, coping with stress, and interventions designed to ameliorate stress.

Naturalistic studies. If one is proposing a mediator of change, is there a sample, population, or setting in which this mediator may be expected to vary naturally, i.e., without investigator intervention? For example, if changing parenting style is proposed to explain why a parent- or family-based treatment of a child clinical problem is effective, naturalistic studies examining families with and without these practices and the short- and long-term child behaviors with which these are associated are relevant. Among naturally occurring instances of the process or construct, is there a dose-response relation?

As an example and following up on the prior example of maternal caregiving among rats, naturalistic studies of “normal” mothering have revealed that stress reactivity in human infants is influenced by maternal caregiving (e.g., sensitivity, availability, lack of intrusiveness) during routine activities (e.g., feeding, meal preparation) very much in keeping with the animal research highlighted

above (Hume & Fox 2006). Low-quality caregiving was associated with greater stress reactivity of their infants (e.g., fearfulness, more right frontal brain asymmetry), an effect that could not be explained by infant temperament. Caregiving in relation to stress response and reactivity “behaves” in a similar way across different research paradigms and draws attention to mediators or mechanisms that might be pertinent to therapy (e.g., trauma, stress, coping).

Naturalistic studies by themselves may not permit strong causal conclusions. Yet, such evidence can be enormously helpful. Many advances in understanding cancer, heart disease, and stroke began by looking for variation in putative mediators (e.g., in health habits, diet) among individuals with varied outcomes (e.g., morbidity, mortality). Observing processes that may be operative in the natural environment and their short- and long-term correlates can be very useful, for both generating and testing hypotheses about mediators and mechanisms.

Qualitative research. Qualitative research is an approach to the subject matter of human experience and focuses on narrative accounts, description, interpretation, context, and meaning. Among the key characteristics is the in-depth study of the phenomena of interest. Individual participants or cases are focused on intensely to examine processes, meaning, characteristics, and contexts. Qualitative research is a rigorous, verifiable, empirical, and replicable set of methodologies that encompasses many different disciplines and diverse design, assessment, and data-analytic strategies (Berg 2001, Denzin & Lincoln 2005). In the context of the present discussion, qualitative research might study the process of therapy, how the patient and therapist experience that process, and what might be critical actions or cognitions and how they relate to improvements outside of treatment. Qualitative research can provide a fine-grained analysis by intensively evaluating the richness and details of the process, includ-

ing who changes and how change unfolds, and who does not change and what might be operative there.

Laboratory studies of therapeutic processes. Such studies are viewed with ambivalence because they do not show whether treatment works in “real-life settings.” Controlled studies of therapy in research rather than clinical settings are more important now than ever before. The careful control afforded such research is precisely what is needed to identify mediators and mechanisms. Translational research without knowing what to translate will have a checkered yield in clinical applications of treatment.

Intervene to Change the Proposed Mediator or Mechanism

An excellent strategy is to conduct an experiment in which the proposed mediator is in fact altered or varied across groups, as illustrated in the treatment study cited above on extinction of fear (Davis et al. 2005). Groups randomly composed might be assigned to low, high, and medium levels of a proposed mediator (as a general concept) or mechanism (as a more specific set of steps expected to lead directly to the outcome). Strong support would be evident from findings that outcome varies directly as a function of levels of the manipulated dose.

Intervening to change a mediator is an excellent strategy. Here, too, assessing more than one mediator would be helpful in understanding why change occurred. Intervening to alter the mediator and assessing the level of that mediator (as a check on the manipulation) and two or more plausible, other mediators that are not manipulated would be an elegant way to evaluate mechanisms. In such a study, one can rule out or make implausible some mediators while providing evidence on behalf of another mediator.

