

Transdisciplinary science applied to the evaluation of treatments for tobacco use

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Transdisciplinary research involves the integration of measures and methods across diverse response systems and levels of analysis, with that integration occurring via a synthesis of theories and models of different scientific disciplines. This paper first discusses the need for transdisciplinary research. The paper then articulates a model to guide the comprehensive evaluation of treatments for tobacco use and discusses how transdisciplinary research might be integrated into this treatment evaluation model. The potential benefits and costs of a transdisciplinary approach are discussed, along with selected research projects from the Transdisciplinary Tobacco Use Research Centers.

Introduction

The goals of this paper are to provide a model for how treatment of tobacco dependence may be studied by using a transdisciplinary approach and how research conducted at the NIH-funded Transdisciplinary Tobacco Use Research Centers (TTURCs) “fits” with this model. We refer the reader to other papers in this special issue for formal definitions of transdisciplinarity, but for the present we will say that transdisciplinary research is characterized by an integration of measures and methodological approaches across different response systems and levels of analysis (e.g., from subcellular to interpersonal and social), with that integration occurring via a synthesis of theories and models of different scientific disciplines. It is not sufficient that diverse measures be employed; rather, the *rationale for their use must reflect integration that emerges from different perspectives characteristic of distinct knowledge bases*—that is,

from the theoretical perspectives of distinct disciplines. Therefore, an appraisal of transdisciplinarity requires not only an examination of diverse measures and methodological approaches (e.g., manipulations, types of intervention) but also an examination of why these were gathered or done and how they are interpreted. Thus, appraisal of transdisciplinarity requires a deep level of analysis and cannot be captured merely by tabulating types of dependent measures used in a research enterprise.

Goals and rationale for a transdisciplinary strategy

Based on research conducted over the past 20 to 30 years, there is increasing recognition that our scientific disciplines represent pragmatic social constructions that do not, in fact, study discrete, independent facets of nature. That is, although we may sequester ourselves, our papers, and our sources of financial support into discipline-defined departments, journals, and grant review panels, diseases and disorders recognize no such boundaries. Mounting research shows striking reciprocal relations (i.e., mutual influences) among thought patterns, emotions, social factors, biochemical/physiologic reactions, genes, immunologic responses, and brain activity in the etiology and maintenance of diseases and disorders. For instance, there is substantial evidence that psychological stressors lead to a host of physiologic reactions, such as increased heart rate and blood

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pressure, and that these, in turn, appear to lead to a variety of pathophysiologic changes, including damage to the endothelium, making it susceptible to inflammation and lipid deposition, and myocardial ischemia (Fuster, Badimon, Badimon, & Chesebro, 1992; Kop, Gottdiener, & Krantz, 2001; Manuck, 1994). These, in turn, lead to increased vulnerability to coronary artery disease. Not only do individual differences in phasic stress reactivity lead to coronary artery disease, but the influence of these phasic events is potentiated by more global person-factors, such as socioeconomic status, and affective or psychopathologic syndromes, such as hostility and depression (Lynch, Everson, Kaplan, Salonen, & Salonen, 1998; Smith & Ruiz, 2002). It is also clear that myocardial infarction (MI) and other serious cardiac events can, in turn, cause depression (Hays, Marshall, Wang, & Sherbourne, 1994). How heart disease subsequently and reciprocally influences affect (e.g., through restriction of activities and reinforcement, or through fear of death) and then again how post-MI affect further influences heart disease (e.g., failure to adhere to dietary, exercise, or medication regimens, and so on) are topics of considerable current research (Smith & Ruiz, 2002). The emerging picture, however, is that coronary heart disease (and other diseases as well) results from a cascade of reciprocal relations among biological, psychological, social, and societal influences—all played out against a backdrop of genetic strengths and vulnerabilities (e.g., Hays et al., 1994). Current knowledge about the origins of heart disease makes a powerful argument for characterizing the interplay of diverse forces or influences over time.

