6

The Importance of How: A Call for Mechanistic Research in Tobacco Dependence Treatment Studies

Danielle E. McCarthy, Daniel Bolt, and Timothy B. Baker

University of Wisconsin-Madison

Roughly a quarter century ago, Richard McFall called on his fellow smoking-cessation researchers to strive to bootstrap theories of smoking behavior from empirical findings and to use these theories to generate treatments (McFall, 1978). He touted theoretical research as "the most advanced research approach" (p. 710), and he lamented the scarcity of good theories of smoking behavior to guide treatment development (McFall, 1978). McFall pointed out that diverse treatments, derived from distinct theories, produced uncannily equivalent treatment effects, and he identified the critical role played by nonspecific factors such as motivation, structure, and self-monitoring in such effects (McFall, 1970; McFall & Hammen, 1971). He outlined the value of adopting constructive or dismantling research strategies, and he used such designs in his own research (McFall, 1978; McFall & Lillesand, 1971). He also highlighted the importance of collecting process measures during the treatment phase and of looking for treatment-specific effects on process measures (Marston & McFall, 1971; McFall, 1978). In summary, McFall pointed

out how little was known about treating smoking, and he outlined a rational path, based on a synthesis of theory and methods, to foster the future development of tobacco treatments.

Despite copious research on tobacco-dependence treatments over the past few decades, many of McFall's laments and calls for action remain unanswered. Tobacco researchers are still enamored with the *horse race* technique of pitting treatments against one another or a straw-man control condition to see which ultimately achieves the highest abstinence rate, without determining how or why one treatment bests another. In this chapter, we renew and elaborate McFall's prescient and neglected call for mechanistic research in tobacco-dependence treatment development and evaluation. We first review the potential conceptual and clinical yield of mechanistic research. We then review conceptual criteria for testing mechanistic or mediational hypotheses (hypotheses that assert that a treatment exerts an effect on a target outcome through a specific, intervening variable called a *mediator*). Finally, we provide examples of mechanistic research methods using data from a smokingcessation clinical trial.

VALUE OF MECHANISTIC RESEARCH

Conceptual Benefits of Mechanistic Research

Mechanisms of action of pharmacological and psychosocial tobaccodependence treatments can be studied using mediational analyses at the physiological, psychological, or behavioral level of analysis. In mediational analyses, investigators examine relations among an independent or initial variable (e.g., treatment), a putative process variable or mediator (e.g., coping skill mastery), and a target outcome (e.g., 6-month abstinence; Kenny, Kashy, & Bolger, 1998). Mediational inferences require (at minimum) that the initial variable influences the mediator as predicted, and that the mediator and the outcome are related as predicted (Kenny et al., 1998; see Fig. 6.1A). In a cessation counseling program, for example, one might expect individual counseling to lead to increased skills for coping with stress or with urges to smoke, which in turn would lead to increased probability of abstinence.

Mechanistic research can yield a deeper level of understanding, and richer theories, of tobacco dependence and treatments than can simple outcome research. Mediational hypotheses are both causal and specific, two important characteristics of well-developed theories. In fact, inferences A.



Β.



FIGURE 6.1 (A) Relations between variables that must be demonstrated to support claims of mediation (e.g., Baron & Kenny, 1986). The treatment variable (X) must be significantly related to the mediator (M) via Path a. The mediator must be significantly related to the outcome variable (Y) via Path b. In the strictest interpretation of mediation, path c linking the treatment variable to the outcome must also be significant. (B) Path c' should be reduced to 0 in the case of complete mediation. The numbers below the arrows depict the standardized regression coefficients among combination medication and counseling treatment versus all other treatments (X), the difference between craving scores on Day 6 versus Day 0 of a quit attempt divided by 7 (M), and CO-confirmed 7-day point-prevalence smoking status 6 weeks post-quit date (Y). Higher values on the mediator indicate increases in craving over the first week post-quit. Combination treatment is associated with lower slopes in craving, which are in turn related to decreased risk of relapse. Significant coefficients (at alpha .05) are noted with an asterisk.

about the effects of treatment, even in randomly controlled clinical trials, require some consideration of possible mechanisms of treatment actions. Demonstration of causality requires that (a) a relationship exist between the putative cause and effect, (b) the cause precede the effect, (c) alternative explanations of the cause-effect relationship have been ruled out, and (d) the putative mechanism linking the cause and effect be plausible, given extant knowledge about the phenomena of interest (Havnes, 1992; Kazdin, 1999). These criteria for the demonstration of causality state that mechanism must be considered, if not tested, before drawing causal inferences. We argue that in treatment research the mechanisms of action deemed plausible should be explicitly stated and tested whenever resources permit. We, like McFall (1978), advocate this admittedly difficult and resource-intensive practice because causation is the key target of experimental research and because examining the mechanisms whereby treatments achieve their effects could improve our understanding of both tobacco dependence and tobacco-cessation processes.

Mechanistic research studies are also more powerful than simple outcome intervention studies because they test multiple theories simultaneously. Theories regarding treatment effects link theories of change and theories about the factors that cause or maintain a target behavior or condition (Eddy, Dishion, & Stoolmiller, 1998). Others have argued that an important part of treatment development is the articulation of a small theory (Lipsey, 1993) to explain the means by which a treatment program affects an outcome. This theory of treatment effects can be parsed into two parts: an action (or program) theory that specifies the manner in which the treatment should affect the mediator, and a conceptual (or psychosocial) theory that specifies the relation between the mediator and the outcome of interest (i.e., why changing the mediator should affect outcome; Chen, 1990, Kenny et al., 1998; MacKinnon, Taborga, & Morgan-Lopez, 2002). When Marston and McFall (1971) stressed the importance of collecting process measures to be able to detect whether "different treatments do, in fact, produce discriminably different response curves during the treatment period" (p. 154), they were highlighting the importance of testing the action theory using process measures.

Because mechanistic research tests both the action and conceptual theories simultaneously, mechanistic research can yield information regarding "the genesis of the outcome variables of interest" and allow researchers to "build and test a theory regarding more general causal mechanisms responsible for the outcome behavior" (Judd & Kenny, 1981, p. 603). In this way, mechanistic research is efficient in that it tests models of a target behavior and models of change simultaneously. For example, testing the relations among counseling treatment, coping skills, and abstinence can tell us whether our action theory is refuted or retained (i.e., whether counseling leads to enhanced coping) and whether our conceptual theory is refuted or retained (i.e., whether coping is associated with increased abstinence likelihood; Collins, Graham, & Flaherty, 1998; MacKinnon, Taborga, & Morgan-Lopez, 2002; Weersing & Weisz, 2002). If the action theory is refuted, this suggests that the treatment was ineffective in changing the target mediator and that our intervention model may need revision. If the conceptual theory is refuted, however, our understanding of the factors that promote abstinence may be flawed, and we may need to select another intervention target. In this way, mechanistic research may help make sense of inconsistent results. McFall (1978) argued that, without process information, "it is difficult to rise above one's failures and to design better treatments" (p. 708). To help us rise above our failures to replicate treatment effects, we can now use mediational meta-analysis procedures to investigate the support for various action and psychosocial theories across treatment studies (Shadish & Sweeney, 1991).

Mechanistic research is also preferable to simple outcome research because the former is less prone to some of the well-known pitfalls of null hypothesis significance testing. A good theory about treatment must make testable predictions about how treatments achieve their effects, rather than simply conducting a horse race among treatments and placebo conditions (McFall, 1978). Making multiple, precise predictions about how variables are related, rather than just proposing relations among a subset, makes tests riskier and reduces the risk of chance findings. This is so because the combination of multiple relations is always less likely than the occurrence of a single relation. and demonstration of mediation requires the co-occurrence of multiple relations. In this way, mediational tests are more than are tests of simple direct treatment effects. Elaborate Treatment models that are not exposed to heightened risk of refutation are less compelling (and less scientific) than are models that have passed such tests (Meehl, 1978).

