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Intervention research, theoretical mechanisms, and causal processes related to externalizing behavior patterns

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Abstract
Intervention research with children and adolescents has suffered from a dearth of relevant theoretical grounding and from the lack of a reciprocal "feedback" mechanism by which clinical trials can inform relevant theorizing and conceptualization. There are hopeful signs, however, of increasing confluence between clinical efforts and theoretical models. Indeed, the key issue I discuss is how intervention studies can yield information about developmental and clinical theory as well as mechanisms related to psychopathology. Specific research examples in the field, particularly those emanating from the Multimodal Treatment Study of Children with attention deficit/hyperactivity disorder (MTA study), reveal that probes of moderator and mediator variables can clearly enhance our knowledge of relevant processes and mechanisms. In fact, recent MTA findings have relevance for models of genetic and epigenetic influence on symptomatology related to attentional deficits and hyperactivity. It would be overzealous, however, to make premature claims regarding etiologic variables from intervention research, as treatment studies typically address variables that are causally far "downstream" from primary causal factors and most clinical trials have statistical power that is barely sufficient for main outcome questions, much less mediational linkages. Overall, the field has severely underutilized experimental intervention research to subserve the dual ends of improving the lives of youth and advancing theoretical conceptualization regarding development and psychopathology.

In recent years, hopeful signs have emerged regarding the realizations that clinical research on children and adolescents requires far greater reliance on pertinent theory than has typically been evidenced and that well-designed intervention trials can aid and abet the cause of elucidating relevant conceptualization and theorizing (e.g., Cicchetti & Toth, 1992; Hinshaw & Park, 1999; Kazdin, 1999, 2001; Kraemer, Wilson, Fairburn, & Agras, in press; Rapport, Chung, Shore, & Isaacs, 2001; Rutter & Sroufe, 2000). In the following pages, I address key problems and issues related to the current state of the art, I lay out some requirements for investigators who wish to provide better linkages between theory and treatment (including updated elucidation of the constructs of moderation and mediation based on the cogent work of Helena Kraemer), I give pertinent examples based on my experience as an investigator in the Multimodal Treatment Study of Children with attention-deficit/hyperactivity disorder (ADHD; MTA Study), and I conclude with some predictions and cautions regarding the degree of etiologic relevance that can emanate from well-designed clinical research. At the outset, I emphasize that the overall mission is a large and daunting one, given the recent emergence of developmental psycho-

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pathology as a discipline, the still nascent nature of the field's knowledge of interactions and transactions among causal risk factors for child and adolescent psychopathology, the problems inherent in mounting controlled intervention trials of sufficient magnitude and exactitude to yield relevant data, and the constraining nature of most of our current models and data analytic strategies. I also point out that whereas connections have been made between *prevention* research and theoretical mechanisms for over a decade (Coie et al., 1993; Koretz, 1991), linkages between clinical intervention and such mechanisms are less well developed.

Theory in Treatment Research—Or Lack Thereof

Outcomes, research methods, and processes

Although a definitive review of treatment research for children and adolescents is clearly beyond the scope of this article, some preliminary grounding is important for framing the crucial issue of the theoretical embeddedness and conceptual relatedness of intervention efforts in the field. I begin with what is known about the effects of treatments and proceed to cover empirical and conceptual limitations of current intervention approaches.

In the first place, regarding outcome research, some clear directions have emerged in the past decade. Indeed, in their authoritative review of treatment research with children and adolescents, Weisz, Huey, and Weersing (1998) provide the following opening statement:

> After decades of sowing, weeding, harvesting, and winnowing, workers in the field of child and adolescent treatment research have produced a bumper crop. There are now scores of structured interventions for diverse forms of psychological dysfunction across a broad age spectrum. Research-based treatments exist for a substantial range of clinically significant problems and disorders. Although a majority of the more than 230 named therapies for youths have not been tested empirically . . . dozens of such therapies have been subjected to empirical scrutiny, with beneficial effects demonstrated in more than 300 studies. (p. 49)

Thus, at an overview level, there are clearly positive directions in the field, with intervention efforts increasingly subjected to rigorous experimental investigation. In addition, because the majority of referrals for child and adolescent treatment involve youth with externalizing or disruptive problems—a category that includes such dimensions as inattention/impulsivity/hyperactivity, defiance, aggression, and delinquency (Hinshaw & Lee, 2002)—the majority of such empirically supported treatments reflect efforts with these kinds of child behavior problems.

Second, what is the magnitude of treatment effects of extant interventions for such problems? Meta-analyses of published, experimental clinical trials (e.g., Weisz, Weiss, Han, Granger, & Morton, 1995; see review in Weisz et al., 1998) reveal that, at a composite level, psychosocially treated groups surpass control groups across a host of outcome measures, with effect sizes ranging between medium and large. Thus, in terms of omnibus findings, it is clear that treatments for children and adolescents "work." Interestingly, effect sizes are roughly similar for internalizing and externalizing or disruptive problems of children and adolescents. I point out, as well, that some outcome studies for aggressive, externalizing behavior have yielded effect sizes that are quite large, even for such supposedly intractable problems as aggressive, recurrent adolescent delinquency (e.g., Henggeler, Schoenwald, & Pickrel, 1995; McMahon & Wells, 1998). On the other hand, with respect to ADHD, the preponderance of evidence points to the superiority of pharmacologic over psychosocial treatments, at least in terms of immediate reduction of core symptoms (Hinshaw, Klein, & Abikoff, 2002; MTA Cooperative Group, 1999a).

Third, despite the positive overall picture, a closer examination of treatments for the typical child or adolescent referred for clinical services reveals a far more sobering outlook. It is clear that so-called research therapy (intervention involving specifically recruited, rigorously selected, homogeneous samples, with a narrow problem focus, treated by specially trained clinicians with limited caseloads and following strict treatment manuals that are

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typically behavioral in nature) has yielded appreciably higher effect sizes than so-called clinic therapy, demarcated by treatments of clinic-referred, heterogeneous, multiproblem cases treated by clinicians with large caseloads and utilizing eclectic, nonbehavioral methods (Weisz et al., 1998). In fact, the average effect sizes for the rare published trials of such clinic therapy are quite low, bordering on zero (Weisz, Donenberg, Han, & Kauneckis, 1995). Thus, the gains evidenced from the kinds of behavioral or cognitive–behavioral interventions utilized with relatively unimpaired youngsters in university-based trials have not yet begun to translate into meaningful benefit for the types of seriously impaired, problem-laden, comorbid youth most often treated in real-world community clinics. This "disconnect" between research- and clinic-based therapy is a major issue for the field.

A related but broader perspective is found in the ongoing debate over the relative merits of "efficacy" investigations, which prioritize internal validity of experimental clinical findings via tightly controlled study of homogeneous, selected samples treated via manualized protocols, versus "effectiveness" investigations, which focus on the external validity or generalizability of clinical gains to the actual world of treatment (e.g., Chambless & Hollon, 1998; Hoagwood, Hibbs, Brent, & Jensen, 1995; Nathan, Stuart, & Dolan, 2000; Seligman, 1995). Whereas the gold standard for efficacy research involves randomized clinical trials (RCTs), which yield the strongest basis for making causal inference regarding treatment effects, effectiveness studies require broader samples treated in real-world conditions, with random assignment not always possible or feasible. The question is whether the kinds of research therapies evaluated on the basis of efficacy trials can demonstrate effectiveness in the real world of highly comorbid and heterogeneous samples and of professional therapists with large caseloads (as opposed to handpicked and extensively trained research staff). Note, however, that despite the extremes painted by this type of description, the terms efficacy and effectiveness do not constitute a true dichotomy. Rather, they signify the poles of a continuum related to the relative importance of internal versus external validity (Chambless & Hollon, 1998). Indeed, it is possible to perform clinical trials of randomly assigned treatments that can still meet the objectives of generalizability, real-world impact, and exportability; it is also possible to expect that clinicians in the community can adopt means of appraising the outcomes of their patients with more rigor than is typically done. In all, there is considerable distance to travel if the gap in effect sizes between research therapies and clinic therapies is to be bridged.

How the field chooses to evaluate therapeutic efforts has enormous impact on the types of inferences that can be made regarding the effects of therapy as well as how therapy exerts such effects. The advantages of experimental investigations or RCTs for making causal inference are unquestioned (Cook & Campbell, 1979). Ethical, economic, and real-world constraints, however, severely delimit the ability of most practitioners or managers of mental health care to randomly assign patients to alternative treatments or to untreated control groups. Although it is unreasonable to make a plea for wholesale adoption of controlled research in all facets of health and mental health care, three key points are salient. First, experimental trials of untested treatments may well be the most ethical steps that can be taken, especially in light of the huge numbers of medical, as well as mental health, interventions currently offered that have never been evaluated for efficacy or effectiveness. Of course, enlightened utilization of controls and thorough respect for the dignity and treatment needs of consumers is paramount in such efforts. Second, the oft-voiced critiques of RCTs—that representative populations of participants cannot be recruited and selected or that results of clinical trials can never generalize to the "real world" (see Seligman, 1995)—may be inaccurate. Indeed, experimental trials can incorporate such features as client and therapist choice of interventions and tailoring of treatments to the individual needs of participants (Jacobson & Christensen, 1996). Third, experimental clinical trials have untapped potential for establishing not only outcomes of treatment but also process–outcome linkages of relevance

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to developmental and clinical theory (Weersing & Weisz, 2002). In fact, the levels of confidence in inferring both causal influence and viable process–outcome linkages from RCTs so far outweigh the inferences that can be made from the best-intentioned naturalistic studies that the former must be promoted whenever feasible. In sum, a key contention of this article is that examinations of therapeutic processes and of moderator and mediator variables, embedded in sound clinical trials, have untapped potential for subserving the dual ends of helping children and families in clinical need and enhancing the field's theoretical understanding of both therapy and psychopathology.

Overall, where is the field? Clearly, there are signs of real hope and real progress, as indicated by published accounts of empirically supported treatments for children and adolescents (Hibbs & Jensen, in press; relevant chapters of Nathan & Gorman, 2002; Pelham, Wheeler, & Chronis, 1998) and the increased focus on linking research with practice as well as with theory (e.g., Cicchetti & Toth, 1999). On the other hand, key issues remain unsolved. For instance, overwhelming stigma still surrounds mental disorder, delimiting treatment seeking (Hinshaw & Cicchetti, 2000; U.S. Department of Health and Human Services, 1999); countless children and families do not have access to adequate insurance coverage or sound treatment; intervention services are fragmented and uncoordinated, and—as indicated above—the promise of laboratory- or university-based experimental treatments has not been realized in the real world of children and adolescents who require intervention. Furthermore, as discussed by Rutter and Sroufe (2000), the potential for experimental treatment studies to illuminate relevant processes, mechanisms, and causal explanations has been virtually untapped to date (see also Loeber & Farrington, 1997; Weersing & Weisz, 2002).