A variation of the intervention approach is worth distinguishing, and I refer to this here as “therapy knockout studies.” The term

draws from genetic work (e.g., gene knockout studies with mice) where a particular gene is omitted or altered and the effects are evident on behavior or some other facet suspected to be controlled by the gene. The general model of this research would be a wonderful extension to psychotherapy mechanisms. More specifically, if the investigator believes or theory predicts that a specific mechanism accounts for change, it would be useful to provide the therapy with an added intervention that is designed to “knock out” (inactivate) the mechanism. If role-play, practice, or warm fuzzy relations are critical to the technique, give two variations of the treatment: the original and the original with an effort to inactivate the mechanism. As with any single study, supportive evidence that treatment worked wonders only when the mechanism was allowed to operate could be explained in multiple ways. Even so, this evidence would be a superb addition to accumulating evidence.

SPECIAL CHALLENGES AND OBSTACLES

There are multiple challenges in considering mediators and mechanisms that extend beyond a few changes in designs or measurement strategies. Consider some of the key challenges briefly.

Mechanism-Outcome Relations

The discussion has implied a simple model in which a single mechanism leads to a single outcome or the effects are strong, simple, and linear. Yet multiple variants have implications for conceptualizing, designing, and interpreting research.

Single agent (influence), multiple outcomes. One complexity occurs when a single influence produces multiple outcomes. For example, cigarette smoking leads to several physical and psychological conditions. In some of these, we know there is a causal re-

lation and have identified the mechanism; in others, we know of increased risk. The pervasiveness of the influence of smoking on so many conditions can introduce complexities in the search for mechanisms because so many biological systems are involved. There may be multiple and different mechanisms for the single agent but different outcomes. On the other hand, some common pathways may exist that help focus research.

Multiple influences, single outcomes.

Similar outcomes may be reached through multiple paths. Thus, we do not expect to see all people with a particular characteristic (high kindness, bipolar disorder) to have reached these delineations through the same path. There are multiple paths. The paths may reflect similar mechanisms activated by different experiences or different mechanisms. For example, low IQ could result from genetic, prenatal, cultural, and postnatal toxic (e.g., lead) influences. This “single outcome” has many paths. Essential to work on mediators and mechanisms is distinguishing different courses or paths and moderating influences. Looking for one explanation or mechanism for one group, one therapy, or one outcome may yield little. Conceptual work on possible moderators and exploratory studies (and yes, fishing expeditions) followed by conceptual work will be critical to look for subgroups.

Nonlinear relations. We are trained to think, love statistics that generate, and perhaps even are victims of a cognitive heuristic (I call it slippery-slope thinking) that attracts us to linear relations. Many critical relations are nonlinear. For example, cholesterol and risk for heart disease is positive and linear; higher cholesterol increases risk. Cholesterol and stroke are U shaped, i.e., nonlinear so that low and high cholesterol increase risk. Nonlinear relations propose a challenge in the sense that dose-response relation (as a linear function) is one clue on the path toward mechanisms, although it is not essential. Looking

at means of groups and using statistics that evaluate and search for linear relations can speed or delay progress. We may find a weak relation or no relation between an agent and outcome (e.g., cholesterol and stroke) for the sample as a whole. Analyses of subgroups and tests of nonlinear relations to identify reliable patterns of mediator-outcome relations are a starting point.

Timing of Change. Assume for a moment that 10 patients receive identical treatment over the course of 20 sessions and that treatment works for each of them for the identical reason, i.e., the same mechanism is responsible for change. It is not likely that the process of change will follow the identical time course so that by session 8, for example, the mechanism has changed in a critical way and symptom change is underway. Indeed, apparently the timeline of therapeutic change can be altered by what patients are told about the duration of treatment prior to beginning treatment (Barkham et al. 1996).

Some patients may make rapid or sudden gains at a particular point in treatment (e.g., Tang & DeRubeis 1999). One could say that at a given point, some have and some have not made change in some qualitative or categorical fashion. Alternatively, one could consider that the point of therapeutic change for all individuals is normally distributed with a mean and standard deviation. In either scenario (sudden gains but not at the identical point or normally distributed changes across several points), assessment of the mechanism is a challenge. Assessment of the mechanism at any one or two points in a study may not capture when change in the mechanism has occurred. A challenge for research is ensuring that one can evaluate mechanism and change that may vary in course among individuals.