Clinical Benefits of Mechanistic Research

The study of mechanisms of treatment effects is an important endeavor for clinical as well as theoretical reasons. Knowledge of the mechanisms of action of specific agents or treatment components may suggest new treatment combinations (Morgenstern & Longabaugh, 2000). For example, if we knew that nicotine replacement and antidepressant medication therapies exerted effects on smoking behavior through distinct mechanisms, we could rationally expect these effects to be additive, even if outcomes are similar for either treatment used alone (e.g., bupropion SR and the nicotine nasal spray; Fiore et al., 2000). If two treatments were found to work through nonspecific mechanisms (e.g., enhanced abstinence self-efficacy) or through similar mechanisms (e.g., withdrawal suppression), we would not expect combining such treatments to improve abstinence rates substantially (although they may do so in a dose-related manner). As such, it is important to uncover the mechanisms of action of our extant treatments because such understanding may suggest a rational basis for combining treatments.

In addition, if we understood how a treatment affects a given risk factor, we could match individuals with that risk factor to the treatment in question. Thus, if we knew that cognitive behavioral therapy for depression (or smoking cessation) altered negative schemata, we could select individuals for CBT based on an assessment of their negative cognitive belief structure (Morgenstern & Longabaugh, 2000). In this way, improved understanding of treatment mechanisms could lead to better treatment matching.

Mechanistic knowledge could also lead to better understanding of moderation effects more generally. It may be that the many individual difference and contextual variables that have been found to moderate treatment effects do so because treatments work through different mechanisms in different people or situations. For example, people with a history of depression have been found to benefit less from nicotine replacement therapies than do people without a history of depression (Smith et al., 2003). Depression-vulnerable individuals may respond less because nicotine replacement therapies ameliorate withdrawal-related distress, but do not reduce the coping-skill deficits that may foster tobacco use among these affectively vulnerable individuals. Mechanistic research has the potential to identify mediating variables that may contribute to the emergence of important interactions between individual differences and treatment. Identifying treatment processes that may account for person-by-treatment interactions may enable us to develop treatments that help treatment-refractory individuals by activating different critical processes or activating them in a different way (e.g., teaching different urge-reduction strategies to men and women). If we know what works in a treatment and how it works, we can generate hypotheses about how to amplify treatment effects on a rational basis, rather than merely extending or intensifying treatment or offering booster sessions based on the premise that more (of some poorly understood entity) is better (Kazdin, 2001).

A better understanding of treatment mechanisms could also enhance the dissemination and delivery of treatments. In general, discovering the potent mechanisms of treatment can lead to more efficient and transportable (Kazdin, 1999; MacKinnon, Taborga, & Morgan-Lopez 2002; Morgenstern & Longabaugh, 2000) treatment delivery. Although many treatments are manualized to facilitate dissemination, these manuals do not identify the critical components or processes of treatment (Kazdin, 2001). If we identified the critical ingredients in treatment and the active processes that result in positive change, we could ensure that these critical components of efficacious treatments are emphasized in treatment manuals and optimized in treatment delivery in diverse settings (Kazdin & Kendall, 1998; MacKinnon & Lockwood, 2003). Thus, mechanistic research has the capacity to separate the wheat from the chaff in multicomponential treatments (Judd & Kenny, 1981). Such knowledge could ensure that the potent components of a treatment are undiluted by unnecessary or iatrogenic components (Judd & Kenny, 1981; MacKinnon, Taborga, & Morgan-Lopez, 2002).

Mechanistic research by itself cannot identify active treatment ingredients, however. The inclusion of appropriate control conditions is essential. In well-designed placebo-controlled, constructive, factorial, fractional, or dismantling studies (Kenny et al., 1998; McFall, 1978), mediational analyses can reveal much about how and why placebo or active control conditions differ from an index treatment. For example, we might find that all treatments, even inert placebo or attentional control conditions, have positive effects through a nonspecific mechanism of action, such as the instillation of hope (e.g., Howard, Lueger, Maling, & Martinovich, 1993; McFall & Hammen, 1971). Mechanistic research, when coupled with appropriate study designs, can help identify qualitative and quantitative differences in the effects of comparison treatments and control conditions, even when they have equivalent impacts on ultimate outcomes such as abstinence measures.

Finally, mechanistic research can help us identify when a treatment is not working. If we know by what mechanism a treatment results in an ultimate desired outcome (and the time frame in which treatment processes unfold), we can assess treatment response early in treatment and modify treatment for people who are not changing in the desired fashion. Psychotherapy researchers have strongly advocated the use of process measures to inform decision making in therapy, but tend to focus on intermediate outcomes, active ingredients, or rate of change rather than mediators (e.g., DeRubeis & Feeley, 1990; Feeley, DeRubeis, & Gelfand, 1999; Goldfried, Greenberg, & Marmar, 1990; Tang & DeRubeis, 1999). In theory, treatment may be titrated on an ongoing basis for participants based on their standing on a mediator, rather than waiting for the treatment failure to culminate. In this and other ways described earlier, mechanistic research could improve the efficiency of clinical interventions.

CONCEPTUAL CONCERNS AND CRITERIA FOR MEDIATION

Design and Assessment Concerns

Experimental Design. First, let us consider when it is appropriate to conduct mediational analyses. Some scholars (West & Aiken. 1997) have argued that merely comparing a treatment package to a control condition is not sufficient for mediational analysis. These authors argue that factorial, fractional, or dismantling designs in which one treatment component is hypothesized to influence a single mediator are better suited to mediational analyses. Other authors merely require that at least two treatments be compared (Holland, 1988; Rubin, 1974) to support causal inferences. Comparisons of two active treatments may be suitable for mediational analyses, even when no significant difference in outcome between treatments is detected (Morgenstern & Longabaugh, 2000). Scholars have argued that the best mediational design (barring direct manipulation of the mediator) is a study comparing "several programs based on different theories of tobacco use and a control group" (MacKinnon, Taborga, & Morgan-Lopez, 2002, p. 578). Such designs allow investigators to test simultaneously multiple theories about treatment effects and more general theories of the determinants of tobacco use. In addition, McFall argued that the minimal treatment condition is a better basis for comparison than a no-treatment control condition due to the apparent effects of nonspecific factors in treatment responses (Marston & McFall, 1971).

Assessment Schedule. The assessment battery and timing of procedures are critical to the study of mediation. Logically, the treatment manipulation must precede the mediator, which in turn must precede the outcome (Holland, 1988; Kazdin, 2000). As others have pointed out; it is not enough merely to assess the constructs in the appropriate order; the constructs must exert effects in the proper order (Cole & Maxwell, 2003). For instance, although the assessment of a mediator may occur after treatment manipulation, variance in the mediator may reflect temporally remote events. For example, beneficial increases in self-efficacy may occur immediately on enrollment in a cessation study, be unrelated to treatment, and yet influence the outcome. Similarly, treatment and mediational processes may overlap in time (i.e., mediational processes may begin while treatment is ongoing). If the temporal ordering of the

treatment and mediator cannot be established, the baseline level of the mediating variable should be included in analyses as a control variable (Cinciripini et al., 2003; Cole & Maxwell, 2003). This allows one to infer that change in the mediator during or after treatment is predictive of outcome and accounts for the treatment effect.

Timing, not just temporal ordering, of the assessments is critically important as well. The magnitude of the effects of a treatment on a mediator, and a mediator on an outcome, naturally varies based on when the relations are assessed. In general, one would want to use research and theory to estimate the time courses of relevant events in the mediational model (e.g., the temporal patterning of both treatment effects and mediator effects). Moreover, one would want to consider what levels of change, and durations of change, would be needed to exert desired effects. For instance, if enhanced coping with major stressors were the mediator, the conceptual model would involve assumptions about the occurrence and timing of stressors in people's lives.