Conceptualization and theory

At a more fundamental level, there is great question about the theoretical and conceptual bases of most treatments that have been offered, evaluated, and promulgated for child and adolescent clients (for a clear statement of the problem, see Kazdin, 1999). This issue goes hand in hand with the one noted just above, namely, that the field has seldom taken advantage of the opportunity for intervention research to inform pertinent theory and conceptualization. Thus, clinical practice, on the one hand, and intervention research, on the other, tend to pursue separate agendas (Nathan et al., 2000) and both suffer from the loss of enhancement and infusion by relevant theory.

At one level, the treatments that are most often evaluated and shown to be effective in the field—behavioral interventions—are empirically derived, without much focus on developmental mechanisms of change other than the invocation of learning principles (for a clear exception, see Dishion & Patterson, 1999). The relevance of theory in behavioral and especially radical behavioral accounts of learning and behavior change is still actively debated (e.g., Goldfried, 1999). That is, we know that behavioral procedures "work" in terms of reducing symptoms or enhancing relevant skills, but we do not know nearly enough about how or why these treatments yield their effects or about the individual difference variables, developmental stages, or cultural contexts in which clinical benefits are optimized. Furthermore, behavioral interventions may show clinical benefits without illuminating causal processes relevant to psychopathology. Indeed, the review of Weersing and Weisz (2002) showed that behaviorally oriented treatments for children's fears and anxieties were less likely than other intervention modalities to measure putative process or mediational factors.

At another level, intervention strategies with a more explicitly theoretical focus (e.g., dynamically based play therapies) have yielded far less convincing evidence for treatment efficacy, much less effectiveness. We are therefore left with the uneasy contention that those treatments with the most conclusive evidence for positive benefits are exerting their effects in theoretically ungrounded ways or are altering behavior patterns without necessarily enhancing deeper change at the level

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of personality variables or family structural change. This latter point is crucial, given the highly embedded nature of nearly all child and adolescent psychopathology in terms of family, school, and community context and interaction patterns.

Even more fundamentally, the problem of theoretical impoverishment may reflect the ignorance of the entire field with respect to causal factors for healthy, as well as pathological, functioning. Despite the tremendous strides our field has made in recent decades (e.g., Cicchetti & Cohen, 1995; Sameroff, Lewis, & Miller, 2000), our core knowledge of the role of basic brain mechanisms, gene–environment correlations and interactions, family systemic factors, and community context in causing and shaping psychopathology is still rudimentary (see discussion in Wakefield, 1992). From this perspective, treatment efforts are theoretically impoverished because of a fundamental lack of knowledge of development, cognition, emotion, social behavior, self-regulation, and related concepts, as well as their interactions and transactions with one another. As a result, translational research—encompassing an approach in which the best basic science is directly and intentionally applied to clinical research efforts and clinical intervention—is a priority, as is clinical research with direct implications for theory building and testing (Institute of Medicine, 2000).

Overall, experts in the field have taken markedly variable stances regarding the importance or necessity of theory for intervention efforts. Whereas some contend that theoretical models and concepts are essential aspects of the development and application of treatment strategies (Kazdin, 1999, 2001), others claim that, at their worst, theories may constrain and even distort scientist–clinicians who aim to effect clinical change (e.g., Fonagy, 1999; Goldfried, 1999). Thus, despite its potential for providing an overarching guide to conceptual relations among psychopathology and intervention strategies, theory can also be used to reify "schools" of therapy, with consequent rigidity of language and thinking.

Taking a practical approach to the lack of theoretical basis for most therapeutic efforts in the field, Kazdin (1999) opens his conceptual overview with the following statement:

> Very little in the way of theory guides therapy research and hypotheses about mechanisms or moderators of change. The net effect is that we really do not understand very much about therapy, why and how it achieves change and for whom it is and is not effective and why, and how to optimize therapeutic change. (p. 533)

He further distinguishes theories (explanatory statements that account for relations among variables and relevant processes) from approaches (overall orienting perspectives, like psychoanalytic or social learning) and theories of dysfunction (which involve knowledge of risk and protective factors, pathways, developmental trajectories, and the like) from theories of therapeutic change, which he defines as comprising conceptual underpinnings of change processes. In short, Kazdin (1999, 2001) contends that without sound theory regarding variables and processes that build and maintain both adaptive and maladaptive patterns of cognition, emotion, and behavior, the field will be unable to make the types of major leaps forward that are urgently needed.

It is important to note, however, that theories of dysfunction are not commensurate with theories of clinical change. That is, how and why an individual or family changes in therapy may or may not invoke the same kinds of factors and variables that led to their condition in the first place. The so-called treatment–etiology fallacy is, in fact, well known (e.g., Cowan, 1989). In medicine, for example, many interventions take place with respect to "levels" that may be far removed from the genetic or psychosocial causal factors that led to the underlying medical problem. For hypertension, diet and exercise regimens or medications that thin the blood can be effective without dealing fundamentally with the genetic propensities or life stressors that led to the high blood pressure in the first place. The same can be claimed for cognitive therapy for depression, an empirically supported treatment targeting cognitive distortions that may actually be secondary manifes-

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tations of depressive disorders rather than primary causes. For productive discussion of the entire issue, see Meehl (1973).

On the other hand, the clear fallacy of contending that treatments must always be directed at primary causes does *not* negate the important point that treatment efforts of the future will stand a far greater chance of succeeding if the field appreciates the causal risk factors (Kraemer et al., 1997) for psychopathology. Thus, the more medicine knows about the genes that relate specifically to medical disorders and to the cellular and physiologic states that accompany disease, the more specific and targeted medical treatments can be. Recent treatments for cancer have, in fact, benefited dramatically from increases in basic knowledge about the development of metastatic cells, allowing such treatments to be directed rationally and intentionally at underlying mechanisms. I point out that the field of prevention science (Coie et al., 1993) is predicated on the proposition that effective preventive intervention *requires* thorough knowledge of relevant risk factors that exert causal influence on outcomes of interest. In short, whereas knowledge of causation is not always essential for treatment, it certainly can be if specific, modifiable, causal risk factors are understood. It also appears particularly relevant for prevention efforts (Koretz, 1991).

Thus, regarding theory, at the one extreme are grand, unified theories of psychopathology, which may have outlived their usefulness for generating testable conceptual or intervention-related hypotheses; at the other are theory-free demonstrations of empirical relations (e.g., technique *X* effects change in outcome *Y*), which are limited in their ability to promote broader benefit because of a lack of understanding of core mechanisms of change. In between lies the productive middle ground of micro-theories or conceptual models (see Dishion & Patterson, 1999) pertaining to (a) causal risk factors and maintaining factors for psychopathology, (b) specific interactive linkages among and between multiple levels (genetic, psychobiological, familial, peer-related, wider social contexts) of causal variables, and (c) intervention processes linked to meaningful clinical change. Experimental clinical research can serve a valuable function by providing an optimal means of evaluating such factors, processes, and models.

In the next section, I provide more explicit discussion of how the field might link relevant theory and conceptualization to outcome research, through consideration of factors that constrain and qualify outcome relationships (i.e., moderator variables) and processes through which intervention strategies yield outcomes of interest (i.e., mediator variables). Such work involves an iterative, active process: interventionists must consider extant theory and conceptualization regarding the choice and implementation of particular treatments as well as the selection of outcome and process measures; and the results of carefully designed treatment investigations must be translatable into information of clear relevance for developmental and clinical theory.

Moderators and Mediators and Their Relation to Outcome

Definitive research on the etiology of mental disorders requires state of the art, multilevel, and integrative research on genetic, psychosocial, and interactive risk factors. Intervention research can be part of this process, albeit with the more limited goal of increasing understanding of change mechanisms and maintaining factors, through specific focus on moderator and mediator processes. Thus, experimental intervention studies provide an unprecedented opportunity to understand causal mechanisms, but the types of independent variables in such investigations are not, for obvious ethical reasons, inclusive of differing alleles of genes, of radically different rearing environments (e.g., abusive vs. nonabusive homes), of delinquent versus prosocial peers, or of safe versus violent neighborhoods, to mention just four examples that have garnered evidence as causal risk factors for externalizing behavior (Hinshaw & Lee, 2002). Still, if the intervention-related variables that *can* be manipulated ethically are linked to relevant theory (e.g., two different interventions emanating from different models of causal processes related to psychopathology) and, if relevant, conceptually derived measures are

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included in the process and outcome battery, the experimental nature of RCTs can be utilized to maximum conceptual and theoretical advantage.

Indeed, Weisz et al. (1998) and Kazdin and Weisz (1998) prioritized the identification of factors related to the specification of clinical subgroups for whom given treatments may be most applicable, conditions under which treatment effects are optimized, and processes through which treatments exert their effects. These statements recall similar pleas, in the adult therapy literature of many years ago, for transcending the simple (though still vital) question of "does therapy work" to more complex questions of which therapies work for which patient subgroups and why (e.g., Kiesler, 1966; Paul, 1967). The subgroup question (which therapies work best for whom) pertains to the identification of *moderator* variables; the "how and why" questions (related to processes and mechanisms underlying therapeutic change) relate to the identification of *mediator* variables (see Kazdin, 1999; Kraemer, Stice, Kazdin, Offord, & Kupfer, 2001; Weersing & Weisz, 2002).

Baron and Kenny model of moderators and mediators

In a classic, highly cited work from the field of social psychology, Baron and Kenny (1986) illuminated the concepts of moderation and mediation from both conceptual and data analytic perspectives. A moderator is a variable that alters the magnitude or even direction of the relationship between two other variables. Termed an effect modifier in the vocabulary of epidemiology, a moderator variable specifies the conditions under which or subgroups in which a statistical association of interest occurs. Most often conceptualized as discrete variables (for example, ethnicity, which would be a moderator if the relation between anxiety and performance differs between, say, African-American and Asian-American participants), moderators may also be continuously distributed (e.g., socioeconomic status [SES]). A mediator, on the other hand, is a variable through which a given association occurs or transpires. To that extent, it constitutes an explanatory variable. Whereas Baron and Kenny (1986) contend that establishing moderation typically involves examining whether the putative moderator variable statistically interacts with the predictor in relation to the criterion variable (e.g., through multiple regression equations) such that the association differs at different levels of the moderator, positing mediation is more complex (though it can be tested via multiple regression as well). That is, for mediation to occur, (a) the predictor must show significant association with the criterion, (b) the predictor must show significant association with the putative mediator and the putative mediator with the criterion, and (c) the predictor–criterion relation must attenuate or dissipate when the mediator variable is statistically controlled. In this way, the predictor–criterion relation is said to be mediated or explained by the mediator variable.