Everything in Moderation

The effects of an intervention may be moderated in ways that exert enormous impact. For

example, a “standard” dose of psychotropic medication (e.g., for clinical depression) can be an overdose or underdose for people of different ethnicities and countries (Lin et al. 1993). Medication effects are moderated by ethnicity. Among the intriguing issues, would medication effects operate similarly if doses were adjusted to each group, or is this not merely a matter of dose? Either way, evaluating or analyzing data for an overall (main) effect of medication and ignoring ethnicity would lead to a weak effect and not encourage pursuit of mechanisms.

It is possible that the mediator or mechanism of change in psychotherapy varies as a function of a moderator variable. Searching for moderators (a priori or post hoc), testing them (statistical power from dividing of the sample into subgroups), and interpreting them (e.g., is the moderator a proxy for some other variable?) have their own special challenges. Rather than looking for main effects of an intervention and a uniform mechanism of change, we may need to identify and characterize subgroups, very much in the way that genetic researchers often profit from looking at special groups and individual outliers.

Measurement Development

Mediators and mechanisms in therapy are often discussed but validated measures of key constructs are not readily available. Many advances in biotechnology as represented by the continued advances in neuroimaging have had enormous impact on the search for neurological mechanisms, although these assessments have nontrivial interpretive challenges. If by mediators or mechanisms, we will be searching for psychological explanations of action, we will need valid measures. In the parent training literature, mentioned above, behavioral observations were used to show that parent-child interactions unfolded in a sequence leading to (conditional probabilities) child aggressive behavior. Among the many virtues of this work was the assessment of

observable actions and charting a sequence that promotes aggression.

Presumably, many mediators of change begin as broad constructs (e.g., changes in cognition). We need valid measures of such constructs and then demonstration of how the constructs operate. There are promising leads. For example, break down of coping skills in high-risk situations is associated with cocaine and other substance abuse. Treatment often targets coping skills as the critical mediator of change in reducing substance use. A role-play measure (Cocaine Risk Response Test) has been developed, evaluated, and integrated into controlled treatment research to evaluate the mediator (Carroll et al. 1999, 2005). Assessment of mediators and mechanisms raises all of the usual questions in measurement development. The topic has not been accorded sufficient attention.

CONCLUSIONS

Enormous progress has been made in psychotherapy research. This has culminated in recognition of several treatments that have strong evidence in their behalf. Despite this progress, research advances are sorely needed in studying the mediators and mechanisms of therapeutic change. It is remarkable that after decades of psychotherapy research, we cannot provide an evidence-based explanation for how or why even our most well studied interventions produce change.

Many researchers might regard the rather large body of research on the therapeutic relationship as a potential exception. Yet, the vast majority of studies rarely rule out the possibility that the relationship is the result of symptom change or some other variable rather than a mechanism responsible for it. I am not challenging the importance of relationships—in

everyday life, I have tried one or two myself. This is a quarrel about the necessary assessment and design requirements that are infrequently included in research. In addition, assuming the timeline were unequivocally established, we need “next-step” research that clarifies how a relationship in therapy leads to symptom change, i.e., through what specific steps. These steps need to be evaluated.

Prior research has provided important groundwork on which future studies could build. For instance, an increasing number of studies are including assessments during the course of treatment (e.g., Beauchaine et al. 2005, Eddy & Chamberlain 2000, Kolko et al. 2000, Kwon & Oei 2003). The designs used in these investigations represent a great improvement over prior studies and signal progress in research on mechanisms of change. Yet, existing studies have attempted to evaluate only a handful of potential mediators and mechanisms of change.

The scientific study of mechanisms of change is certainly not an easy path on which to embark. A given treatment might work for multiple reasons. Just as there is no simple and single path to many diseases, disorders, or social, emotional, and behavioral problems (e.g., lung cancer, attention-deficit/hyperactivity disorder), there may be analogous complexity in mechanisms for a given treatment technique or therapeutic outcome. Two patients in the same treatment conceivably could respond for different reasons. The complexities are critically important to understand because of a point made above, namely, the best patient care will come from ensuring that the optimal variation of treatment is provided. Understanding mechanisms of treatment is the path toward improved treatment.