Kenny et al. (1998) noted that, to detect mediation, one ideally wants the relation between the treatment and the mediator, and the relation between a mediator and outcome, to be large. This can be difficult to achieve, however, given that these relations tend to be complementary (i.e., as one increases, the other decreases) because their combined effect cannot exceed the overall relation between the treatment and outcome (Kenny et al., 1998). Ideally, then, the mediator would be assessed at the midpoint between the independent variable (treatment) and outcome (Kenny et al., 1998). At first blush, it may seem best to assess the mediator when it is most tightly related to treatment. Such an approach would create a strong test of the action theory guiding the treatment. A strong correlation between the treatment and mediator creates a high level of collinearity, however, and this interferes with estimation of mediatoroutcome relations. In this way, strengthening the test of the action theory may undermine the test of the conceptual theory linking the mediator and outcome. A complementary cost is incurred if the timing of assessments is modified to maximize the association between the mediator and outcome (thus favoring the conceptual theory over the action theory).

In tobacco-cessation research, the preferred outcomes for treatment studies are quite distal from the initiation of treatment (e.g., abstinence rates 6–12 months after the target quit date). From a public health perspective, such distal endpoints are attractive because they capture a socially meaningful outcome (Wiggins, 1973). From a mechanistic perspective, however, more proximal outcome measures may be preferable. Examining hypothesized mediational relations over a shorter timeframe may reduce the influence of the myriad processes and factors that likely influence long-term abstinence, but that are unrelated to treatment (e.g., having a spouse who uses tobacco). Evidence shows that smoking-cessation treatments tend to affect survival (prevent relapse) most in the first days or weeks of treatment (McFall & Hammen, 1971; Piasecki, Fiore, McCarthy, & Baker, 2002). Thus, examination of short-term treatment effects and outcomes may be especially sensitive and appropriate for testing treatment and mediator effects.

The nature of the assessment of the media-Assessment Battery. tor also has important implications for the conduct and interpretation of mediational analyses. The grave and insidious impact of error in the measurement of a putative mediator is well documented (Baron & Kenny, 1986; Judd & Kenny, 1981; Kenny et al., 1998; MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002; West & Aiken, 1997). Typically, error in the measurement of the mediator leads to underestimation of the mediated effect and overestimation of the direct (unmediated) effect, thus increasing the likelihood of retaining the null hypothesis that the mediated effect is not significant. For this reason, researchers recommend examination of effect sizes and confidence intervals instead of reliance on significance testing in mediational research (Baron & Kenny, 1986; MacKinnon, Taborga, & Morgan-Lopez, 2002; MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002). In multiple mediator models, error in the measurement of one mediator can lead to bias in the estimation of other mediators as well (West & Aiken, 1997). As such, constructs including the mediator should ideally be assessed using multiple indicators (Cole & Maxwell, 2003; Hoyle & Smith, 1994), preferably those that are maximally dissimilar from one another to reduce the likelihood of retaining method variance in the latent mediator construct (Cole & Maxwell, 2003). Latent variable approaches can remove error variance from the target construct (i.e., mediator) if multiple indicators are used, particularly if the indicators are diverse. For example, self-report Likert-type items tapping withdrawal symptoms could be supplemented with observer ratings of irritability and objective measures of negative affect (e.g., eyeblink startle responses). Although this more complicated approach adds to the assessment burden for participants and the analytical complexity of the data, the latent variable approach is deemed the best approach to mediational analyses (Hoyle & Smith, 1994; Kenny et al., 1998) because it can isolate error in the measurement of the mediator.

Nuisance Variables. It is essential to assess and control for variables other than treatment that might influence both a mediator and outcome. This issue is critical to the internal validity of a mechanistic study. Omitted variables have the potential both to inflate estimates of the path between the mediator and outcome and increase the estimate of the direct effect (Herting, 2002). In the real world, in which multicausality is the rule rather than the exception (Cole & Maxwell, 2003), it may not be possible to identify and assess all the possible confounding variables that could threaten the internal validity of a mechanistic study. In light of this, it may be best to adopt statistical strategies, such as controlling for earlier levels of the mediator and outcome when estimating later causal relations (assuming that an unestimated fourth variable has already exerted its effects; Cole & Maxwell, 2003; Hoyle & Smith, 1994).

Sample Size. A final design consideration is sample size. For a variety of reasons, mediational analyses are frequently underpowered (Baron & Kenny, 1986; MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002). As such, medium to large samples are often required to test mediational hypotheses sensitively. Multiple mediator models or models containing complex causal chains require especially large sample sizes (West & Aiken, 1997). Interestingly, when there are strong relations between treatment and the mediator, larger sample sizes $[N(1-r_{rm}^{2})]$ are required to detect mediation (Kenny et al., 1998). This occurs because a strong relation between the treatment variable and mediator results in collinearity when examining these variables' unique relations with outcome (Baron & Kenny, 1986). This suggests that more potent treatments require larger sample sizes to detect mediation, contrary to what one would expect. As such, caution should be applied to interpretation of negative results in even moderate or large samples. For this reason, some have advocated that authors report effect sizes or confidence intervals in addition to significance tests (Baron & Kenny, 1986; MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002).

Conceptual Criteria for Mediation

Scholars have discussed the criteria necessary for the demonstration of mediation for at least the past five decades (MacCorquodale & Meehl, 1948; Rozeboom, 1956). Today, there is one prevailing set of criteria adopted by most researchers. Essentially, mediation is established using a multiple correlation approach (Judd & Kenny, 1981; West & Aiken, 1997) to parse the direct and indirect effects of an initial (Kenny et al.,

1998) variable (e.g., treatment) on an outcome, where the indirect effect passes through a mediator. The typical goal of mediational analyses is to identify the variable(s) that account for a treatment effect on an outcome.

In a seminal, oft-cited article, Baron and Kenny Core Criteria. (1986) defined the term mediator and established clear criteria for the demonstration of mediation. As they define the term and as we use it here, a mediator is a variable that "accounts for the relation between the predictor and criterion" (p. 1176). In our case, a mediator is a variable that accounts for the success of a tobacco-dependence treatment in preventing relapse. How does a mediator account for treatment effects? In a simple, single-mediator model (see Fig. 6.1), a mediator must meet the following criteria, according to Baron and Kenny (1986): (a) A treatment condition significantly accounts for variance in the mediator, (b) the mediator accounts for variance in relapse outcome, and (c) controlling for mediator relations with treatment and outcome eliminates or reduces the relation between the treatment and outcome. These relations can be tested optimally with structural equation modeling (SEM) techniques using a series of nested models (Hoyle & Smith, 1994; Kenny et al., 1998). SEM is optimal because it permits use of a latent variable approach in which error variance can be removed from the mediator and outcome. Some SEM programs can now handle dichotomous outcome variables (e.g., MPlus), thus permitting use of SEM in situations that violate the assumption of multivariate normality. For manifest variables, multiple or logistic regression strategies can be used to test the significance of individual and partialed paths (Kenny et al., 1998).

A generic mediation model is depicted in Figure 6.1A. To infer mediation and corroborate a process model, one must show that "Each variable in the causal chain affects the variable that follows it in the chain, when all variables prior to it, including the treatment, are controlled" (Judd & Kenny, 1981, p. 605). The essential steps for demonstrating mediation are showing that the treatment and the mediator are associated (i.e., Path *a* is significant) and that the mediator and the outcome are associated (i.e., Path *b* is significant) when treatment is statistically controlled (Kenny et al., 1998). In addition, if a significant association is found between the treatment and the outcome (Path *c* is significant), one expects to find that this association is reduced or eliminated when the mediator is statistically controlled in analyses (Path *ć* is reduced or nonsignificant). Complete mediation requires that the direct path from treatment to outcome be

145

reduced to zero when the mediator is included in the model (as shown in Fig. 6.1B; Baron & Kenny, 1986; Judd & Kenny, 1981). Over the years, scholars have softened on the issue of complete mediation and grown more accepting of partial mediation (e.g., Kenny et al., 1998, vs. Judd & Kenny, 1981), which is the most likely case in most models. Thus, the original criterion articulated by Judd and Kenny (1981)—that only one predictor (viz., the most proximal cause in the causal chain) should be significant in each of the three regression equations tested has been relaxed considerably, in apparent recognition of the fact that there are few mediating variables that are sufficient to explain all of a treatment's effect on an outcome.