Baron and Kenny (1986) provide excellent statistical and conceptual explanation of these concepts, incorporating structural equation modeling as well as multiple regression approaches to their verification. In addition, Holmbeck (1997) provides a cogent elaboration and clarification, with examples from clinical and pediatric psychology as to their application and (all too often) misapplication. In particular, Holmbeck describes the mistaken attribution of mediation in situations that actually demonstrate moderation and the overzealous claim of mediation in situations where no predictor–criterion association has been found in the first place. He contends that the latter situations are examples of indirect effects rather than mediation per se.

Elaboration and extension to clinical trials by Kraemer

To provide a framework for discussion of moderation and mediation with respect to treatment research, Kraemer et al. (in press) first discuss the usual conditions and assumptions of a clinical trial. In the typical hypothesis-testing approach, the average response of participants in the intervention condition (or conditions, in a comparative treatment RCT) is contrasted with the parallel response in the

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control (or alternate treatment) condition, with random assignment the key experimental feature used to infer causal relations between intervention and outcome. Note that it is the effect size of the intervention rather than its statistical significance per se that has important policy implications (see Kraemer et al., 1999, in press). However, even when statistically reliable and strong enough to warrant clinical attention, the average response is clearly *not* manifest in each and every participant; this variability of response to treatment is crucially important to explore. Such variability is likely to be greater in an effectiveness study than in an efficacy trial, given that heterogeneous, real-world participant selection is likely to characterize the former. Thus, although the core objective of a clinical trial is to answer, as unambiguously as possible, the core outcome question, far more information can be gleaned from appropriate analysis of moderators and mediators, which help us to understand the variability in treatment and comparison groups. Such analyses go far beyond the disparaging terms of "fishing" or "hunting" explorations, as they provide illumination of the processes of change (Kraemer et al., in press).

When moderation and mediation are extended from field research to clinical trials, conceptual and methodologic confusion is possible. In fact, Kraemer et al. (2001, in press) contend that the mathematical models underlying moderation and mediation are quite similar, if not identical, as both concepts ultimately involve the interaction of treatment assignment with the putative moderator or mediator. Hence, conceptual distinctions are mandated.

Moderation. In RCT, Kraemer et al. (in press) define a moderator as a variable that, by definition, occurs prior to randomization. Examples include participant gender or SES, severity of initial psychopathology, comorbidity, intelligence, sociocognitive information processing skills, neighborhood factors, and the like. Crucially, putative moderator variables are measured before the participants are randomly assigned to treatment conditions. This temporal "location" prior to treatment, (i.e., the status of putative moderators as baseline variables) is crucial for unambiguous interpretation of moderator versus mediator effects. Indeed, because of their baseline status, potential moderator variables are, by definition, uncorrelated with treatment assignment. As a result, when examining treatment effects within subgroups defined by cutoff scores on moderator variables (e.g., in high vs. low SES families), the investigator can be reasonably certain that the initial randomization is preserved within these subgroups. An exception could occur when randomization "breaks down" in numerically small subgroups, but moderators are theoretically uncorrelated with assignment to treatment.

As shown mathematically in Kraemer et al. (2002), if O is the response or outcome variable, T is treatment condition, and M is the putative moderator, the following formula applies:

$$O = \beta_0 + \beta_1 T + \beta_2 M + \beta_3 MT + \text{error}.$$

Here, β_0 is the intercept, β_1 is the main effect of treatment, β_2 is the main effect of the putative moderator, β_3 is the interactive effect of the putative moderator with treatment, and error is measurement error, which is assumed to be uncorrelated with both treatment and the putative moderator variable. Note that in treatment or prevention research, if a baseline variable is associated with treatment response equally across treatment groups (or equally across treatment and control conditions), it is considered a *predictor* of outcome (Kraemer et al., in press; Owens et al., in press). Hence, a significant value of β_2 indicates prediction. On the other hand, if β_3 is significant and of reasonable magnitude, the implication is that the baseline variable (M) is differentially associated with treatment response across conditions, therefore serving as a moderator.[1]

1. It is important to note the specification of Kraemer et al. (in press) that moderator and mediator variables can be identified only in the context of a *contrast* between two or more treatment conditions. As a result, although analyzing correlates of treatment response to a single intervention may be helpful for uncovering variables

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When moderation is evident, the investigator examines subgroups defined by the moderator variable (e.g., high versus low SES or comorbid versus noncomorbid participants). Indeed, as developed in the section on the MTA study, considering potential moderator variables as dichotomous may greatly aid in their clinical interpretability. Examination of these subgroups helps to specify *where* a treatment effect is "located" in the sample of interest—that is, in which subpopulations—generating more specific causal hypotheses for subsequent research. As stated by Kraemer et al. (in press, p. 4) " . . . moderators may identify subpopulations with possibly different causal mechanisms or course of illness. Thus moderators may also provide unique new and valuable information to guide future restructuring of diagnostic classification and treatment decision making."

Recent moderator findings in the field of adult intervention are provocative. For example, Smeraldi et al. (1998) found that a polymorphism within the promoter region of the gene regulating the serotonin transporter moderated the effects of antidepressant medication on outcomes of clinical importance. That is, the efficacy of the medication depended on the presence (vs. nonpresence) of the specific allele. Appropriate moderator studies may therefore have great relevance for specifying, not only the environmental or phenotypic "types" for which treatments show optimal effects, but also which genetic makeups predict response to intervention. Such results have potentially far-reaching implications for aiding the cause of "matching" patients to treatments, an objective that is still a crucial (although elusive) goal for many in the field. Note, however, that the identification of genetic moderators, in the example given, still begs the question of identifying *how* the polymorphism's influence on the transporter molecule affects medication responsivity—that is, the mechanism by which treatment response in the particular subgroup was *mediated.*

Mediation. Mediator variables relate to detection of *how* and *why* a treatment exerts its effects on pertinent outcomes. A mediator signifies a process through which a treatment works. Unlike moderators (which, by definition, are baseline measures), mediators occur after random assignment, exerting their effects during the period of active intervention. As such, they are correlated with treatment assignment. Note that the same variable could be used as a moderator or a mediator, but temporal ordering is salient: whereas baseline level of a child's academic achievement might moderate treatment outcome (e.g., social skill), the *change* in achievement during intervention could mediate treatment response with respect to social skill.

Utilizing the same mathematical formula as found above for moderation, a mediator is defined as the variable M with either a main effect (full mediation; $\beta_2 > 0$) or an interactive effect with treatment (partial mediation; $\beta_3 > 0$) on the outcome of interest. The interactive effect is more intuitively obvious: The mediator influences outcome more strongly in the treatment than in the control group or in treatment group A versus treatment group B, showing that it signifies a relevant process through which the treatment exerted its effects. The main effect, however, is also possible, in which the mediator influences outcome even though it does not do so differentially across treatment and control conditions (Kraemer et al., in press).[2]

of potential conceptual relevance, such analysis does not, by definition, uncover moderators of mediators. Moderation, in particular, involves the specification of *differential treatment response in different subgroups*, identified by the moderator variable.

2. Another situation could occur as follows: a post-random-assignment variable (which cannot, by definition, be a moderator) is *not* influenced by treatment (thus, it cannot be a mediator), yet it has an interactive effect with treatment on the outcome. In this case, the *treatment condition serves as a moderator of that variable* (Kraemer et al., in press). Kraemer et al. consider the example of a treatment program for depression in which the losses of participants' family members or contacts are tracked during treatment. If those in active intervention cope better with the loss experience than those in the control group or alternate treatment group, treatment could be said to moderate the reaction to such

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Thus, the distinction between moderators and mediators is made on conceptual grounds: (a) temporal order (moderators are baseline measures, mediators occur after treatment assignment) and (b) association (moderators are inherently uncorrelated with treatment assignment, mediators are associated with such assignment). Note that, because putative mediators follow random assignment to treatment, they are not "protected" by randomization. Mediators could therefore represent influences of selection bias or other factors not associated with the treatment variable per se. Thus, although not inherently causal of outcome, mediators may help to gain understanding of the processes by which treatment exerts its effects. Moderation and mediation may work simultaneously, as well. Weersing and Weisz (2002) provide the helpful reminder that mediation may not initially be detectable because of the potential for moderation of mediator effects (i.e., mediator processes occur only in certain subgroups).

An initial example of mediation pertains to the understanding of attrition during treatment. Attrition, of course, is not a baseline variable but rather a response that occurs during the intervention period. Following the primary analyses of a clinical trial, which consist of intention to treat (ITT) analyses of *all* participants initially randomized (Hinshaw, 1999), analysis of "completers" (those not showing attrition) may help to understand how a treatment works for those participants who actually received the full intervention. Yet such analysis undoubtedly engenders selection biases, as differential attrition across treatment arms is not random. Understanding that completer analyses are mediational in nature prevents the erroneous conclusion that restricting outcome analyses to participants completing the entire intervention is an unbiased estimate of treatment effects.

Other mediator variables could include response of participants to a particular domain (e.g., how well a treatment influences peer relations), which is then examined for its association with the outcome of primary interest (e.g., reduction of delinquency). Once again, if (a) the treatment exerts effects on the outcome of interest (in this example, delinquency), (b) the putative mediator (peer relations) is influenced by treatment and associated with reduction in delinquency, and (c) this variable interacts with treatment assignment (or even exerts a main effect) in relation to outcome, then the intervention's outcome is explained or mediated by its effects on enhancing peer relations. Such mediators carry important theoretical implications, pointing to processes by which treatments exert their effects and aiding in the search for intraindividual, social, or wider factors that maintain, propel, or decrease psychopathology.

Finally, Kraemer et al. (in press) point out that mediator variables must be preselected with an eye toward theory. It makes no sense, for instance, to claim mediator status for a variable that is quite highly associated, postintervention, with the outcome of interest, as such a variable may simply be an alternate outcome measure. Similarly, initial change in the outcome measure early in treatment could meet criteria for being a mediator, but in such a case the mediation is mathematically significant but conceptually trivial. Mediators should be measured during the course of treatment or should reflect change during the period of intervention (rather than constituting postintervention variables), because it is impossible to assert temporal precedence of the mediator if both it and the outcome are measured simultaneously (Weersing & Weisz, 2002).

Implications of significant moderation or mediation. In the framework of Kraemer et al. (2001, in press), analysis of moderator and mediator effects is secondary to the primary, hypothesis-driven analyses that address the core aims of the clinical trial. Hence, one should typically not design a clinical intervention study around detection of moderator or mediator effects. For one thing, the study may barely contain adequate statistical power to address the core clinical hypotheses, much less the potential moderator or mediator vari-

a stressor, signifying that the variable may still be important for identifying a process through which treatment is shown to exhibit its effects. A cogent example regarding parental discipline is found in the subsequent section on the MTA study (Hinshaw et al., 2000).