Research on addictive disorders suggests similarly complex causal relations, amenable to diverse levels of analysis. For instance, there is mounting evidence of a strong genetic influence on personality factors, such as impulsivity (behavioral undercontrol), that mark a heightened risk of addiction (Slutske et al., 2002). Moreover, researchers have recently demonstrated strong interactive effects between socioregional environments and the genetic influences on adolescent alcohol use (Dick, Rose, Viken, Kaprio, & Koskenvuo, 2001), with a four- to five-fold difference in the magnitude of genetic effects between environmental extremes. Additionally, the transgenerational impacts of parental drinking are blunted by children's autonomic reactions (suppression of vagal tone) to a psychological stressor (El-Sheikh, 2001).

Examples such as those cited above suggest that diseases/disorders cannot be properly understood without assessing them both from different theoretical perspectives and across different levels of analysis,¹ and with integration across these dimensions. We further assert that *treatment* must be studied from such a transdisciplinary perspective because the complexity and multifaceted natures of diseases/disorders are affected by treatments that themselves

have complex, multifaceted impacts—influencing neuropharmacology, metabolism, cognition, social relations, behavior, and so on. Moreover, all of these actions may be modulated by individual differences that themselves may reflect genetic, personality/temperament, socioeconomic, and learning history influences (and others, as well; see Comings et al., 1997; Hatsukami, Skoog, Allen, & Bliss, 1995; Lerman & Berrettini, 2003; Lerman & Niaura, 2002; Perkins, 2001; Piasecki, Fiore, & Baker, 1998; Sabol et al., 1999; Zelman, Brandon, Jorenby, & Baker, 1992). Finally, this multidisciplinary approach not only cuts across multiple disciplines and levels of analysis in the development of innovative treatments but also demands a multidisciplinary approach to anticipating and addressing issues related to the clinical integration and delivery of these new treatments.

Not only are we concerned with integrating methodological approaches and measures, but transdisciplinary research also requires that we address fundamental differences in perspectives and values underlying these methodological approaches. For example, transdisciplinary groups working in a variety of areas have grappled with the values embedded in the choice of research design and strategies, and with contrasting intellectual starting points regarding the role of biology, social context, and behavior (Schrecker, Acosta, Somerville, & Bursztajn, 2001) in addiction, as well as in other conditions. A recent paper by Schrecker and colleagues (2001) articulates the importance of using multiple, diverse research methods and the importance of analyzing core methodological assumptions—that is, background assumptions about how the world works, which are unavoidably embedded in the choice of research design and strategies. These assumptions may have significant ethical implications when they are embodied in research leading to findings that are

¹The term *levels of analysis* is related to transdisciplinarity but is distinct from it. For instance, psychologists may study intracellular events, responses captured by brain images, overt behavior, interpersonal behavior, and group behavior. Research done at these different levels of analysis would certainly be associated with different assessment approaches, methodologies, and assumptions. In this sense, diversity in levels of analysis captures much of what we mean by transdisciplinarity. Thus, in some cases, intradiscipline differences can dwarf interdiscipline differences. However, it is true that disciplines often bring more to the table than differences in level of analysis and attendant methodologies. For instance, the psychologist studying group processes may make very different assumptions, use different methods, and test different theories than would cultural anthropologists, communication scientists, and sociologists who are also studying group processes. Thus, when we use the term *transdisciplinary*, we mean that, ideally, the research enterprise reflects a theoretical synthesis across distinct disciplines, and that the researchers employ multiple levels of analysis.

subsequently regarded as authoritative, whether in clinical practice or in public policy (Schrecker et al., 2001).

Given that treatments exert multifaceted, reciprocal causal effects, and given that each discipline carries with it certain biases and perspectives, we believe that a transdisciplinary approach to tobacco treatment evaluation and analysis will yield a fuller, more comprehensive understanding of how treatments exert their effects. This understanding, in turn, has the potential to lead to:

1. More accurate predictions of treatment effects and more accurate early markers of treatment response.
2. Greater cumulative progress in the development of new and superior treatments.
3. Greater understanding of the range of treatment effects across diverse outcomes and populations.
4. Greater understanding of issues related to the clinical integration of new treatments.
5. Superior ability to match patients to optimal treatments.
6. Greater understanding of how to spur treatment seeking and treatment adherence among tobacco users.
7. Richer theoretical models that reflect diverse values, beliefs and conceptual assumptions of various disciplines; and research designs that reflect a methodological self-consciousness.