The first criterion for mediation articulated by Baron and Kenny (1986) and others (a significant relation between the initial variable and outcome) has been disputed in the literature. In the strictest sense, it does not make sense to conduct mediational analyses in the absence of a significant treatment effect because there is no need to account for a nonexistent treatment effect (Baron & Kenny, 1986; McFall, 1978). Mediation is simply a special case of an indirect treatment effect on outcome, however. Indirect effects that pass through an intervening variable, such as a mediator, may be of substantive interest even in the absence of a direct effect of treatment on outcome (Holmbeck, 1997). Examination of the relations between a mediator and treatment and a mediator and outcome may suggest ways to improve treatments (e.g., by revising treatments to capitalize on the indirect effect) even in the absence of a significant direct effect. Some scholars have argued that establishing a significant treatment effect on outcome should not be a prerequisite for mediational analyses (Collins et al., 1998; MacKinnon, 2000; McFall, 1978) and have pointed out that this assumption is not appropriate in the case of small effect sizes or suppression (Shrout & Bolger, 2002). Similarly, if a treatment has a large effect on outcome that does not reach statistical significance due to low power, it may still be worthwhile to explore mediation. If a treatment is expected to have a distal effect on outcome that is mediated through complex causal chains or may be susceptible to other intervening influences (as is certainly the case when long-term abstinence rates are the target outcome), the investigator may wish to relax this criterion (Shrout & Bolger, 2002). If the treatment is expected to have a more proximal effect, then one may wish to retain this criterion (Shrout & Bolger, 2002). In addition, this criterion may not be appropriate in comparative treatment trials (Morgenstern & Longabaugh, 2000). In this study design, a treatment is compared to an alternative active treatment of known efficacy. Although the target

treatment may not perform significantly better than the alternative treatment, it may still influence outcome in a way that bears explaining by means of mediational analyses. In other words, a treatment should not go unexplored because it was compared against another efficacious treatment rather than against a straw-man or placebo control. If a new treatment fares as well as an accepted treatment, then much may be gained by studying and comparing the mechanisms of action of both. Kenny and colleagues suggest that mediational analyses in treatment failures may also yield interesting and informative results (Kenny et al., 1998).

Some authors have suggested an additional criterion for mediation and a means to test the criterion: the significance of the indirect or mediated effect. MacKinnon and colleagues have adapted and evaluated numerous standard error estimates and significance testing approaches to identify tests of mediated effects that have the greatest power and best Type-I error rates (MacKinnon, 1994; MacKinnon & Lockwood, 2003; MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002). The magnitude of a mediated effect is equal to the product of two path coefficients (a and b from Fig. 6.1). In a simple, three-variable model, this is also equivalent to the difference between the direct effect estimated without the mediator in the model vs. with the mediator in the model (c-c') from Fig. 6.1). This difference yields an estimate of the overall indirect effect in multiple mediator models. In an appropriately sized and powered model, it is possible to test the significance of the mediated effect in addition to testing the significance of Paths a, b, c, and c' as suggested by Kenny and colleagues (Baron & Kenny, 1986; Judd & Kenny, 1981; Kenny et al., 1998). The mediated effect (ab) can be tested for significance using the formula $z' = ab/\sqrt{a^2 \sigma_b^2 + b^2 \sigma_a^2}$ against an empirical z distribution (available on the web at http://www.public.asu.edu/~davidpm/ripl /freqdist.pdf) that takes into account deviations from normality that occur when one tests the product of coefficients (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002). Based on a comparison of several pointestimation and significance testing procedures, MacKinnon and colleagues (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002) recommended that investigators test the joint significance of Paths a and b and test the significance of the estimated mediated effect using the z' formula above if both Paths a and b are significant.

Stage-Sequential Approach. Although Kenny and colleagues' guidelines for mediation (Baron & Kenny, 1986; Judd & Kenny, 1981) are the most often cited and followed, alternative frameworks exist.

Collins and colleagues (Collins et al., 1998) have argued that mediation can be conceived as a cascade of events (coded categorically) initiated by the independent variable. Collins and colleagues (1998) define the following three independent criteria for establishing mediation: (a) the probability of an individual undergoing change in the mediator followed by change in the outcome is greater in the treatment group versus control group, (b) being in the treatment group increases the probability of change in the mediator occurring (when not already in the mediator stage), and (c) change in the mediator increases the probability of the outcome at every level of the initial, or treatment, variable (when not already in the outcome stage). This last criterion emphasizes that the mediator should be linked to the outcome regardless of treatment condition (i.e., this part of the chain reaction should exist regardless of whether the first domino is knocked over). In simpler terms, mediation is suggested when more people who experience the treatment (e.g., combination treatment vs. single modality treatments) and the specified (higher or lower) level of the mediator (e.g., urges to smoke) end up with the target outcome (e.g., 6-week abstinence).

Collins and colleagues' categorical framework has great illustrative value, but low statistical sophistication. Simple chi-square or logistic regression tests are conducted to examine whether treatment or mediator status influences subsequent outcomes in the hypothesized sequence of events. No estimate or test of a mediated effect is provided and all variables are treated as categorical. The Collins approach offers a way to characterize the potential clinical significance of a mediational effect, however, by depicting the proportions of individuals who are likely to experience a target sequence of treatment, mediator level, and outcome. We use this model to illustrate, rather than to test, mediational effects in the analyses described next.

SAMPLE MEDIATIONAL ANALYSES

The preceding review reflects significant advances in methods to test mediational hypotheses. To date, few of these advances have been applied to tobacco dependence treatment research. For example, little is known about how bupropion, the only nonnicotine agent currently approved as a firstline pharmacotherapy for tobacco cessation (Fiore et al., 2000), improves abstinence rates. Although some mediational research has been conducted regarding bupropion (see Lerman et al., 2002), past studies have not used state-of-the-art mediational analytical strategies, as described earlier.

In this chapter, we explore one possible mechanism (craving reduction) by which combined bupropion pharmacotherapy and individual smoking cessation counseling may increase short-term abstinence rates. We focus on this treatment combination for three primary reasons. First, bupropion efficacy has been established almost exclusively (but see Hall et al., 2002) in the context of co-occurring counseling (Richmond & Zwar, 2003). Second, problem-solving skills training and social support interventions are recommended in all smoking cessation interventions (Fiore et al., 2000), including those involving bupropion (Richmond & Zwar, 2003). Third, both bupropion and counseling are thought to work, in part, by reducing cravings for cigarettes, although through different pathways (e.g., bupropion may influence mesolimbic dopamine activity directly, whereas counseling may lead to avoidance of triggers and active coping with cravings). For these reasons, we present results of analyses testing the hypothesis that craving reduction mediates the effect of combined bupropion treatment and counseling on short-term abstinence rates. Although there are many other interventions and candidate mediators that likely influence successful cessation, we have selected this combined treatment condition and craving reduction primarily to illustrate different approaches to mediational analysis. We do not claim that craving reduction is the sole or primary mechanism of treatment action, although we have substantive reasons to investigate the potential mediating role of craving, in particular, as outlined next.

Recent research employing real-time data collection methods has demonstrated that cravings or urges to smoke are tightly linked to subsequent smoking among abstainers and ad libitum smokers 'Shapiro, Jamner, Davydov, & James, 2002; Shiffman et al., 1997, 2002, 2004). Some evidence suggests that craving is only weakly related to drug selfadministration and relapse, however (Tiffany, 1990). A more recent study using ecological momentary assessment reported that increases in craving on the quit day were predictive of point-prevalence smoking status at 3 months post-quit (McCarthy, Piasecki, Fiore, & Baker, 2006). In addition, a new cognitive neuroscience model of drug motivation affords a central role to craving as an index of conflict between competing response options (e.g., smoking and sitting in a movie theater; Curtin, McCarthy, Piper, & Baker, 2006). Thus, in light of recent research and theory, craving appears to be an important target for additional research.

We next report the results of different tests of the hypothesis that the beneficial effects of combined bupropion and counseling treatment on abstinence are mediated, in part, through reductions in craving. We use the traditional regression approach, SEMs with the mediators treated as latent variables, and then present results from SEMs using the stage-sequential approach to depict relations among treatment, craving, and abstinence using data from a recently completed randomized, placebo-controlled clinical trial of bupropion SR (sustained release) and counseling.