ACKNOWLEDGMENT

Completion of this chapter was facilitated by support from the National Institute of Mental Health (MH59029).

LITERATURE CITED

- Adolphs R. 2003. Cognitive neuroscience of human social behavior. *Nat. Rev. Neurosci.* 4:165–178
- American Psychiatric Association. 2000. Practice guideline for the treatment of patients with major depressive disorder (revision). *Am. J. Psychiatry* 157(Suppl. 4):1–45
- Barber JP, Connolly MB, Crits-Christoph P, Gladis L, Siqueland L. 2000. Alliance predicts patients' outcome beyond in-treatment change in symptoms. *J. Consult. Clin. Psychol.* 68:1027–32
- Barkham M, Rees A, Stiles WB, Shapiro DA, Hardy GE, Reynolds S. 1996. Dose-effect relations in time-limited psychotherapy for depression. *J. Consult. Clin. Psychol.* 64:927–35
- Baron RM, Kenny DA. 1986. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J. Personal. Soc. Psychol.* 51:1173–82
- Beauchaine TP, Webster-Stratton C, Reid MJ. 2005. Mediators, moderators, and predictors of 1-year outcomes among children treated for early-onset conduct problems: a latent growth curve analysis. *J. Consult. Clin. Psychol.* 73:371–88
- Berg BL. 2001. *Qualitative Research Methods for the Social Sciences*. Needham Heights, MA: Allyn & Bacon. 4th ed.
- Brent DA, Kolko DJ. 1998. Psychotherapy: definitions, mechanism of action, and relationship to etiological models. *J. Abnorm. Child Psychol.* 26:17–25
- Burns DD, Spangler DL. 2001. Do changes in dysfunctional attitudes mediate changes in depression and anxiety in cognitive behavioral therapy? *Behav. Ther.* 32:337–69
- Carroll KM, Nich C, Ball SA. 2005. Practice makes progress? Homework assignments and outcome in treatment of cocaine dependence. *J. Consult. Clin. Psychol.* 73:749–55
- Carroll KM, Nich C, Frankforter TL, Bisighini RM. 1999. Do patients change in ways we intend? Assessing acquisition of coping skills among cocaine-dependent patients. *Psychol. Assess.* 11:77–85
- Caspi A, McClay J, Moffitt TE, Mill J, Martin J, et al. 2002. Role of genotype in the cycle of violence in maltreated children. *Science* 297:851–54
- Champagne FA, Francis DD, Mar A, Meaney M. 2003. Variations in maternal care in the rat as a mediating influence for the effects of development on behavior. *Physiol. Behav.* 79:359–71
- Davis M, Myers KM, Chhatwal J, Ressler KJ. 2006. Pharmacological treatments that facilitate extinction of fear: relevance to psychotherapy. *NeuroRx* 3:82–96
- Davis M, Myers KM, Ressler KJ, Rothbaum BO. 2005. Facilitation of extinction of conditioned fear by D-cycloserine. *Curr. Direct. Psychol. Sci.* 14:214–19
- Denissenko MF, Pao A, Tang M, Pfeifer GP. 1996. Preferential formation of benzo[a]pyrene adducts at lung cancer mutational hotspots in *P53*. *Science* 274:430–32
- Denzin NK, Lincoln YS, eds. 2005. *The SAGE Handbook of Qualitative Research*. Thousand Oaks, CA: Sage. 3rd ed.
- DeRubeis RJ, Evans MD, Hollon SD, Garvey MJ, Grove WM, Tuason VB. 1990. How does cognitive therapy work? Cognitive change and symptom change in cognitive therapy and pharmacotherapy for depression. *J. Consult. Clin. Psychol.* 58:862–69
- DeRubeis RJ, Feeley M. 1990. Determinants of change in cognitive therapy for depression. *Cogn. Ther. Res.* 14:469–82
- Eddy JM, Chamberlain P. 2000. Family management and deviant peer association as mediators of the impact of treatment condition on youth antisocial behavior. *J. Consult. Clin. Psychol.* 68:857–63