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ables. For another, the range of potential moderators or mediators may be large, potentially requiring severe reduction of per-comparison alpha levels in the service of experiment-wise protection. Moderator and mediator analyses are therefore exploratory, but not in a pejorative sense of that term.

What, then, are the implications of moderation and mediation (Kraemer et al., in press)?

> Any strong moderator should be considered as a stratification variable in the next RCT (randomized clinical trial), and a formal test . . . done on the now "a priori" hypothesis of a moderator x treatment interaction. . . . Any strong mediator should be considered in restructuring treatments to be evaluated in the next RCT, and a formal test there done on the now "a priori" hypothesis that the treatment effect would be increased by appropriate manipulation of mediators. (p. 18)

Thus, moderator and mediator variables should be explicitly incorporated into the next generation of treatment research in a given field. Meaningful moderator or mediator variables identified in RCTs can also be investigated in the nonintervention research, as risk or protective factors. In all, moderator variables and mediator processes may provide unprecedented evidence of potentially causal relations operating with respect to child and adolescent psychopathology, providing a major conceptual step forward, although (a) their relevance for understanding primary causes of psychopathology may be limited with respect to intervention research, which usually targets maintaining, rather than truly etiologic, factors; and (b) mediator variables are not protected by randomization and may thus incorporate selection biases and other confounding forces.

Summary. Potential confusion in a clinical trial as to whether a variable is a mediator versus a moderator can be resolved by specifying (a) temporal precedence (moderators are baseline variables, mediators follow the treatment assignment) and (b) correlation (moderators are uncorrelated with treatment assignment, mediators are correlated with intervention). Both types of variables may be valuable for explanation, with moderators specifying subgroups of interest and conditions under which treatment effects are optimized and mediators elucidating processes through which treatment effects operate and psychopathology or impairment may be diminished. Of necessity, moderator and mediator analyses are secondary to the core hypotheses in a clinical trial, yet they are an essential part of the ongoing process of linking theory and conceptual models to intervention research.

Extant Literature Linking Outcome Research to Theoretical Mechanisms and Processes

Although the preceding discussion provides a set of guidelines for enhancing the conceptual and theoretical yield from treatment outcome research, extant literature that provides clear tests of moderator variables and, particularly, mediator processes in child and adolescent research is extremely limited. The reader should note, however, that (a) many child interventionists include potential moderator and mediator variables in their assessment batteries even if formal tests are not conducted (Weersing & Weisz, 2002) and (b) conceptual contributions from intervention research can be found even in the absence of evaluation of moderator and mediator processes. For example, nearly two decades ago Coie and Krehbiel (1984) presented a provocative investigation of two contrasting interventions for children with the dual problems of academic underachievement and peer rejection. In brief, they contrasted academic tutoring, social skills group treatment, the two factors combined, and an untreated control group, with outcome measures intentionally spanning both achievement and social reputation. In this way, they intentionally evaluated the specificity or generality of the treatment strategies. The results showed that academic remediation ameliorated both academic skills and social performance, whereas the social intervention produced gains that were far more limited. Furthermore, only the academic skill intervention yielded effects that maintained for a year posttreatment. Although (like any single intervention) this report cannot be considered definitive and although the two interventions were not matched for intensity, it

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is noteworthy in its suggestion that treatments with different targets showed different levels of emanative effects into domains of conceptual interest.

Similarly, in an investigation of a low-risk sample of families and children experiencing the transition to kindergarten, Cowan and Cowan (2002a) contrasted group interventions focusing on parenting strategies versus couples communication. Couples intervention yielded improvement in terms of both couple interaction and parenting, whereas the parenting intervention showed specific effects on parental skill but did not reciprocally affect couple interaction. In addition, the two interventions showed differential patterns of outcome with respect to the child's internalizing versus externalizing behavior problems. Again, although formal tests of mediational processes were not performed, the conceptual yield was rich (see also Cowan and Cowan, 2002b).

In the adult literature, the now-classic report of Baxter et al. (1992) contrasted two treatments for obsessive–compulsive disorder: serotonergic medications and behavior therapy. Each intervention yielded clinical improvement; furthermore, both interventions yielded parallel levels of observable change in neural activity in the caudate region, as indicated through functional imaging via positron emission tomography scans. Thus, the effects of two extremely different treatment modalities were "located" at a similar neural loci, providing provocative and theoretically rich information regarding the mechanisms underlying learning-based and phamacologic approaches.

With regard to externalizing behavior disorders, there has been increasing interest in ascertaining the factors that predict good versus poor outcome and completing versus dropping out of treatment. Early examples include the work of Dumas and Wahler (1983), who identified the factor of maternal insularity (signifying low SES mothers with limited social support) as a predictor of poor outcome in parent–child interventions designed to reduce family disharmony and externalizing behavior (see also Webster–Stratton & Hammond, 1990). Kazdin (1995) has provided key work in the field, showing that dysfunction at several levels (parent, child, and family) predicts both early termination and poor outcome in therapeutic work with aggressive, conduct-problem youth. Systematic appraisal of moderators has been less salient, however, probably given the large sample sizes needed to detect, with adequate statistical power, the kinds of interactions between baseline variables and treatment assignment required of moderation (for an initial example, see Kazdin & Crowley, 1997). In the realm of interventions for anxious children, Barrett, Dadds, and Rapee (1996) found that age of the participant moderated outcome of individual-versus family-based treatments: A family-based approach was optimal for 7- to 10-year-olds, whereas individual treatment was as effective as the family treatment for preadolescents and early adolescents (ages 11–14 years). As discussed by Ollendick and Vasey (1999), such results suggest that parenting interventions are crucial for middle childhood, whereas the more mature early adolescent age group may have sufficient cognitive and emotional maturity to benefit from instruction without the explicit need of parental support.

As for mediation, the Oregon Social Learning Center has provided essential leadership toward the end of intentionally exploiting experimental clinical trials for conceptual elucidation. Groundbreaking work in the field was performed by Dishion, Patterson, and Kavanagh (1992), who examined the impact of behavioral parent management training on measures of child antisocial behavior. The parental treatment, contrasted with a randomly assigned control condition, yielded improvements in the outcome measure and also effected change in the putative mediator variable of maternal use of negative discipline. Because the latter changes were associated, postintervention, with the reductions in child antisocial behavior, the inference was appropriately made that improved parental discipline mediated the change in the outcome variable and therefore that parental discipline is causally related to antisocial behavior in the child. Given the developmental timing of the intervention, however, one cannot make the inference that such parenting styles are primary causes of antisocial behavior.

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In another investigation, Patterson and Forgatch (1995) showed that behavioral family intervention yielded improvements in two outcome measures for adolescents (fewer out of home placements and lower arrest rates) and improvements in the family process measures of parental discipline, parental monitoring, and family problem solving. The amelioration of these family measures was correlated, following treatment, with improvements in the ecologically valid outcome measures, suggesting mediational linkages between key family variables and important, ecologically valid outcomes related to antisocial behavior. Note that all three of the family measures were associated with improvements in rates of nonhome placement, although only the monitoring and family problem-solving scores were correlated with reduced arrest rates.

In additional research with seriously aggressive, substance abusing adolescents, utilizing the empirically established intervention termed multisystemic therapy (MST), Huey, Henggeler, Brondino, and Pickrel (2000) used path analysis and "soft modeling" to demonstrate that therapist adherence with the MST objectives predicted both enhanced family relations and lowered levels of association with deviant peers, both of which were correlated with reductions in the targeted outcome of reduced delinquency. Because the path models were conducted only for youth who had undergone treatment, however, these variables cannot be considered as true mediators of outcome.

In an exemplary use of mediator methodology with respect to externalizing behavior, Eddy and Chamberlain (2000) evaluated two types of residential care for youth displaying high rates of criminal offenses, with treatments involving random assignment to group care, constituting group-home services as referred from juvenile courts versus multidimensional treatment foster care (MTFC), which involved the intensive behavioral training of specialized foster parents (Chamberlain & Reid, 1998). The intention was to ascertain whether the intentional and intensive training and supervision related to the foster care intervention would enhance family management skills and lower rates of deviant peer association, and whether, in turn, these putative mediators would explain any treatment differences in outcomes related to antisocial behavior. Utilizing SEM, Eddy and Chamberlain (2000) found that all essential conditions for mediation were met: the MTFC condition was associated with improved family management and reduced deviant peer association in the target youth; these two mediator variables were associated with reductions in the outcome measure of antisocial behavior (indexed by both official reports and self-reports of delinquent behavior); and the significant and strong causal effect of MTFC in reducing the antisocial behavior outcome was markedly attenuated (estimated path coefficient of zero in the final model) with the inclusion of the mediators in the SEM. In fact, 32% of the variance in the outcome measure was accounted for by the latent variable comprising the mediator constructs. Although the sample size ($N = 52$) was small for use of SEM methods, and although participants were restricted largely to white, rural adolescents, the investigation is extremely heuristic for its careful testing of a mediational model, its inclusion of seriously antisocial youth, and its theoretical relevance regarding the importance of family management practices and deviant peer association as causally linked to reductions in the level of delinquent behavior patterns.

As noted earlier, prevention science is founded on the principles that systematic examination of risk factors is a prerequisite for development of preventive intervention strategies and that the results of preventive interventions can inform developmental psychopathology models (Coie et al., 1993; Conduct Problems Prevention Research Group, 1992; Koretz, 1991). Along this line, the large-scale Fast Track prevention program (Conduct Problems Prevention Research Group, 1997, 2002) has examined mediator processes as well as predictor variables related to the initial, elementary-grade outcomes of their integrated, multipush intervention for first graders at risk for aggression and delinquency (see discussion in Hinshaw, 2002). Furthermore, in another prevention-related trial with young children, Vitaro, Brendgen, Pagani, Tremblay, and McDuff (1999) showed that improvement

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in externalizing behavior was partially mediated by enhancement of peer relations.

Most pertinent work in the ADHD field includes investigations that suggest mediator processes but without formal tests. For example, Anastopoulos, Shelton, DuPaul, and Guevremont (1993), Barkley, Guevremont, Anastopoulos, and Fletcher (1992), and Pisterman et al. (1989) all showed positive effects of behaviorally oriented parent intervention on child outcomes as well as treatment-related changes in family process but did not examine more specifically whether the intervention-related improvements in family interaction mediated or explained the treatment–outcome linkages. The MTA study, however, marks a point in the history of research in the field during which both moderator and mediator strategies were intentionally built into the design and analysis of the clinical trial (see subsequent section).