In sum, a transdisciplinary approach should facilitate the development of a rational basis for understanding, developing, and refining treatments for tobacco dependence and use.

While a transdisciplinary approach, in theory, should lead to greater research progress, it is important to note that there are potential disadvantages to

this approach. These include: (a) The cost of *each* research study could be potentially greater since studies should involve relatively greater numbers of investigators, measures, and so on, (b) The effort to achieve breadth of analysis and integration may encourage superficial investigation that does not characterize particular mechanisms in a programmatic, focused manner, (c) Assembling transdisciplinary research teams poses significant challenges. For instance, to promote meaningful communication, some team members may require training in different disciplines. Or it may simply be very difficult to identify compatible, highly competent colleagues who value the contributions of different disciplines, (d) The considerable investment of time and money required for transdisciplinary research may decrease an investigator's ability to assess objectively the worth or status of a treatment or study. In any event, at present, transdisciplinarity is a promissory note. This approach itself requires study to determine whether it is cost-effective, relative to traditional approaches, in terms of yield of research advances and progress.

A conceptual model for the transdisciplinary analysis of tobacco dependence treatment research

Figure 1 depicts a treatment appraisal model. The model is not wholly unique, nor is it uniquely relevant to a transdisciplinary perspective. However, we will use this model to illustrate the potential benefits of, as well as challenges to, transdisciplinary integration. Moreover, the model makes clear that a comprehensive transdisciplinary treatment evaluation strategy must be applied to the multiple facets of a treatment

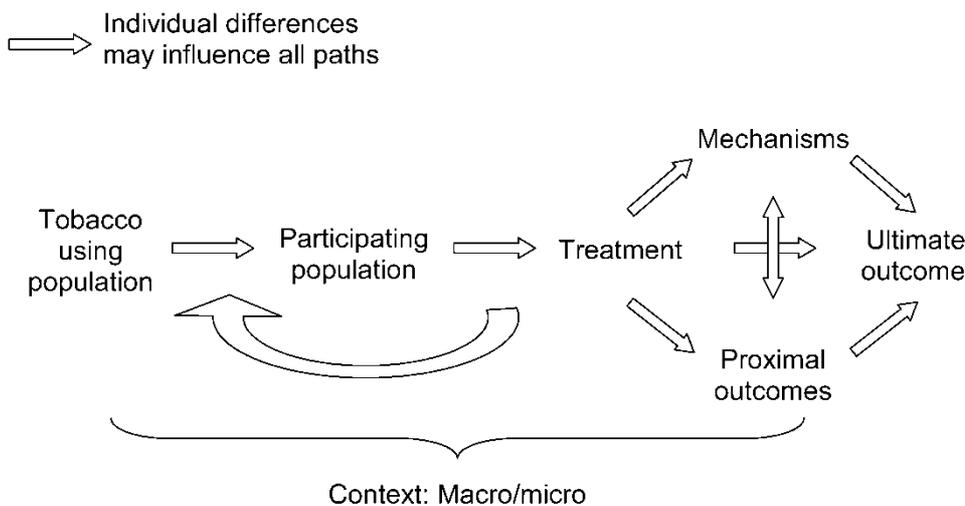


Figure 1. Potential facets of tobacco treatment evaluation and possible interrelationships among the facets. The figure depicts assessment or evaluation opportunities as a population of smokers is recruited for treatment, is treated, and then undergoes both short- and long-term reactions to treatment. The smoker's status along the paths linking treatment evaluation facets might be influenced both by individual differences among participants and by the contexts including the smokers, the treatments, and the evaluation-enterprise.