- Foley D, Wormley B, Silberg J, Maes H, Hewitt J, et al. 2004. Childhood adversity, MAOA genotype, and risk for conduct disorder. *Arch. Gen. Psychiatry* 61:738–44
- Grawe K. 2004. *Psychological Therapy*. Cambridge, MA: Hogrefe & Huber
- He J, Vupputuri S, Allen K, Prerost MR, Hughes J, Whelton PK. 1999. Passive smoking and the risk of coronary heart disease—a meta-analysis of epidemiologic studies. *New Engl. J. Med.* 340:920–26
- Hofmann SG. 2000. Treatment of social phobia: potential mediators and moderators. *Clin. Psychol. Sci. Pract.* 7:3–16
- Hofmann SG, Meuret AE, Smits JA, Simon NM, Pollack MH, et al. 2006. Augmentation of exposure therapy with D-cycloserine for social anxiety disorder. *Arch. Gen. Psychiatry* 63:298–304
- Hollon SD, Beck AT. 2004. Cognitive and cognitive behavioral therapies. In *Bergin and Garfield's Handbook of Psychotherapy and Behavior Change*, ed. MJ Lambert, pp. 447–92. New York: Wiley. 5th ed.
- Holmbeck GN. 2002. Post-hoc probing of significant moderational and mediational effects in studies of pediatric populations. *J. Pediatr. Psychol.* 27:87–96
- Horvath AO, Bedi RP. 2002. The alliance. In *Psychotherapy Relationships That Work: Therapist Contributions and Responsiveness to Patients*, ed. JC Norcross, pp. 37–69. New York: Oxford Univ. Press
- Hoyle RH, Smith GT. 1994. Formulating clinical research hypotheses as structural equation models: a conceptual overview. *J. Consult. Clin. Psychol.* 62:429–40
- Hume AA, Fox NA. 2006. Ordinary variations in maternal caregiving influence human infants' stress reactivity. *Psychol. Sci.* 17:550–56
- Ilardi SS, Craighead WE. 1994. The role of nonspecific factors in cognitive-behavior therapy for depression. *Clin. Psychol. Sci. Pract.* 1:138–56
- Jaffee SR, Caspi A, Moffitt TE, Dodge K, Rutter M, et al. 2005. Nature x nurture: genetic vulnerabilities interact with physical maltreatment to promote behavior problems. *Dev. Psychopathol.* 17:67–84
- Kazdin AE. 2000. *Psychotherapy for Children and Adolescents: Directions for Research and Practice*. New York: Oxford Univ. Press
- Kazdin AE. 2003. *Research Design in Clinical Psychology*. Needham Heights, MA: Allyn & Bacon. 4th ed.
- Kazdin AE. 2005. *Parent Management Training: Treatment for Oppositional, Aggressive, and Antisocial Behavior in Children and Adolescents*. New York: Oxford Univ. Press
- Kazdin AE. 2006. Mechanisms of change in psychotherapy: advances, breakthroughs, and cutting-edge research (do not yet exist). In *Strengthening Research Methodology: Psychological Measurement and Evaluation*, ed. RR Bootzin, PM McKnight, pp. 77–101. Washington, DC: Am. Psychol. Assoc.
- Kazdin AE, Nock MK. 2003. Delineating mechanisms of change in child and adolescent therapy: methodological issues and research recommendations. *J. Child Psychol. Psychiatry* 44:1116–29
- Kazdin AE, Weisz JR, eds. 2003. *Evidence-Based Psychotherapies for Children and Adolescents*. New York: Guilford
- Kazdin AE, Whitley MK. 2006. Pretreatment social relations, therapeutic alliance, and improvements in parenting practices in parent management training. *J. Consult. Clin. Psychol.* 74:346–55
- Kenny DA, Kashy DA, Bolger N. 1998. Data analysis in social psychology. In *Handbook of Social Psychology*, ed. D Gilbert, ST Fiske, G Lindzey, Vol. 1, pp. 233–65. New York: McGraw-Hill. 4th ed.