Overall, despite increased interest in making treatment research conceptually relevant and despite the inclusion of potential moderator and mediator variables in the vast majority of treatment research on externalizing problems (Weersing & Weisz, 2002), the amount of research that explicitly tests for moderation and mediation is limited. I attribute this dearth of investigations to several factors: dissociation of much treatment research from relevant theory, conceptualization, and model building (e.g., Kazdin, 1999); lack of knowledge of core principles of moderation and mediation among those investigators interested in theory–clinical practice linkages; and practical limitations of most existing research (e.g., small samples, inadequate power for tests of mediator or moderator variables). Much of the seminal work in the field has emanated from the Oregon Social Learning Center (e.g., Dishion et al., 1992; Eddy & Chamberlain, 2000; Patterson & Forgatch, 1995; see also Dishion & Patterson, 1999) and from advocates of the use of prevention trials to subserve conceptual as well as practical ends (e.g., Conduct Problems Prevention Research Group, 1997; Redmond, Spoth, Shin, & Lepper, 1999). I now elaborate on the MTA study, a large-scale RCT for children with ADHD, designed intentionally to test moderator variables and mediational processes.

The Example of the MTA Study

By any account, the MTA constitutes a landmark investigation in the field. This six-site RCT, funded by the National Institute of Mental Health (NIMH) with additional support from the U.S. Department of Education, constitutes the largest clinical trial (to date) sponsored by NIMH, for any disorder. Its primary objectives were to compare intensive, long-term treatment strategies for children with carefully diagnosed ADHD (combined type), in contrast to a randomly assigned control group receiving regular community care (Richters et al., 1995). Although designed as a well-controlled experimental study, the MTA selected a broad and generalizable sample of children with ADHD (including full representation of common comorbidities) and prioritized ITT analyses of the primary outcomes, consistent with effectiveness as well as efficacy goals. Furthermore, the investigation's design and statistical consultant was Helena Kraemer, who steered the investigators to follow tests of core hypotheses with systematic exploration of moderators and mediators.

Study background

As detailed elsewhere (e.g., Barkley, 1998; Hinshaw, 1999), ADHD is an impairing, cross-situational, and typically chronic disorder of attention, impulse control, and regulation of motoric behavior, with origins in early childhood and strong psychobiological underpinnings. Despite considerable controversy in recent years regarding the increasing prevalence of the diagnosis and of medication prescriptions to treat it (DeGrandpre & Hinshaw, 2000), ADHD is a valid diagnostic entity that yields clear impairments in key domains of functioning (achievement, family interactions, peer relations, risk for accidental injury) that are of developmental importance. Furthermore, ADHD is one of the most heritable conditions in all of psychopathology, with other biological risk factors (e.g., low birthweight,

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maternal smoking or alcohol use during pregnancy) also salient as risk factors (Tannock, 1998). Although the core deficit (or deficits) of ADHD are not fully known, considerable speculation and evidence surrounds deficits in executive functions and core problems with inhibitory control (Barkley, 1997; Hinshaw, Carte, Sami, Treuting, & Zupan, 2002; Nigg, 2001). Deficient or harsh parental discipline is not believed to be a primary etiologic factor for most cases of ADHD (but see Carlson, Jacobvitz, & Sroufe, 1995), although nonexperimental research indicates that reciprocal, transactional patterns of negative parenting in response to the child's difficult temperamental style may serve to exacerbate the underlying behavioral tendencies and to fuel comorbid behavior disorders in the disruptive or externalizing spectrum (Johnston & Mash, 2001). Study of ADHD may yield important insights into both normal and atypical development of self-regulation and the interplay of biological or genetic risk with environmental factors (Hinshaw, 1999).

By the early 1990s, a host of investigations had revealed that behaviorally based interventions (conducted with parents and teachers as the agents of change) and stimulant medications yielded significant improvement in the core symptomatology of ADHD, at least in the short run: the average behavioral intervention spans 8–10 weeks of treatment, and most medication trials are about half that length. As described in Richters et al. (1995), NIMH realized that a key public health priority was to fund a systematic, multicenter trial of longer term psychosocial and pharmacologic treatments, in the hope of placing a significant "dent" in the trajectory of ADHD. Following a request for applications and competitive review of submitted proposals, six sites received awards to initiate the MTA in 1992. Extensive planning then took place for the next 1.5 years before the study took to the field, with active treatment completed in 1997.

In brief, the MTA constituted a four-group, between-subjects design, featuring parallel recruitment, participation selection, randomization, treatment implementation, and assessment procedures implemented across the study's six sites in the United States and Canada. The participants were 579 children, aged 7.0–9.9 years, carefully diagnosed with ADHD (combined type) following a rigorous, multigated screening and diagnostic algorithm. Following the screening and baseline assessment procedures, they were randomly assigned to one of four treatment conditions, each spanning 14 months: (a) medication management, including an initial, 28-day titration procedure to identify the optimal dose of stimulant medication followed by monthly medication sessions for the remainder of the trial; (b) behavioral treatment, an intensive regimen of 35 parent training sessions (group and individual), school consultation from the psychologist who conducted the parent training sessions, an 8-week summer treatment program (STP), and the provision of a half-day classroom aide for 3 months following the STP; (c) combined treatment, featuring the provision of all components of (a) and (b), with the stipulation that adjustments to the behavioral treatment were made prior to increasing the dosage of medication; and (d) community care, a naturalistic control condition in which families sought treatment from community providers following provision of a report and referral list from the MTA staff. (A no-treatment control group would have been unethical and unfeasible for a treatment study of over a year in length.) It is important that each of the first three treatment conditions comprised a designed *strategy* of manualized yet responsive intervention procedures geared to the child's and family's needs, rather than a fixed, static set of techniques. Thus, for example, if the child receiving medication did not show optimal response to a stimulant, other medications could be systematically tried; in parallel, the behavioral or psychosocial interventions were geared to the child's baseline skill level and problem behaviors, with continuous monitoring and adjustment of the program throughout the period of active treatment.

Several features bear mention. First, although the age range of the sample was intentionally kept narrow (Grades 1–4) and although rare comorbidities demanding substantially different treatment regimens were excluded (e.g.,

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psychosis, Tourette disorder), the sample was intentionally selected to span a wide range of socioeconomic and ethnic backgrounds and to include common comorbid disorders. Thus, at baseline, fully 19% of the sample were receiving public assistance; nearly 33% lived in single-parent homes; and with respect to comorbidities, 34% of the sample displayed a comorbid anxiety disorder, 40% displayed oppositional defiant disorder (ODD), and 14% were diagnosed with conduct disorder (CD). In addition, one-fifth of the sample were girls. Not only does such diversity extend the generalizability of findings but it greatly enhances opportunities for examination of potentially important moderator variables, with the potential for isolating subgroups with particularly strong or weak response to treatment.

Second, the treatments were carefully manualized, and monitoring of therapist adherence to protocol and therapist competence in delivering the interventions was diligently performed. Third, although a single, global outcome measure is often desired in RCT's, the MTA decided to evaluate outcome across six domains: ADHD symptomatology, ODD and aggressive symptomatology, internalizing symptomatology, parent–child relations, academic achievement, and peer interactions and social skills. Each domain was measured via multiple methods and informants (see Hinshaw et al., 1997). Not only did this multidomain assessment strategy afford a broad examination of study impact across both symptoms and realms of impairment, but it also allowed for tests of change in a given domain (e.g., parenting) as a potential mediator of change in another (e.g., child problem behavior). For additional design considerations, see Arnold et al. (1997).

Primary outcomes

The MTA Cooperative Group (1999a) presented random-effects regression analyses of the primary outcome measures, with ITT procedures utilized. That is the core analyses were conducted with the independent variable of treatment *as assigned*, without consideration of treatment completion or supplementation during the trial. Only through such ITT analyses can the initial randomization be preserved and unbiased estimates of the assigned treatment strategies be made (Hinshaw, 1999). Treatment site was also included as a key independent variable, to test for generality of the patterns of treatment response observed.

First, although all four treatment conditions showed improvement across the 14 months of active intervention, for the outcome domain of core ADHD symptomatology, the medication management (MedMgt) and combined (Comb) treatments, which did not differ significantly, were superior to the behavioral (Beh) and community care (CC) conditions (which did not differ). The effect size of the difference between the "medication algorithm" conditions (MedMgt and Comb) versus the others was medium to large. Second, for other symptom domains as well as the realms of academics, peer relations, and family interactions, only the Comb condition was consistently superior to CC, with the other group differences smaller and typically nonsignificant. Third, and crucially, although site differences existed with respect to several demographic variables, in no case was there evidence of site by treatment interactions. Given that site is a baseline variable, uncorrelated with treatment, these analyses were actually the first moderator analysis of the investigation, undertaken to preserve the integrity of the initial treatment analyses. That is, the presence of such interactions could have questioned the viability and generalizability of the entire study's results: for example, perhaps treatment differences would have been idiosyncratic to a given site's staffing patterns or treatment implementation.

Although the Comb condition was ranked best for a majority of the outcome measures, its superiority to MedMgt was not found in the core analyses, whereas the latter treatment outperformed Beh across several domains and measures. Part of the reason lay in the Bonferroni corrections needed for the primary analyses, which featured nearly 20 core outcome variables across six domains. It is important that MTA investigators published secondary analyses of outcome, utilizing a dichotomous measure of "excellent response" to treatment (defined as near the normal range in terms of

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parent and teacher ratings of ADHD and disruptive symptomatology; Swanson et al., 2001) and a composite measure, based on factor analysis, cutting across the multiple measures of outcome (Conners et al., 2001). In each case, Comb significantly outperformed MedMgt. For instance, Swanson et al. found "excellent response" in 68% of the Comb participants, 56% of MedMgt, 34% of Beh, and 25% of CC, with the Comb versus MedMgt contrast now significant. In addition, Conners et al. found a statistically significant effect size (Cohen's *d*) of approximately .25 for the Comb versus MedMgt contrast in terms of the composite outcome measure. Thus, beyond the primary analyses, the combination of optimal medication procedures plus intensive psychosocial intervention yielded results that were superior to single-modality treatments, even high-quality medication alone.

As the MTA has evolved from an experimental RCT to a naturalistic follow-up of outcomes in the period beyond the 14 months of active intervention, initial findings suggest that the effect size of the "medication algorithm" conditions (i.e., MedMgt and Combined) over the nonmedication groups (i.e., Beh and CC) has begun to attenuate, even for core symptoms of ADHD (MTA Cooperative Group, 2002). It is currently unknown whether longer term follow-up will yield evidence of progressive "equalization" of outcome across the four randomly assigned conditions—which would suggest a chronic disease model for ADHD in which symptom suppression attenuates in the absence of ongoing, high-quality pharmacologic intervention—or whether optimal, intensive, multimodal intervention during childhood will exert protective effects with respect to the troublesome adolescent outcomes often associated with ADHD (e.g., delinquency, substance abuse).