evaluation enterprise. A thorough appraisal of treatments requires much more than a simple determination of efficacy. Treatments may be characterized with respect to their appeal to the target population, mechanisms of action, moderation by individual differences, and so on, and all of these may be affected by the contexts in which the patient and treatments exist. It is important to recognize that all such facets of treatment appraisal may be conceptualized and researched from a transdisciplinary perspective. The TTURCs are performing research that exemplifies some, but not all, components of the model. In what follows, we will discuss the relevance of the treatment appraisal model for transdisciplinary tobacco treatment research, and will then present examples of how TTURC research both within and across TTURCs, is addressing the different facets of this model.

Smoking population

Reading Figure 1 from left to right, it is apparent that an informed analysis of a treatment requires an analysis of the population available for treatment. The population available for treatment is a product of numerous factors. For instance, as with all other elements of the model, population may be affected by the macro and micro contexts that include members of the population. No simple, clear-cut distinction can be made between micro and macro contexts. The distinction is used here merely to indicate the range or continuum of contextual factors that might influence model elements. For instance, the population of smokers available at any one point in time might reflect societal factors, such as prohibitions against smoking and taxation levels, that would presumably shrink the numbers and perhaps range of smokers available for treatment. Contextual effects could also be appraised at less global (more micro) levels—for instance, a family's interaction pattern (e.g., expressed emotion; Wendel, Miklowitz, Richards, & George, 2000) might affect the development of smoking and thus affect the population of smokers (albeit the effect would be slight). The point here is that the appropriateness and potential applicability of treatment cannot be gauged without considering the nature of the smoking population to which treatment might ultimately be applied. For instance, have smokers become "hardened," or more dependent, and therefore require more intense treatment? Or has the population of smokers become less affluent or lower SES and therefore requires inexpensive, very accessible interventions?

One example of how the TTURCs are appraising the nature of the smoking population is research conducted at the University of Wisconsin TTURC that is designed to yield a multidimensional and continuous index of nicotine dependence (the

Wisconsin Index of Smoking Dependence Motives, WISDM) (Piper et al. in press). A wide array of indices, tapping multiple levels of analysis, will be used to validate the WISDM, such as biochemical assays, behavioral economic (demand elasticity) response patterns, and clinical indices (e.g., relapse vulnerability). Some of these indices are clinically significant and some only theoretically significant; however, all can be used to validate the WISDM since all are unambiguously linked to dependence via a well-articulated model of the dependence construct. The WISDM has been administered to representative populations of smokers in order to characterize the level of nicotine dependence of smokers outside the treatment context.

Participating population

Not every smoker in the population will enter or participate in treatment. Treatment *participation* (i.e., the population that actually enters treatment) may be influenced by several factors:

- *Contextual factors* may affect treatment participation across a range of conceptualizations of context. At a societal level, participation may be spurred by increases in the price of cigarettes or by stigmatization of smoking and associated actions, such as smoking bans and antismoking campaigns. At a more proximal or micro level, a worried and persistent spouse or child may similarly prod treatment entry and participation. The transdisciplinary approach fosters a concern not only for measuring "context" at different levels (e.g., societal, family) but also for considering how contextual factors may work together to exert additive or interactive effects in fostering receptivity or resistance to treatment. For instance, one could study the extent to which tobacco use in an individual's family might lessen the impact of more remote societal influences that otherwise would encourage participation.
- *Individual differences* could certainly affect which tobacco users enter treatment. Researchers have long studied how motivational factors, personal health status, and socioeconomic factors might influence the individual tobacco user's likelihood of entering treatment. Other factors might include genotype, intelligence/educational status, coping style, and so on.
- *Treatment availability and accessibility* no doubt influence participation. Although this issue has not been explored intensively, there is evidence that individuals may be reluctant to enter lengthy or demanding treatments (Fiore et al., 1990; Lichtenstein & Hollis, 1992), while they are more willing to use over-the-counter pharmacotherapy in a self-directed quit attempt (Centers for Disease

Control, 2000; Hu, Sung, Keeler, & Marciniak, 2000). Moreover, *type* of treatment may exert effects that cannot be explained by treatment intensity per se. For example, some smokers remain interested in hypnosis treatments despite an absence of supporting efficacy data (Fiore et al., 2000).