- Kolko DJ, Brent DA, Baugher M, Bridge J, Birmaher B. 2000. Cognitive and family therapies for adolescent depression: treatment specificity, mediation, and moderation. *J. Consult. Clin. Psychol.* 68:603–14
- Kraemer HC, Kazdin AE, Offord DR, Kessler RC, Jensen PS, Kupfer DJ. 1997. Coming to terms with the terms of risk. *Arch. Gen. Psychiatry* 54:337–43
- Kraemer HC, Stice E, Kazdin AE, Offord DR, Kupfer DJ. 2001. How do risk factors work together? Mediators, moderators, independent, overlapping, and proxy-risk factors. *Am. J. Psychiatry* 158:848–56
- Kraemer HC, Wilson GT, Fairburn CG, Agras WS. 2002. Mediators and moderators of treatment effects in randomized clinical trials. *Arch. Gen. Psychiatry* 59:877–83
- Kwon S, Oei TPS. 2003. Cognitive processes in a group cognitive behavior therapy of depression. *J. Behav. Ther. Exp. Psychiatry* 34:73–85
- Lambert MJ, ed. 2004. *Bergin and Garfield's Handbook of Psychotherapy and Behavior Change*. New York: Wiley. 5th ed.
- Lin K, Poland RE, Nagasaki G, eds. 1993. *Psychopharmacology and Psychobiology of Ethnicity*. Washington, DC: Am. Psychiatr. Press
- MacKinnon DP, Lockwood CM, Hoffman JM, West SG, Sheets V. 2002. A comparison of methods to test mediation and other intervening variable effects. *Psychol. Methods* 7:83–104
- MacKinnon DP, Taborga MP, Morgan-Lopez AA. 2002. Mediation designs in tobacco prevention research. *Drug Alcohol Depend.* 68:S69–83
- McGuire WJ. 1997. Creative hypothesis generating in psychology: some useful heuristics. *Annu. Rev. Psychol.* 48:1–30
- Meyer-Lindenberg A, Buckholtz JW, Kolachana B, Ahmad R, Hariri AR, et al. 2006. Neural mechanisms of genetic risk for impulsivity and violence in humans. *Proc. Natl. Acad. Sci. USA* 103:6269–74
- Meyer-Lindenberg A, Hariri AR, Munoz KE, Mervis CB, Mattay VS, et al. 2005. Neural correlates of genetically abnormal social cognition in Williams syndrome. *Nat. Neurosci.* 8:991–93
- Myers KM, Davis M. 2002. Behavioral and neural analysis of extinction: a review. *Neuron* 36:567–84
- Nathan PE, Gorman JM, eds. 2007. *Treatments That Work*. New York: Oxford Univ. Press. 3rd ed. In press
- Orlinsky DE, Rønnestad MH, Willutzki U. 2004. Fifty years of psychotherapy process-outcome research: continuity and change. In *Bergin and Garfield's Handbook of Psychotherapy and Behavior Change*, ed. MJ Lambert, pp. 307–89. New York: Wiley. 5th ed.
- Patterson GR. 1982. *Coercive Family Process*. Eugene, OR: Castalia
- Patterson GR, Reid JB, Dishion TJ. 1992. *Antisocial Boys*. Eugene, OR: Castalia
- Perepletchikova F, Kazdin AE. 2005. Treatment integrity and therapeutic change: issues and research recommendations. *Clin. Psychol. Sci. Pract.* 12:365–83
- Pruessner JC, Champagne F, Meaney MJ, Dagher A. 2004. Dopamine release in response to a psychological stress in humans and its relationship to early maternal care: a positron emission tomography study using [C]raclopride. *J. Neurosci.* 24:2825–31
- Reid JB, Patterson GR, Snyder J, eds. 2002. *Antisocial Behavior in Children and Adolescents: A Developmental Analysis and Model for Intervention*. Washington, DC: Am. Psychol. Assoc.
- Ressler KJ, Rothbaum BO, Tannenbaum L, Anderson P, Graap K, et al. 2004. Cognitive enhancers as adjuncts to psychotherapy. Use of D-cycloserine in phobic individuals to facilitate extinction of fear. *Arch. Gen. Psychiatry* 61:1136–44
- Shrout PE, Bolger N. 2002. Mediation in experimental and nonexperimental studies: new procedures and recommendations. *Psychol. Methods* 7:422–45