Moderators and mediators in the MTA investigation

Moderators. The companion article to the primary outcome article (MTA Cooperative Group, 1999b) began the systematic exploration of moderator variables. Based on existing literature, five putative moderators were tested: the gender of participants, prior medication treatment, family receipt of public assistance, the presence of comorbid disruptive behavior disorder (ODD or CD), and the presence of comorbid anxiety disorder. As befits potential moderators, all of these variables were defined at baseline (with the comorbid conditions evaluated via extensive structured interviews) and were therefore uncorrelated with treatment assignment. In a series of random-effects regression analyses, each was interacted with the treatment assignment variable. Whereas male versus female status of the participants, prior treatment history, and comorbid ODD or CD status yielded no clear patterns of significant interactions, comorbid anxiety disorder status did show clear evidence as a moderator. Specifically, whereas children *without* anxiety comorbidity showed essentially the same treatment response pattern as did the entire sample, the 34% of MTA children *with* anxiety comorbidity revealed a different pattern, in that their response to Beh was statistically and clinically indistinguishable from their response to MedMgt. Furthermore, their response to Comb was even stronger than their response to the unimodal treatments. It was *not* the case that ADHD/anxious participants responded any worse to medication than did their nonanxious peers but rather that they showed an enhanced response to psychosocial treatment compared to the noncomorbid group. This differential pattern of response held across parent-reported ADHD symptoms and internalizing symptoms, even though the MTA behavioral treatment did not target anxiety and internalizing symptomatology per se. March et al. (2000) and Jensen et al. (2001) provide further elaboration of these findings.

Furthermore, receipt of public assistance in the MTA moderated two outcomes. Unlike middle-class and upper-class families, for whom MegMgt and Comb treatments led to equivalent improvements with respect to social skills and social competence at school, for the public assistance subgroup (about one-fifth of the sample at baseline) only multimodal treatment (Comb) led to noteworthy enhancement of social skill. It may be the case, then, that for disenfranchised and highly stressed families, a multifaceted approach to intervention is opti-

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mal with respect to the extremely important developmental outcome of social interactions and social skills. Also, regarding the outcome measure of parent-reported positive interaction with their child at home, it was found that whereas middle- and upper-class families showed little differentiation across the four treatment conditions, those receiving public assistance showed a *decrease* in positive interactions in the MedMgt condition, whereas the other three treatments revealed mild increases. Perhaps for these impoverished families, the improvement in child symptomatology associated with effective, regular medication allowed parents to tend to other problematic aspects of their lives, incurring the potential cost of decreasing positive interactions with their child with ADHD. Along this line, Rieppi et al. (2002) provide a comprehensive set of random-effects regression analyses exploring the moderating effects of SES in the MTA Study.

One problem regarding the moderator analyses of MTA Cooperative Group (1999b) is that the five putative moderator variables were considered one at a time, in separate regression analyses; another is that it is difficult to make easy clinical interpretations of the results of complex random-effects regression models. Thus, Owens et al. (in press) recently analyzed the conjoint influence of these and additional baseline measures (e.g., severity of ADHD symptomatology, parental depression) through the use of receiver operating characteristic (ROC) analyses. For this research, the outcome measure was the dichotomous "excellent response" measure of Swanson et al. (2001). Too detailed to recount in full here, these analyses indicate that ADHD symptom severity, child IQ, and maternal depression all serve to moderate favorable outcome, such that less severely symptomatic children and those with above-average IQ scores (and, among those two subgroups, children with less depressed mothers) displayed higher rates of response to MedMgt and Comb treatments than did severely symptomatic, below-average intelligence children whose mothers showed higher levels of depressive symptomatology. On the other hand, none of these variables, alone or in combination, moderated the response of children receiving Beh or CC treatments. The advantage of ROC analyses is their clinical interpretability and their ability to handle multiple moderator variables simultaneously.

Mediators. The first postrandomization variable investigated in the MTA was attendance level for the experimental treatment conditions (MTA Cooperative Group, 1999b). Here, MTA investigators prespecified levels of acceptable attendance for medication sessions with the family's pharmacotherapist in the MedMgt and Comb conditions and the parent training, school consultation, STP, and classroom aide components of the Beh and Comb conditions. These percentages were typically between 75% and 80% of the sessions offered. The dichotomized variables ("as-intended" attendance vs. "lower than intended" attendance) were interacted with treatment assignment in extensions of the core random-effects regression analyses. Overall, mediation was detected, with intriguing implications: whereas attendance did not matter at all for the Beh condition (i.e., the two attendance subgroups showed virtually identical treatment response with respect to key outcomes of the study), it mattered substantially for MedMgt (and, to a lesser extent, for Comb). That is, the subgroup with less-than-intended attendance to pharmacotherapy sessions showed substantially worse core outcomes than did the participants with high attendance. This finding makes sense when one considers that families could not obtain medication prescriptions without attending these visits. Yet how could level of attendance be wholly unrelated to treatment outcome in the behavioral intervention? In fact, subsequent work (unpublished) reveals that it is the family's and teacher's active follow-through with the implementation of contingencies (rather than attendance per se) that appears to mediate outcome for this treatment. Hence, these initial mediator findings suggest that the primary ITT analyses of the MTA study probably underestimated the actual potency of response to medication, given that the omnibus analyses, which included low attenders, served to attenuate the overall effectiveness of the medication strategy. They also suggest that attendance

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alone is not the optimal measure for understanding the "take" of psychosocial treatment.

A second mediator (MTA Cooperative Group, 1999b) was obtained from service utilization data collected via telephone interviews with all families during the trial. Such data allowed us to ascertain the crucial variable of what services and treatments were being utilized by families in the CC condition—that is, those assigned to usual community care. It is provocative that 68% of this group obtained stimulant medications for their children during the 14 months of the MTA intervention phase. This figure reflects the marked increase in use of medication for children with ADHD during the 1990s. It also demonstrates the research risks involved in selecting a naturalistic, "treatment as usual" condition as the randomly assigned comparison group, as fully two-thirds of the CC group received the same treatment as did children in the Comb and MedMgt conditions. Because the use of medication by CC participants is clearly a post-randomization variable, we analyzed it as a mediator.

In brief, as shown in Figure 1, where the outcome variable is teacher-reported inattention symptoms, the 68% of the CC group who were actively medicated showed a better response to treatment (indicated by a response curve falling more sharply across the trial, signifying symptom reduction) than did the 32% who were never medicated. On the other hand, children in the MedMgt condition showed a significantly greater response than did the medicated subgroup of CC. Note also that the 14-month outcome scores in the Beh condition are equivalent to those for the CC/medicated subgroup, suggesting that active behavioral intervention works about as well as medication in the community in terms of reducing ADHD symptoms, but not as well as optimal medication practices, as exemplified by MedMgt and Comb. A similar pattern of results was found for other outcomes.

In fact, an explicit comparison of the actual treatment procedures used in the MegMgt condition versus those employed by the community practitioners of the CC group (revealed via the service utilization interviews) is heuristic. MedMgt involved an initial, 28-day titration period followed by monthly, 30-min maintenance visits, with the standard of care including three times daily, 7 day per week dosing and mandatory contact between the pharmacotherapist and the child's teacher between visits. In contrast, the average community pediatrician saw the family approximately every 6 months, for under 10 min, utilizing 5 day per week, twice daily dosing and without any contact with teachers. It therefore appears likely that the enhanced and effective MTA medication management practices accounted for superior outcome in contrast to the "same" treatment offered in the community. Recall, however, that the variable of medication use in the CC group was not randomly assigned but rather was a mediator, occurring after randomization and quite possibly involving selection effects. In recent propensity analyses (unpublished), results indicate that even when accounting for such selection biases, results indicate the superiority of the MTA medication algorithm. In this case, then, mediator analyses clearly point the way toward explicit recommendation for more optimal medication intervention procedures in the future, with the clear suggestion that optimal prescription and monitoring leads to better outcome than typical practices in the community.

Finally, Hinshaw et al. (2000) undertook a hypothesis-driven approach to mediator analyses in the MTA, positing that a family's improvement in their parenting style during the course of active intervention would mediate improvement in the important outcomes of school-related externalizing behavior and social skills. Utilizing the results of Wells et al. (2000), who showed that three parent self-report second-order factors—positive parenting, negative/ineffective discipline, and parental monitoring—accounted for considerable variance in parenting styles, Hinshaw et al. calculated change scores (end of treatment minus baseline) for each measure as potential mediator variables. Only the negative/ineffective discipline and positive parenting factors showed significant improvement as a function of MTA treatments, however. Specifically, Comb and Beh conditions outperformed CC regarding negative/ineffective discipline and

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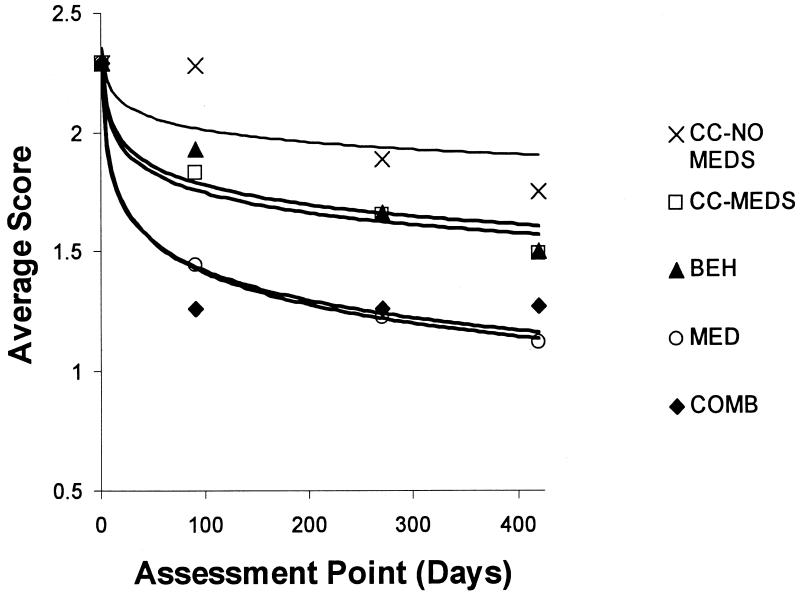


Figure 1. Random random-effects regression curves for the MTA study; the randomly assigned Comb, MedMgt, and Beh conditions and the CC condition are split into those receiving medication (68%) versus those not receiving medication (32%) during the 14-month treatment period. *X* axis, time since initiation of treatment; *y* axis, teacher-reported inattention from the SNAP rating scale (Swanson, 1992), on which 3 = *very much* and 0 = *not at all* for the 9-item composite.