Adult smokers who reported being motivated to Current Study. quit were randomly assigned to receive either active or placebo bupropion SR in conjunction with eight sessions of brief (10-minute) individual cessation counseling or a no counseling, assessment control condition (McCarthy et al., in preparation). The study used a 2 (active drug vs. placebo) x 2 (counseling vs. no counseling) factorial design. Bupropion SR and placebo medication treatment began 1 week before quitting. Participants began taking one 150-mg pill in the morning 1 week before the ouit day and then increased to two 150-mg pills per day at 4 days prior to quitting. Participants were instructed to continue taking 300 mg per day for 8 weeks post-quit. Counseling consisted of two prequit sessions, a session on the quit day, and five post-quit sessions over the first month of the quit attempt. Counseling focused on coping, problem solving, and intratreatment social support, in accordance with recommendations in the Treating of Tobacco Use and Dependence Clinical Practice Guideline (Fiore et al., 2000). Participants attended an information session and five office visits (including a baseline assessment session) in the 3 weeks prior to their quit date. Participants attended another eight office visits over 8 weeks following the quit date and then completed monthly follow-up phone calls, with office visits for biochemical verification of abstinence claims at 6 and 12 months post-quit. In addition to attending visits, participants carried electronic diaries (EDs) for 2 weeks preceding and 4 weeks following the target quit date. Participants were instructed to complete brief (2- to 3-minute) reports in response to prompts at wake-up, three to five randomly selected times throughout the day, and bedtime.

Participants were regular smokers recruited via mass media who reported smoking at least 10 cigarettes per day and whose expired carbon monoxide (CO) level exceeded 9 parts per million at baseline. Potential participants were screened for serious psychopathology (bipolar disorder or psychosis), contraindications to use of bupropion SR (e.g., uncontrolled hypertension, history of seizure disorder, history of eating disorder, current heavy drinking), and current depression. Four hundred and sixty-three participants passed all screening, enrolled in the study, and attended the first study visit. Participants provided ratings of affect, withdrawal symptoms, and smoking behavior each evening before bedtime. Smoking status was assessed at in-person visits via self-report and confirmed by CO testing at each visit.

Mediational analyses were conducted using data from the 297 (64.1%) participants who did not relapse in the first week of the quit attempt. *Relapse* was defined as reporting smoking on three consecutive evening ED reports in the week beginning with the quit day. Participants who relapsed during the first week were excluded from mediational analyses to permit estimation of the mediator untainted by heavy and consistent smoking in the post-quit period. Candidate mediators were assessed each evening for 4 weeks following the quit day, via the ED. Specific with-drawal symptoms and affect ratings were collected via the ED nightly. For purposes of illustration, we focus on one candidate mediator: craving level at the outset of the quit attempt. Craving scores represent the average of two items derived from the Wisconsin Smoking Withdrawal Scale (Welsch et al., 1999) rated "on average since the last evening report" on an 11-point scale ranging from "No!!" to "Yes!!." The items were: "Bothered by the desire to smoke" and "Urge(s) to smoke."

We examined whether the estimated level of craving on the quit day (i.e., the estimated quit day intercept) or the change in craving over the first week of the quit attempt mediated the effects of combined treatment versus all other treatments on point-prevalence abstinence 6 weeks post-quit. We tested this hypothesis using two approaches to mediational analyses. First, we present results from a simple regression approach. Second, we present contrasting structural equation models that were used to estimate the critical paths in the mediational model and test the significance of the mediated effect as recommended by MacKinnon and colleagues (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002). We then present data from the SEM approach in the stage-sequential format to facilitate interpretation of the clinical significance of statistically significant effects.

The mediator was assessed during the first week of the quit attempt, when none of the 297 participants eligible for these analyses had relapsed. Because we excluded all participants who relapsed in the first week of the quit attempt, we can be confident that estimates of craving severity closest to the quit day were not influenced by relapse. The outcome in these analyses was biochemically verified 7-day point-prevalence abstinence 6 weeks post-quit (i.e., after the period of mediator assessment concluded). As such, we can have confidence that the mediator and outcome did not overlap in time. Treatment was ongoing during the mediator assessment period, however.

Six-week abstinence rates among the 297 people who did not relapse in the first week were as follows: 30% in the placebo condition, 31% in the counseling-only condition, 44% in the medication-only condition, and 51% in the combination treatment condition. Receiving both bupropion SR and counseling was associated with a significant increase in the likelihood of abstinence $\chi^2(1, N = 297) = 6.38, p < .02)$, relative to all other treatment conditions. Thus, the data meet one criterion for mediation: the treatment is related to the proximal (6-week) outcome, as one would expect. In the analyses reported next, we focus on the contrast between the combination treatment and the other three study conditions, captured using a single dummy-coded variable (0 = single or placebo treatment, 1 = combination treatment). We contrasted the combination treatment with the single-treatment conditions and the control condition because inspection of raw data suggested that the combination condition had unique relations with candidate mediators, whereas the single-treatment conditions were similar to the placebo condition.

Simple Regression Analyses

In the first set of mediational analyses, separate regression models were constructed to test Paths a, b, c, and c', as depicted in Figure 6.1. The candidate mediator tested using regression was a difference score between the craving summary score on the seventh day of the quit attempt minus the craving summary score from the quit day, divided by 7 days. Only 243 participants who maintained abstinence for at least 1 week provided ratings on both Days 1 and 7 and were included in these analyses. Other researchers have used simple difference scores as candidate mediators in formal mediational analyses (Lerman et al., 2002).

Path a linking treatment and the mediator was tested using linear regression. The combined treatment condition was not associated with craving difference scores. Thus, Path a did not reach significance in the regression modeling approach. Figure 6.1 depicts the significant standardized regression coefficient linking the combination condition versus all other treatments with the craving difference score.

Path *b* linking the difference score and 6-week relapse was tested using logistic regression, given the dichotomous outcome (0 = abstinent, 1 = smoking). Treatment was included as a control variable in this regression model. Logistic regression coefficients were standardized to permit estimation of the magnitude of the reduction in the direct effect of treatment on smoking outcome that occurred when controlling for the mediator in the regression analyses. The standardized logistic regression coefficient shown in Figure 6.1 was derived using the formula: beta_{yx} = $(b_{yx}S_x \times R)/s_{\text{logity}}$ (Menard, 1995). Path *b* was significant (Unstandardized *B* = 1.02, S*E* = .37, Wald = 7.73, *p* < .005), suggesting that increased craving from the quit Day to 1 week post-quit was associated with higher risk of relapse between Weeks 2 and 6 post-quit.

Path c is significant, as reported earlier (see Fig. 6.1 for the standardized coefficient for the combination treatment effect on relapse). Path c' appears to be slightly reduced in magnitude (from -.17 to -.15, a 12% reduction) when the mediator is included in the logistic regression model. Given the lack of relationship between treatment and craving difference scores in these analyses, however, this reduction in the direct effect cannot be interpreted as evidence of mediation.

In summary, regression analyses failed to establish one of the core criteria for mediation: evidence of a relationship between treatment and the mediator. Failure to find a treatment-mediator association in this analysis may reflect the crude nature of the mediator used here (a difference score) and the influence of error in the measurement of the mediator.

Structural Equation Modeling (SEM)

In SEM, mediation is studied through effects represented statistically as latent variables. In the current analysis, latent variables represented features of change in craving scores for each evening of the first week following the quit date. The relationship between the predictor (combined treatment vs. all other treatment conditions) and criterion (relapse) was first assessed through a probit regression model. The resulting regression estimate of -0.39 (SE = 0.162, t = -2.43) was statistically significant (although modest in magnitude, standardized beta = -.18), suggesting a lower likelihood of relapse in the combined treatment condition.

The mediational model tested attempted to explain the effects of the combined treatment on relapse through changes in craving following the quit attempt. The model thus considered up to seven post-quit craving scores, in addition to the combined treatment and relapse variables.