- Snyder J, Stoolmiller M. 2002. Reinforcement and coercion mechanisms in the development of antisocial behavior: the family. In *Antisocial Behavior in Children and Adolescents: A Developmental Analysis and Model for Intervention*, ed. JB Reid, GR Patterson, J Snyder, pp. 65–100. Washington, DC: Am. Psychol. Assoc.
- Tang TZ, DeRubeis RJ. 1999. Sudden gains and critical sessions in cognitive-behavioral therapy for depression. *J. Consult. Clin. Psychol.* 67:894–904
- Tremblay RE, Masse B, Perron D, LeBlanc M, Schwartzman AE, Ledingham JE. 1992. Early disruptive behavior, poor school achievement, delinquent behavior, and delinquent personality: longitudinal analyses. *J. Consult. Clin. Psychol.* 60:64–72
- Twain M, Warner ACD. 1874. *The Gilded Age: A Tale of Today*. Hartford, CT: Am. Publ.
- Weersing VR, Weisz JR. 2002. Mechanisms of action in youth psychotherapy. *J. Child Psychol. Psychiatry* 43:3–29
- Whisman MA. 1999. The importance of the cognitive theory of change in cognitive therapy of depression. *Clin. Psychol. Sci. Pract.* 6:300–4
- Zigler E, Glick MA. 1986. *A Developmental Approach to Adult Psychopathology*. New York: Wiley



Contents

Mediators and Mechanisms of Change in Psychotherapy Research <i>Alan E. Kazdin</i>	1
Evidence-Based Assessment <i>John Hunsley and Eric J. Mash</i>	29
Internet Methods for Delivering Behavioral and Health-Related Interventions (eHealth) <i>Victor Strecher</i>	53
Drug Abuse in African American and Hispanic Adolescents: Culture, Development, and Behavior <i>José Szapocznik, Guillermo Prado, Ann Kathleen Burlew, Robert A. Williams, and Daniel A. Santisteban</i>	77
Depression in Mothers <i>Sherryl H. Goodman</i>	107
Prevalence, Comorbidity, and Service Utilization for Mood Disorders in the United States at the Beginning of the Twenty-first Century <i>Ronald C. Kessler, Kathleen R. Merikangas, and Philip S. Wang</i>	137
Stimulating the Development of Drug Treatments to Improve Cognition in Schizophrenia <i>Michael F. Green</i>	159
Dialectical Behavior Therapy for Borderline Personality Disorder <i>Thomas R. Lynch, William T. Trost, Nicholas Salsman, and Marsha M. Linehan</i>	181
A Meta-Analytic Review of Eating Disorder Prevention Programs: Encouraging Findings <i>Eric Stice, Heather Shaw, and C. Nathan Marti</i>	207
Sexual Dysfunctions in Women <i>Cindy M. Meston and Andrea Bradford</i>	233
Relapse and Relapse Prevention <i>Thomas H. Brandon, Jennifer Irvin Vidrine, and Erika B. Litvin</i>	257

Marital and Family Processes in the Context of Alcohol Use and Alcohol Disorders <i>Kenneth E. Leonard and Rina D. Eiden</i>	285
Unwarranted Assumptions about Children's Testimonial Accuracy <i>Stephen J. Ceci, Sarah Kulkofsky, J. Zoe Klemfuss, Charlotte D. Sweeney, and Maggie Bruck</i>	311
Expressed Emotion and Relapse of Psychopathology <i>Jill M. Hooley</i>	329
Sexual Orientation and Mental Health <i>Gregory M. Herek and Linda D. Garnets</i>	353
Coping Resources, Coping Processes, and Mental Health <i>Shelley E. Taylor and Annette L. Stanton</i>	377

Indexes

Cumulative Index of Contributing Authors, Volumes 1–3	403
Cumulative Index of Chapter Titles, Volumes 1–3	405

Errata

An online log of corrections to *Annual Review of Clinical Psychology* chapters (if any)
may be found at <http://clinpsy.AnnualReviews.org>