The above review reveals that there are numerous opportunities to explore how individual features of tobacco users render them more or less attracted to treatments, and how this relationship could be affected by the contexts that include both the treatment and the individual. In closing, evaluating treatments and their potential impacts will be informed by analyses of how many and which sorts of tobacco users can be engaged in treatment. In addition, the development of strategies to enhance treatment participation and exposure is a vital intervention goal.

Several TTURCs are conducting research that is designed to assess how features of treatment may influence the nature of the presenting population. For instance, the University of Minnesota TTURC will investigate whether an altered treatment goal influences smokers' interest and participation in treatment. Specifically, these investigators will assess whether reducing tobacco toxin exposure, or a harm reduction treatment (strategies designed to permit continued nicotine intake but with reduced health risk), encourages a greater number of smokers or different types of smokers to enter treatment (Lemmonds, Mooney, Reich, & Hatsukami, in press). Moreover, Minnesota researchers will determine whether interest in potential exposure reduction products is moderated by individual differences such as information processing style (Tiffany, 1990). Other TTURCs are addressing the question of how to induce a greater portion of the smoking population to enter treatment. For instance, the University of Wisconsin TTURC retains an abstinence treatment goal but offers one treatment, *Quitting Smoking for Life*, over the Internet (Gustafson et al., 1999). Perhaps more smokers will participate in treatment or use it at higher rates, if treatment is available in-home, 24 hours per day, and the type and amount of involvement are under a smoker's control.

Treatment

The range of efficacious/effective treatments certainly provides fodder for transdisciplinary research. For instance, some treatments directly alter neuropharmacology through the use of medications, while others involve verbal psychotherapy aimed at changing behaviors and cognitions thought to promote tobacco use. Others involve changing reinforcement contingencies for drug use (e.g., by exacting a monetary cost for drug use), and still others involve changing social

systems (e.g., engineering social support). In addition, treatments may have different end points, since some aim to increase interest in quitting rather than quitting success per se, and others may aim to reduce, not curtail, an individual's level of tobacco exposure. Finally, it is important to note that not every treatment is targeted at every smoker. Thus, some treatments may be designed for the pregnant tobacco user, the heavily dependent tobacco user, or the adolescent tobacco user.

Not only are treatment elements different, but this diversity is reflected in the various mechanisms that are thought to underlie treatment impacts. Moreover, there is substantial evidence that the most efficacious treatments are multifaceted—that is, they involve pharmacotherapy and a variety of psychosocial interventions (e.g., Fiore et al., 2000). Thus, a well-informed appraisal of treatments and their hypothesized mechanisms is fostered by knowledge of neurochemistry, social psychology, cognitive behavior therapy, learning theory, and other literatures.

Although most intensive tobacco use treatments are multifaceted, their constituents are typically determined by happenstance and tradition rather than by a transdisciplinary analysis of which treatments should complement one another. One promise of a transdisciplinary approach is that diverse treatments could, in theory, be combined on the basis of complementary modes of action. Integrating research and theory from neuropharmacology, psychology, economics, etc., could foster novel treatment combinations. Thus, understanding how a pharmacotherapy affects neurotransmitter systems could suggest ideal behavioral adjuvants. For example, the fact that bupropion exerts dopaminergic effects suggests that it may reverse withdrawal-associated anhedonia (Harrison, Liem, & Markou, 2001). Thus, it is possible that bupropion would work well with a behavioral treatment that exposes individuals to pleasurable activities. This particular example is offered merely to illustrate how a transdisciplinary approach may make novel treatment combinations available for research evaluation. Since the transdisciplinary integration of treatment elements is in its infancy, compelling models or data are not yet available.