FIGURE 6.2 This figure depicts the structural equation model fit to the data. Loadings of craving scores collected nightly on Days 1 through 7 of the quit attempt were fixed at 1.0 for the quit-day intercept latent variable (crav_int). Loadings of craving Scores 1 and 7 were fixed at 0 and 6, respectively, for the latent slope variable (crav_slp). Intervening craving scores' loadings were not fixed to allow for nonlinear change in craving over the first week post-quit. Craving scores were allowed to have correlated residuals to account for autocorrelation across repeated measures. Treatment represents the contrast between combined counseling and bupropion SR treatment versus all other treatment conditions. The outcome variable is relapse, a dichotomous variable indicating that a person did not achieve CO-confirmed 7-day point-prevalence abstinence 6 weeks post-quit. Residual correlations were estimated.

Preliminary models applied only to the craving scores suggested highly nonlinear changes in craving scores during the first week post-quit. Moreover, even after accounting for individual variations in craving change, the residuals for craving scores collected closer in time tended to correlate positively, consistent with the presence of an autocorrelation structure. Thus, the SEM model used to represent the mediating effects of craving allowed for both nonlinear change (through use of estimated time scores among measures collected from Day 1 to Day 6 post-quit; Muthen & Muthen, 1998–2004, p. 83) and a first-order correlation structure among the craving score residuals (Muthen & Muthen, 1998–2004).

The latent variables, denoted in Figure 6.2 as *craving intercept* and *craving slope*, represent the quit-day level of craving and the average daily change in craving during the first week after quitting, respectively.

Both latent variables were considered potential mediators of the effects of the combined treatment on smoking relapse. The model in Figure 6.2 was fitted using Mplus (Muthen & Muthen, 1998–2004). Due to the presence of missing data (some respondents had missing reports) and the use of categorical outcome variables, the weighted least squares with mean- and variance-adjustment (WMLSV) estimation method (the default in Mplus) was used. Based on standard goodness-of-fit criteria, the model provided a close approximation to the data ($\chi^2 = 18.44$, df = 12, p = .08; RMSEA = .043; CFI = .94; TLI = .98; WRMR = .450).

Table 6.1 displays the model estimates associated with measurement of the latent mediators. The mean craving intercept and slope estimates represent the average growth trajectory across all smokers, and imply an average craving score of 7.66 on the quit day, and an average daily decline in craving of 0.21. The estimated time scores associated with the daily craving measures (displayed as the craving slope estimates) indicated the pattern of craving changed over the first week. For example, assuming 6 days of change from Day 1 to Day 7 (fixed loadings of 0 and 6 anchor the first and last measurements), it appears that the most substantial change on average occurred from Day 1 to Day 2 (2.57/6.00 = 43%), with slower rates of change in subsequent days.

To evaluate the mediational effects of the craving intercept and slope, we examined the estimates reported in Table 6.2. For each parameter, the raw estimate, standard error, and standard estimates are reported, along with the ratio of the raw estimate to standard error, which can be interpreted as approximate z statistics.

For the craving intercept, neither the path from combined treatment (a_{CINT}) nor the path to relapse (b_{CINT}) was statistically significant. By contrast, the corresponding paths for the craving slope were more substantial, with statistical significance attained for the path from craving slope to relapse (b_{CSLP}) and a marginally significant estimate for the path from treatment to craving slope (a_{CSLP}) . This suggests a greater mediating role for craving slope. Specifically, the combined treatment leads to a greater decline in craving scores over the first week post-quitt, and this greater decline, in turn, results in a lower likelihood of relapse. The direct effect of the combined treatment on relapse also declined in magnitude to -.26 in the mediational model, an effect that was no longer statistically significant.

To test the significance of the indirect effects associated with the two hypothesized mediating variables, we tested the two product coefficients,

	Estimate	Std. Error	Est./Std Error
Craving Intercept:			
Days 1-7	.00		
Craving Slope:			
Day 1	0.00		
Day 2	2.57	.40	6.43
Day 3	3.44	.46	7.46
Day 4	4.02	.51	7.91
Day 5	5.18	.54	9.68
Day 6	5.90	.49	12.14
Day 7	6.00		
Residual Variance:			
Days 1-7	2.05	.45	4.61
Adjacent Residual Covariance:			
Days 1-7	.64	.38	1.71
Mean Craving Intercept	7.66	.18	43.48
Mean Craving Slope	21	.03	-6.40
Residual Variance, Craving Intercept	3.10	.69	4.52
Residual Variance, Craving Slope	.07	.02	4.03
Residual Covariance,	.00	.06	.01
Craving Intercept and Slope			

TABLE 6.1 Mediational Model Estimates, Craving Measurement Parameters

 $a_{\text{CINT}} x b_{\text{CINT}}$ and $a_{\text{CSLP}} x b_{\text{CSLP}}$. For the craving intercept, the indirect effect estimate of -.001 had an estimated standard error of .017 using the delta method, whereas the craving slope indirect effect estimate of -.135 had an estimated standard error of .087. To evaluate the significance of the indirect effects, we compared the ratio of the indirect effect estimate to its standard error against z' tables developed by MacKinnon (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002). The ratio for craving slope = .135/.087 = .1.56 exceeded in magnitude the critical value associated with $\alpha = .05$ (approximately -1.00), suggesting a significant indirect effect through craving slope. By contrast, the ratio for the craving intercept = .001/.017 = .053 was not significant.

In summary, SEM fit to the data supported the hypothesis that craving patterns over time mediate treatment effects on relapse in a tobacco quit attempt. Specifically, the combination of bupropion SR treatment and counseling was associated with steeper declines in craving ratings over the first week of the quit attempt, which were associated with reduced risk of relapse. When this indirect effect was taken into account, the

Mediational Model Estimates, Structural Parameters						
and version and and and and and and and and and an	Estimate	Std. Error	Est. /Std. Error	Std. Estimate		
Craving Intercept on Treatment (a _{CINT})	02	.31	05	00		
Craving Slope on Treatment (a _{CSLP})	11	.06	-1.93	18		
Relapse on Craving Intercept (b _{CINT})	.05	.06	.96	.09		
Relapse on Craving Slope (b _{CSLP})	1.26	.44	2.89	.33		
Relapse on Treatment (c)	26	.17	-1.53	12		

TABLE 6.2 Mediational Model Estimates, Structural Parameters

direct effect of combination treatment on relapse was nonsignificant and nonessential to model fit. The estimated mediated effect was statistically significant for craving slope as well. As such, these data suggest that combination treatments increase early success rates by helping reduce cravings from peak levels quickly during the first week of a quit attempt.

Stage Sequential Approach

To illustrate the potential clinical significance of the significant mediated effect detected in SEM analyses, we performed a median split on factor scores derived from the SEM model and inspected the proportions of participants who experienced each possible stage sequence in the sample. These data are presented in Figure 6.3. The mediator is the factor score for the slope in craving over 1 week post-quit for each of the 293 individuals with enough data to be included in these analyses. A median split was performed on these factor scores. Scores below the median of -.23 indicated a rapid decline in craving over the first week post-quit. Scores above the median slope indicated persistent, worsening, or slow-to-resolve cravings. Presenting the data in the stage sequential framework suggests that the effect of combined treatment on standing on the mediator (estimated slope in craving over 1 week post-quit above vs. below the median) was substantial (a 20% difference across conditions) and of potentially great clinical significance. The 28% to 30% increase in the probability of abstinence associated with steeper declines in craving versus stable or increasing craving trends within each treatment group was also substantial and of likely clinical significance. Overall, these data suggest that the combined treatment was



FIGURE 6.3 Results of SEM analyses as stage-sequential processes. Path coefficients represent the probability that a person will enter each category. Those in the combined treatment condition were more likely to have steeper reductions in craving over the first week post-quitt (i.e., their factor scores fell below the median for changes in craving) than were those in the single treatment or placebo conditions. In both treatment groups, a more rapid decline in craving was associated with an increased probability of abstinence at 6 weeks post-quit, relative to those whose craving slope factor scores were above the median.

associated with an increase in the probability of the desired sequence of rapidly declining craving and abstinence occurring from 23% (in the single or no treatment groups) to 40%. This near doubling in the rate of rapidly reduced craving followed by short-term success in quitting suggests that the combined treatment may offer substantial clinical benefit, in addition to being statistically significant in SEM analyses.