Comb and Beh outperformed MedMgt regarding positive parenting. Thus, only these two parenting measures met the initial criterion for mediation: namely, that treatment condition exerted a significant influence on them.

When we next entered parenting change scores into the random-effects regression models (including the variables of treatment condition, site, time of assessment, and all interactions), only the negative/ineffective discipline score yielded the crucial interaction with treatment condition. Note that this parenting factor taps harsh discipline practices, unresponsive parenting strategies, and such inconsistent and ineffective practices as promising rewards but failing to follow through with them (Hinshaw et al., 2000; Wells et al., 2000).

First, in the case of teacher-reported social skills, measured by the Total Social Skills factor from the Social Skills Rating System (Gresham & Elliot, 1989), the improvement in negative/ineffective discipline for Comb versus CC interacted significantly with treatment assignment with respect to school-based social skills, such that Comb participants whose parents showed the greatest improvements in their discipline styles displayed optimal social improvement. In other words, "the synergistic effects of medication plus behavioral treatments in enhancing teacher-reported social skills, relative to community treatment, were explicable (mediated) by reductions in negative and ineffective parenting influenced by the Comb condition" (Hinshaw et al., 2000, p. 564). Second, with regard to teacher-reported disruptive behavior (see Figure 2), the pattern was slightly different. Here, although the Comb versus Beh contrast regarding to improvement in negative or ineffective discipline was not significant—recall that both Comb and Beh led to greater improvements in this variable than did CC—the interaction of this parenting contrast with reduction of ADHD and ODD symptomatology at school was significant and large. The three plots of Figure 2 display the trajectories of treatment response for the four MTA treatment conditions separately for families (a) showing the least amount of improvement in negative/ineffective discipline (Figure 2a; 29% of the total sample), (b) showing

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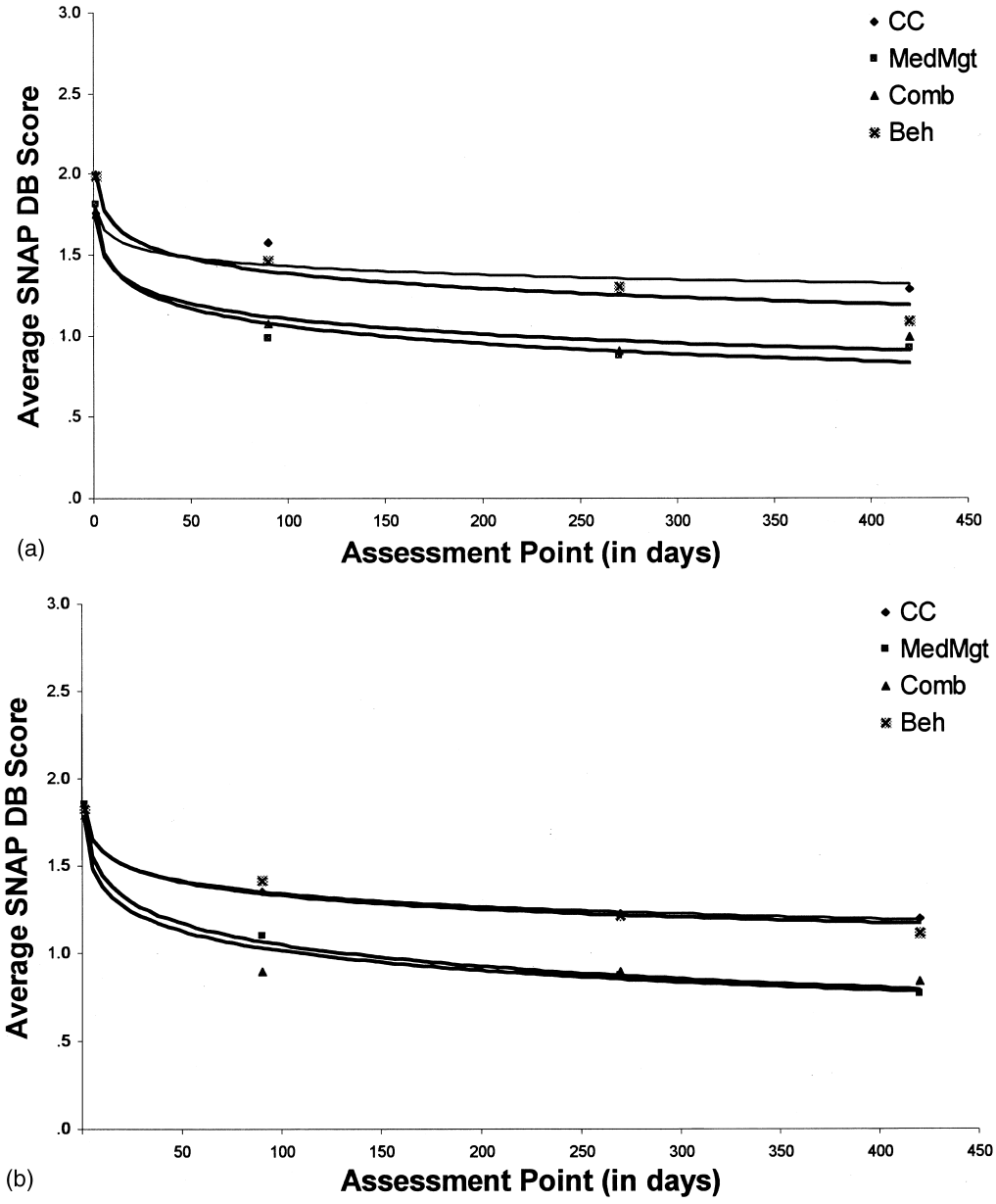


Figure 2. A series of graphs depicting the outcomes across 14 months moderation by treatment condition of negative or ineffective parental discipline in relation to teacher-reported ADHD and ODD symptoms (3 = *very much* and 0 = *not at all*; note that 0.7 = normative range): (a) the subgroup of participants with small decrease or increase in negative or ineffective discipline, (b) the subgroup of participants with moderate decrease in negative or ineffective discipline, and (c) the subgroup of participants with a large decrease in negative or ineffective discipline. Note that in the latter subgroup, Comb is associated with large and clinically significant improvement in teacher-reported ADHD and ODD symptoms.

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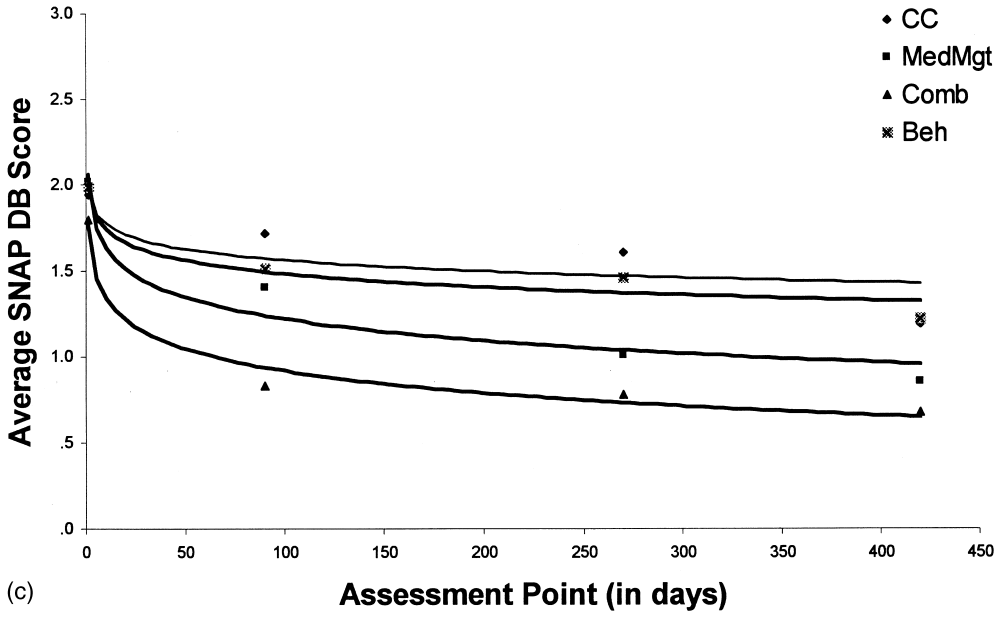


Figure 2. Continued.

modest improvement in this score (Figure 2b; 46% of the total sample), and (c) showing substantial improvement for this variable (Figure 2c; 25% of the total sample). Whereas in Figures 2a and 2b the response trajectories for MedMgt and Comb were each significantly steeper than for Beh or CC, Figure 2c reveals that in families who displayed optimal improvements in negative/ineffective discipline, Comb showed the clearest and most dramatic improvement in teacher reports of disruptive behavior, surpassing the trajectory for Beh and for CC. Indeed, Figure 2c reveals that only the Comb condition showed normalization of their mean ADHD and disruptive behavior scores at school, as the normative mean for this measure is approximately 0.7 on the 0–3 scale. Hence, when accompanied by clear improvement in family discipline style, multimodal treatment (Comb) was the only MTA treatment that led to clinically significant improvement in terms of school-reported externalizing behavior, thus yielding normalization.

Note, however, that this latter effect does not technically signify a mediational pattern, because even though the crucial interaction attained significance (with large and clinically significant effects), the Comb versus Beh contrast did not reveal a significant benefit regarding the mediator itself, that is, negative/ineffective discipline. In other words, even though the treatment contrast did not yield effects on the putative mediator, the discipline variable was associated differentially with outcome in the Comb and the Beh treatments. As described in Hinshaw et al. (2000):

> Thus, we interpret that significant interaction as indicating that treatment assignment *moderated* the relationship between Negative/Ineffective discipline and reduced disruptive behavior at school. That is, for the Comb condition, reduced parental Negative/Ineffective discipline was associated with improvement in disruptive behavior; but such a relationship was not found for Beh. (p. 563)

Despite the potential importance of this set of findings (see below), a pertinent question is whether the negative/ineffective discipline factor (as a mediator of change in social skills, and as a factor moderated by treatment condition in producing clinically significant improvement in externalizing behavior) is *causally* related to such clinical change. In other words, whereas RCTs can lead to attribu-

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tion of the causal influence of a treatment condition on an outcome of interest, does the same reasoning hold true for a mediator variable? The answer here is less certain: recall again that a mediator is, by definition, a variable occurring after random assignment and therefore subject to selection bias. It is conceivable that additional variables related to combination treatment, such as altered parental expectations, could have produced *both* the social skills or symptomatic improvements *and* the enhancement of discipline style (see discussion in Conduct Problems Prevention Research Group, 1997). In addition, perhaps the improvements in school behavior (facilitated by the medication component of Comb) actually allowed the parents to relax their previously negative and ineffective discipline practices in the presence of the psychosocial supports of the Comb treatment. Thus, whereas mediator variables cannot be established definitively as causal in nature, they are clearly suggestive of important processes related to clinical change.