CONCLUSIONS

In the first part of this chapter, we presented diverse rationales for conducting mediational analyses and proposed diverse means of doing so. In the second part of the chapter, we provided examples of the divergent results that may emerge from application of different analytic methods to the same mediational hypothesis. Although we cannot be sure which pattern of results best approximates the true state of nature, we advocate for the latent variable approach that yielded positive results in this sample. The use of difference scores for the regression analyses was admittedly crude, particularly in comparison to the nonlinear growth in craving modeled in the SEM analyses. Even if we had aggregated several reports of craving, rather than using a difference score, measurement error would still have influenced results of our mediational tests. Only a latent variable approach can perform the critical step of removing error from the measurement of the mediator in social science research. In addition, SEM offers flexibility in the construction of the measurement model, permitting nonlinearity and addressing autocorrelation among repeated measures, as illustrated earlier. Performing a median split on factor scores on the latent craving slope construct allowed us to capture the potential clinical significance of the effects detected in the SEM analyses. Such presentation aids in the interpretation of mediational effects and their likely magnitude in populations of interest.

In the illustrative analyses presented here, we did not adhere to all of the best practices guidelines for mediation. For example, we did not include in the SEM analyses control variables that likely influence standing on the mediator, outcome, or both. Removing variance that is unrelated to predictors of interest will increase the sensitivity of the target tests. Tobacco dependence level and cohabitation with a smoker are but two possible influences on craving and relapse. We also neglected to include potential moderators of the hypothesized mediational pathway, such as gender. A more thorough test of mediational hypotheses would include control variables and examine moderating effects.

In addition, we permitted temporal overlap between treatment and the mediator in the analyses presented earlier, without controlling for pretreatment mediator levels in an effort to avoid excessive complexity in these illustrative analyses. Ideally, one could temporally divorce treatment and the mediator. In ongoing treatments such as bupropion SR therapy and multisession individual counseling, such temporal ordering can be difficult. In such cases, statistical control of pretreatment mediator levels is highly recommended. In earnest mediational analyses, we might also elect to examine a continuous rather than dichotomous outcome to increase the sensitivity of tests of treatment and mediator effects. Rather than focusing on abstinence versus relapse, we might have focused on smoking heaviness, smoking trajectory, or latency to lapse or relapse. Although these continuous outcomes are of less vital public health importance, they may be related to treatment or mediators in such a way that suggests new action or conceptual models, and thus, treatment innovation.

Each of the methods used in our sample analyses has associated costs and benefits. We have noted some of the potential limitations of the choices we made in our illustrative analyses, as well. We do not wish to suggest that the method we used is necessarily the best method. Instead, we hope that the preceding discussion and examples have highlighted some of the potential benefits of tackling mediation in research and the hidden costs of common analytic choices.

Two other observations are warranted in closing. First, the results presented here are of substantive importance. Our analyses suggest that cigarette craving early in a quit attempt is an important influence on quitting success. Additionally, SEM analyses suggest that the evaluated treatments work, in part, by suppressing craving. This finding is important, if replicated, because it underscores the importance of craving, and it suggests that treatments may be improved by enhancing their ability to reduce craving.

Second, the results are important because they constitute suggestive evidence that the field of tobacco research may now be in the position to heed some of McFall's earlier counsel and explore the mechanisms by which treatments exert their effects. The availability of ecological momentary assessment data and powerful statistical techniques may now permit us to fulfill McFall's vision for the field.

REFERENCES

- Baron, R. M., & Kenny, D. A. (1986). The moderator-mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. Journal of Personality and Social Psychology, 51, 1173–1182.
- Chen, H. T. (1990). Theory-driven evaluations. Newbury Park, CA: Sage.
- Cinciripini, P. M., Cinciripini, L. G., Wallfisch, A., Haque, W., & Van Vunakis, H. (1996). Behavior therapy and the transdermal nicotine patch effects on cessation outcome, affect and coping. *Journal of Consulting and Clinical Psychology*, 64, 314–323.
- Cinciripini, P. R., Wetter, D. W., Fouladi, R. T., Blalock, J. A., Carter, B. L., Cinciripini, L. G., & Baile, W. F. (2003). The effects of depressed mood on smoking

cessation: Mediation by postcessation self-efficacy. Journal of Consulting and Clinical Psychology, 71, 292–301.

- Cole, D. A., & Maxwell, S. E. (2003). Testing mediational models with longitudinal data: Questions and tips in the use of structural equation modeling. *Journal of Abnormal Psychology*, 112, 558–577.
- Collins, L. M., Graham, J. W., & Flaherty, B. P. (1998). An alternative framework for defining mediation. *Multivariate Behavioral Research*, 33, 295–312.
- Curtin, J. J., McCarthy, D. E., Piper, M. E., & Baker, T. B. (2006). Implicit and explicit drug motivational processes: A model of boundary conditions. In R. Weirs & A. W. Stacy (Eds.), Handbook of Implicit Cognition and Addiction. Thousand Oaks, CA: Sage.
- DeRubeis, R. J., & Feeley, M. (1990). Determinants of change in cognitive therapy for depression. Cognitive Therapy and Research, 14, 469–482.
- Eddy, J. M., Dishion, T. J., & Stoolmiller, M. (1998). The analysis of intervention change in children and families: Methodological and conceptual issues embedded in intervention studies. *Journal of Abnormal Child Psychology*, 26, 53-69.
- Feeley, M., DeRubeis, R. J., & Gelfand, L. A. (1999). The temporal relation of adherence and alliance to symptom change in cognitive therapy for depression. *Journal* of Consulting and Clinical Psychology, 67, 578–582.
- Fiore, M. C., Bailey, W. C., Cohen, S. J., et al. (2000). Treating tobacco dependence and use. Clinical practice guideline. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service.
- Goldfried, M.R., Greenberg, L. S., & Marmar, C. (1990). Individual psychotherapy: Process and outcome. Annual Review of Psychology, 41, 659-688.
- Hall, S. M., Humfleet, G. L., Reus, V. I., Munoz, R. F., Hartz, D. T., & Maude-Griffin, R. (2002). Psychological intervention and antidepressant treatment in smoking cessation. Archives of General Psychiatry, 59, 929–937.
- Haynes, S. N. (1992). Models of causality in psychopathology: Toward dynamic, synthetic, and nonlinear models of behavior disorders. Needham Heights, MA: Allyn & Bacon.
- Herting, J. R. (2002). Evaluating and rejecting true mediation models: A cautionary note. *Prevention Science*, *3*, 285–289.
- Holland, P. W. (1988). Causal inference, path analysis, and recursive structural equation models. Sociological Methodology, 18, 449-484.
- Holmbeck, G. (1997). Toward terminological, conceptual, and statistical clarity in the study of mediators and moderators: Examples from child-clinical and pediatric psychology literatures. *Journal of Consulting and Clinical Psychology*, 65, 599–610.
- Howard, K. I., Lueger, R. J., Maling, M. S., & Martinovich, Z. (1993). A phase model of psychotherapy outcome: Causal mediation of change. *Journal of Consulting and Clinical Psychology*, 61, 678–685.
- Hoyle, R. G., & Smith, G. T. (1994). Formulating clinical research hypotheses as structural equation models: A conceptual overview. *Journal of Consulting and Clinical Psychology*, 62, 429–440.
- Judd, C. M., & Kenny, D. A. (1981). Process analysis: Estimating mediation in treatment evaluations. *Evaluation Review*. 5. 602–619.

- Kazdin, A. E., & Kendall, K. C. (1998). Current progress and future plans for developing effective treatments: Comments and perspectives. Journal of Clinical Child Psychology, 27, 217–226.
- Kazdin, A. E. (1999). Current (lack of) status of theory in child and adolescent therapy research. *Journal of Clinical Child Psychology*, 28, 533-543.
- Kazdin, A. E. (2000). Understanding change: From description to explanation in child and adolescent psychotherapy research. *Journal of School Psychology*, 38, 337–347.
- Kazdin, A. E. (2001). Bridging the enormous gaps of theory with therapy research and practice. Journal of Clinical Child Psychology, 30, 59-66.
- Kenny, D. A., Kashy, D. A., & Bolger, N. (1998). Data analysis in social psychology. In D. Gilbert, S. T. Fiske, & G. Lindzey (Eds.), *Handbook of social psychology* (Vol. 1, 4th ed., pp. 233–265). New York: McGraw-Hill.
- Lerman, C., Roth, D., Kaufmann, V., Audrain, J., Hawk, L., Liu, W., Niaura, R., & Epstein, L. (2002). Mediating mechanisms for the impact of bupropion in smoking cessation treatment. Drug and Alcohol Dependence, 67, 219–223.
- Lipsey, M. W. (1993). Theory as method: Small theories of treatments. In L. B. Sechrest & A. G. Scot (Eds.), New directions for program evaluation (NIH Research Monograph No. 142, pp. 140–183). Rockville, MD: National Institute on Drug Abuse.
- MacCorquodale, K., & Meehl, P. E. (1948). On a distinction between hypothetical constructs and intervening variables. *Psychological Review*, 55, 95–107.
- MacKinnon, D. P. (2000). Contrasts in multiple mediator models. In J. S. Rose, L. Chassin, C. C. Presson, & S. J. Sherman (Eds.), Multivariate applications in substance use research: New methods for new questions (pp. 141–160). Mahwah, NJ: Lawrence Erlbaum Associates.
- MacKinnon, D. P. (1994). Analysis of mediating variables in prevention and intervention studies. In A. Cázares & L. Beatty (Eds.), Scientific methods for prevention intervention research (NIDA Monograph No. 139, pp. 127–153). Rockville, MD: National Institute on Drug Abuse.
- MacKinnon, D. P., & Lockwood, C. M. (2003). Advances in statistical methods for substance abuse prevention research. *Prevention Science*, 4, 155–171.
- MacKinnon, D. P., Lockwood, C. M., Hoffman, J. M., West, S. G., & Sheets, V. (2002). A comparison of methods to test mediation and other intervening variable effects. *Psychological* Methods, 7, 83–104.
- MacKinnon, D. P., Taborga, M. P., & Morgan-Lopez, A. A. (2002). Mediation designs for tobacco prevention research. Drug and Alcohol Dependence, 68, S69–S83.
- Marston, A. R., & McFall, R. M. (1971). Comparison of behavior modification approaches to smoking reduction. Journal of Consulting and Clinical Psychology, 36, 153–162.
- McCarthy, D. E., Bolt, D. M., Lawrence, D. L., Piasecki, T. M., Fiore, M. C., & Baker, T. B. (in preparation). A randomized controlled clinical trial of bupropion SR and individual smoking cessation counseling. Manuscript in preparation.
- McCarthy, D. E., Piasecki, T. M., Fiore, M. C., & Baker, T. B. (2006). Life before and after quitting smoking: An electronic diary study. *Journal of Abnormal Psychology*, 115, 454–466.
- McFall, R. M. (1970). Effects of self-monitoring on normal smoking behavior. Journal of Consulting and Clinical Psychology, 35, 135–142.

- McFall, R. M. (1978). Smoking cessation research. Journal of Consulting and Clinical Psychology, 46, 705–712.
- McFall, R. M., & Hammen, C. L. (1971). Motivation, structure, and self-monitoring: Role of nonspecific factors in smoking reduction. *Journal of Consulting and Clinical Psychology*, 37, 80–86.
- McFall, R. M., & Lillesand, D. B. (1971). Behavior rehearsal with modeling and coaching in assertion training. *Journal of Abnormal Psychology*, 77, 313-323.
- Meehl, P. E. (1978). Theoretical risks and tabular asterisks: Sir Karl, Sir Ronald, and the slow progress of soft psychology. *Journal of Consulting and Clinical Psychology*, 46, 806–834.
- Menard, S. (1995). Applied logistic regression analysis (Sage University Paper series on Quantitative Application in the Social Sciences, 07-106). Thousand Oaks, CA: Sage.
- Morgenstern, J., & Longabaugh, R. (2000). Cognitive-behavioral treatment for alcohol dependence: A review of evidence for its hypothesized mechanisms of action. Addiction, 95, 1475–1490.
- Muthen, L. K., & Muthen, B. O. (1998–2004). Mplus user's guide (3rd ed.). Los Angeles, CA: Muthen & Muthen.
- Piasecki, T. M., Fiore, M. C., McCarthy, D. E., & Baker, T. B. (2002). Have we lost our way? The need for dynamic formulations of smoking relapse proneness. Addiction, 97, 1093–1108.
- Richmond, R., & Zwar, N. (2003). Review of bupropion for smoking cessation. Drug and Alcohol Review, 22, 203–220.
- Rozeboom, W. W. (1956). Mediation variables in scientific theory. Psychological Review, 63, 249-264.
- Rubin, D. B. (1974). Estimating causal effects of treatments in randomized and nonrandomized studies. Journal of Educational Psychology, 66, 688-701.
- Shadish, W. R., & Sweeney, R. B. (1991). Mediators and moderators in metaanalysis: There's a reason we don't let dodo birds tell us which psychotherapies should have prizes. Journal of Consulting and Clinical Psychology, 59, 883–893.
- Shapiro, D., Jamner, L. D., Davydov, D. M., & James, P. (2002). Situations and moods associated with smoking in everyday life. Psychology of Addictive Behaviors, 16, 342–345.
- Shiffman, S., Engberg, J. B., Paty, J. A., Perz, W. G., Gnys, M., Kassel, J. D., & Hickcox, M. (1997). A day at a time: Predicting smoking lapse from daily urge. Journal of Abnormal Psychology, 106, 104–116.
- Shiffman, S., Gwaltney, C. J., Balabanis, M. H., Liu, K. S., Paty, J. A., Kassel, J. D., Hickcox, M., & Gnys, M. (2002). Immediate antecedents of cigarettes smoking: An analysis from ecological momentary assessment. *Journal of Abnormal Psychology*, 111, 531–545.
- Shiffman, S., Paty, J. A., Gwaltney, C. J., & Dang, Q. (2004). Immediate antecedents of cigarette smoking: An analysis of unrestricted smoking patterns. *Journal of Abnormal Psychology*, 113, 166–171.
- Shrout, P. E., & Bolger, N. (2002). Mediation in experimental and nonexperimental studies: New procedures and recommendations. Psychological Methods, 7, 422-445.
- Smith, S. S., Jorenby, D. E., Leischow, S. J., Nides, M. A., Rennard, S. I., Johnston, J. A., Jamerson, B., Fiore, M. C., & Baker, T. B. (2003). Targeting smokers at

increased risk for relapse: Treating women and those with a history of depression. Nicotine and Tobacco Research, 5, 99–109.

- Tang, T. Z., & DeRubeis, R. J. (1999). Sudden gains and critical sessions in cognitivebehavioral therapy for depression. *Journal of Consulting and Clinical Psychology*, 67, 894–904.
- Tiffany, S. (1990). A cognitive model of drug urges and drug-use behavior: Role of automatic and nonautomatic processes. *Psychological Review*, 97, 147–168.
- Weersing, V. R., & Weisz, J. R. (2002). Mechanisms of action in youth psychotherapy. Journal of Child Psychology and Psychiatry, 43, 3-29.
- Welsch, S. K., Smith, S. S., Wetter, D. W., Jorenby, D. E., Fiore, M. C., & Baker, T. B (1999). Development and validation of the Wisconsin Smoking Withdrawal Scale. Experimental and Clinical Psychopharmacology, 4, 354–361.
- West, S. G., & Aiken, L. S. (1997). Toward understanding individual effects in multicomponent prevention programs: Design and analysis strategies. In K. J. Bryant, M. Windle, & S. G. West (Eds.), The science of prevention: Methodological advances from alcohol and substance abuse research (pp.167–210). Washington, DC: American Psychological Association
- Wiggins, J. S. (1973). Personality and prediction: Principles of personality assessment. Reading, MA: Addison-Weslev.