Developmental and clinical implications

What theoretical implications can be gleaned from this complex set of moderator and mediator analyses? First, many of the potential moderator variables analyzed (e.g., male versus female status of participants, prior treatment history, comorbidity with aggressive spectrum disorders) did not turn out to moderate treatment outcomes. This lack of effect was most striking for the variable of comorbid ODD or CD status. Indeed, given the possibility that highly aggressive children with ADHD are distinct from their nonaggressive counterparts in terms of such crucial variables as neuropsychological functioning, parental history of mental disorder, sociocognitive information processing, and the like (e.g., Hinshaw, 1999), the former subgroup could well be judged to require multimodal intervention for optimal benefit. Perhaps, however, on the basis of their generally similar response to treatment, these two subgroups are not as distinct as believed. I hasten to point out, however, that clearly distinct clinical entities may respond similarly to selected treatments: for example, obsessive–compulsive disorder and major depression both show significant improvements with serotonin selective reuptake inhibitors. Nonetheless, the finding that highly aggressive, conduct disordered preadolescents with ADHD did not require more intensive treatment in order to yield meaningful improvement is striking, both clinically and conceptually. It suggests, among other things, that successful treatment of core ADHD symptoms via well-prescribed and well-monitored medication in middle childhood is beneficial for reducing aggression and therefore that much of the aggression (particularly the reactive, explosive type) shown by youth with ADHD may be secondary to their core impulsivity and poor behavioral regulation, emanating developmentally as a result of ADHD symptoms and resultant frustrations. Again, however, speculating as to underlying mechanisms of psychopathology on the basis of similarity of treatment response is likely to yield both logical and clinical error.

On the other hand, the distinct pattern of response of the participants with comorbid anxiety disorders is clearly of both clinical and theoretical importance. Clinically, anxious children with ADHD should, in the next generation of treatment research, be evaluated for response to even more intensive psychosocial or behavioral intervention procedures. It is also possible that the primary treatment option for such youngsters should be a nonmedication approach, which would avoid exposing these children to pharmacologic regimens unnecessarily. Moderator analyses may thus pave the way for therapeutic specificity.

At a conceptual level, this finding was unexpected and adequate explanations are not yet available. Several key questions are salient: are children with above-threshold anxiety somehow more responsive to behavioral contingencies? Do these children have parents who were more amenable to implementing the psychosocial treatments that were offered (e.g., establishing reward programs, participating in anger management, coordinating programs with school personnel)? Are the comorbid children somehow at a "higher" developmental level in terms of social representation, such that they are able to understand and

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comply with the reasonable, yet firm, limits imposed by parents and teachers who learn a more consistent way of disciplining through psychosocial treatment procedures? Although the answers are not yet clear, subsequent research should be undertaken to understand the factors that *mediate* or explain the effects of important *moderators*, like comorbid anxiety. Nonetheless, it is fascinating to speculate as to the enhanced responsiveness of children with major anxiety disorders to psychosocial treatment.

A final point with respect to moderator research is that much of the enterprise, at present, is quite atheoretical. Very little in the way of empirical evidence or theoretical argument suggests precisely which moderator variables should be expected to interact with treatment assignment. In fact, most variables associated with poor response to intervention (e.g., poverty, family insularity) are probably *predictors*, exerting their effects across any kinds of treatment offered. On the other hand, when variables like participant age or developmental level (Barrett et al., 1996) or, as noted earlier, genotype (Smeraldi et al., 1998) show evidence as moderators, the search for mechanisms underlying such differential treatment response should be renewed with vigor.

It is at the level of mediator processes that the most compelling conceptual and theoretical ramifications may emerge from clinical or prevention trials, given that mediators reflect processes occurring during the period of active intervention. The most striking example in the MTA pertains to the finding that change in family discipline style, obtained via parental self-report, was associated with clinically significant improvement in social skills and externalizing behavior for children and families assigned to the study's multimodal treatment condition (Comb). At a clinical level, the subgroup of families receiving Comb who showed the greatest improvements in their parenting had children who attained, as a group, fully normalized levels of externalizing behavior at school. That such enhancement, associated with a change in parenting style, was not found in the unimodal or community treatment conditions strongly suggests that it takes optimal pharmacologic management *plus* optimal psychosocial treatment to yield normalization of externalizing behavior in the presence of parenting improvement.

Why is this finding important for developmental theory? The clearest reason is that a host of carefully controlled behavior genetic investigations over the last decade have revealed extremely high heritabilities for ADHD, in terms of both the continuum of symptoms and categorical diagnoses. Indeed, the figures range between .70 and .90, making ADHD more heritable than schizophrenia or major depression and equivalent to bipolar disorder or autistic disorder, the most heritable psychiatric conditions under current investigation (see Tannock, 1998). These levels are sufficiently strong, in fact, that it is now actively contended that ADHD is so constitutional and genetic in nature that parent socialization essentially does not matter for children with this condition.

What are the implications of heritability statistics for within-individual change and growth? For one thing, heritability, the proportion of group variance in a trait or disorder attributable to genes rather then environments, does not translate into gene–environment configurations for the individual case. Indeed, explanations at the level of interindividual differences in development must be kept separate from ontogenetic explanations of intraindividual change. Furthermore, according to Gottlieb (1992, 1995, 1998), the genetic "dogma"—that genes reductionistically predetermine development—should be replaced by the notion of probabilistic epigenesis, which emphasizes the multidetermined, organismic processes operating at a "supragenetic" level in which genetic forces develop. Gottlieb's perspective is that genes do not place constraints on phenotypes but rather interact and transact with other levels of the organism and environment to mold development. The provocative, transactional ideas underlying probabilistic epigenesis are too detailed to recount in full here; the interested reader is invited to consult the work of Gottlieb.

Returning to the mediator and moderator findings in the MTA, the fact that a parenting variable (improvement in negative/ineffective

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discipline) was found to mediate the externalizing behavior patterns and social skills of children receiving combination treatment argues that socialization *does* indeed matter for a condition as heritable as ADHD. In other words, experience is influential for children who presumably have, at an aggregate level, a substantial genetic liability for problems in self-regulation (for earlier statements regarding the importance of considering the separability and interdependence of genetic and experiential levels of analysis, see Meehl, 1973).[3] The present findings—that parental discipline style is related to meaningful clinical change in a condition with extremely strong heritability—undermine the common misconception that heritability implies genetic destiny (Gottlieb, 1998). They also challenge the field to explore even further the limits of familial, environmental, and cognitive remediation for improving conditions (like ADHD) with strong psychobiological underpinnings. I note that the tenets of probabilistic epigenesis are undergoing strong debate in the field; and I do not contend that *any* psychosocial influence will automatically lead to significant alterations in the development of children with conditions as psychobiologically based as ADHD. Indeed, years of unsuccessful experience for children with attentional deficits and hyperactivity in treatments like play therapy clearly indicate that environmental influences are not, a priori, ameliorative. Finding the right environmental circumstances operating at the optimal developmental stages is one of the field's essential tasks.

Overall, the significant and clinically meaningful mediation of multimodal (combination) treatment via parental socialization carries strong implications for developmental theory, emanating from the careful moderator and mediator analyses in a clinical trial. Whether parental socialization at earlier periods of development (e.g., toddlerhood, preschool) is etiologically related to subsequent ADHD cannot be determined from the MTA results, which emanated from middle childhood. However, the MTA findings do increase suspicion that the complex interplay of genetic liability, temperament, and parenting style (as well as peer socialization and wider societal influences, such as those emanating from television or the widespread use of computers) is transactionally responsible for the symptom complex termed ADHD—and certainly that environmental remediation is an important change factor in the life course of ADHD.

Summary

The MTA provides a recent, salient example of the intentional use of large-scale RCT for theoretical and clinical purposes related to treatment moderation and mediation. Clinically, the hope is that future investigations of treatments for ADHD can make use of (a) enhanced psychosocial interventions for children with comorbid anxiety disorders, given the moderator status of such comorbidity; (b) facilitation of attendance at medication follow-up visits and active implementation of behavioral procedures at home and at school, given the mediational status of such variables; (c) optimal medication procedures (e.g., multiple dosing or viable long-acting formulations; regular contact between physician and teacher; more frequent and intensive monitoring than is the usual community standard), given the demonstration that such medication practices outperform regular community care; and (d) even greater attention to the optimal means of facilitating families' improvements in discipline style, given the significant role that improvement in negative/ineffective discipline plays in mediating and facilitating clinically significant change. Conceptually, such findings should challenge basic and clinical researchers to develop more comprehensive and accurate conceptions of change processes related to ADHD and externalizing behavior patterns. Certainly, the family discipline data yield a rich set of implications for epigenetic developmental theory.

3. Meehl's (1973) arguments are as valid today as when he first made them. Among other things, he makes clear the essential point that vulnerabilities at a genetic level do not rule out, a priori, that environmental changes at other "levels" of dispositions could interact with the vulnerability to produce a rich variety of phenotypic outcomes.

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Concluding Remarks

I have attempted to demonstrate the importance of extending clinical trials into the crucial realm of identifying moderator and mediator variables and processes. As emphasized repeatedly, this effort subserves the dual objectives of enhancing the clinical impact of treatment research and facilitating the evolution of relevant developmental and clinical theory. Although the variables that can be manipulated in RCTs are often far removed from primary etiologic factors, the identification and validation of moderator and mediator variables can facilitate the field's understanding of maintaining factors for psychopathology, processes related to clinically significant change, and conceptual models for the field. Indeed, it is only through far better understanding of core theoretical constructs related to psychopathology and of the social, as well as psychobiological, contexts in which psychopathology exists that treatment research can make important strides.

What can be done? Intervention researchers must take greater advantage of extant theoretical concepts and design prevention and treatment studies yielding conceptual information that can be translated back to ongoing theory development and model building. Although RCTs must be designed with primary efficacy and effectiveness questions and hypotheses foremost in mind, there is every reason to include putative moderator and mediator variables in the assessment battery, to calibrate assessment points to the periods of maximal predicted change, and to analyze for moderator and mediator effects and processes in a systematic manner (Kraemer et al., in press). Although the transactional nature of the way in which risk, protective, moderating, mediating, and explanatory factors work together to create pathology and resilience requires the development of conceptual models and data analytic strategies that transcend the linear models built into most of our current methods (Jensen, 1999; Kazdin, 1999), the continued interplay among theory, method, intervention research, and conceptual models can provide mutual enhancement of clinical and developmental science.

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