One vital dimension of treatment evaluation concerns the micro and macro contexts in which treatments must be implemented and exist. Micro contexts might include characteristics of the health care or clinical setting that might affect the likelihood that new treatments will be offered, or the presence of preexisting treatments with which a new treatment must be integrated. Macro contexts might include the policies of insurers to pay for/reimburse treatments or state-provided treatments such as quit lines. In short, micro and macro contexts can either facilitate or hamper the realization of benefits that might ensue from a new treatment.

In anticipating and addressing micro and macro issues likely to affect clinical integration of new treatments, Shortell, Gillies, Anderson, Erickson, and Mitchell (1996) identify four domains: strategic, structural, cultural, and technical. The strategic domain emphasizes the recognition by leaders in the health care delivery system that integration and standardization of a new treatment or guideline across the system are essential for long-term clinical and financial success. The structural domain addresses the capacity of the organizational system to support the integration and dissemination of new practices or guidelines, including creating financial incentives and organizational structures that promote organizational learning and its dissemination. The cultural domain describes the extent to which the beliefs, values, and norms of the system foster or inhibit implementation of new practices or guidelines. The technical domain encompasses the degree to which personnel in the system have the training and skill to achieve clinical integration of new practices and guidelines.

Thus, a comprehensive treatment evaluation program should involve an analysis of the contexts in which *each* treatment is to be both evaluated and, eventually, disseminated. Such an analysis would really gauge the fit between a treatment and the relevant contexts.

In several areas of current scientific development, the clinical integration of new treatments may raise ethical and public policy issues (e.g., treatment assignment based on genotype). Thinking through these concerns in a transdisciplinary fashion may well require the consideration of perspectives, methods, and viewpoints of scholars and researchers from diverse fields (e.g., ethics, public policy, sociology, psychology, law).

In sum, an informed treatment appraisal demands that the natures of treatments be meaningfully assessed. Does the treatment comprise diverse elements (support, education, pharmacology)? Do treatment elements have complementary goals and mechanisms of action? Are the treatment and the treatment delivery system appropriate for the targeted population, staff, and context in which they will be used? These are just a few examples of the kinds of complex concerns related to clinical integration of new, beneficial treatments. Without identifying and addressing such concerns, the full benefit of cutting-edge research leading to new, efficacious treatments will never be fully realized.

Consistent with a transdisciplinary approach, the various TTURCs are evaluating a wide range of treatments. For instance, treatments being evaluated comprise individual pharmacotherapies (e.g., NRT, bupropion SR; Lerman, Ruth, et al., 2002; Lerman, Shields, et al., 2002), combinations of pharmacotherapies (e.g., NRT + naltrexone [Krishnan-Sarin, Meandzija, & O'Malley, in press], bupropion SR + nicotine gum),

as well as a variety of counseling strategies. Some treatments fall outside the typical range of cessation modalities. For instance, the Minnesota TTURC is examining the impact of reducing the number of cigarettes smoked as a treatment goal. Other treatments involve novel delivery systems (e.g., the computer-delivered Internet access system developed by an industrial engineer [Gustafson et al., 1999] being used at the Wisconsin TTURC).

Mechanisms and proximal outcomes

As Figure 1 makes clear, we posit that short-term treatment effects can be conceptualized as actions on mechanisms or proximal outcomes. We discuss mechanisms and proximal outcomes together, since the distinction is based on the goals and theoretical perspectives of the researcher and since they may frequently be thought to have reciprocal relations. A mechanism is an effect of treatment that is thought to mediate or produce desired proximal and ultimate outcomes. Change in a mechanism need not be intrinsically desirable or undesirable. Rather, it may be meaningful only in relation to other, significant outcomes. For instance, if a desired outcome of treatment is increased tobacco abstinence at 1 month posttreatment and the treatment modality is tobacco refusal skills, then presumably the mechanism via which treatment works is inculcation of enhanced refusal skills—which could be assessed with behavioral observation, peer or social network ratings, and self-report. Although proximal outcomes and mechanisms may be characterized on bases such as intrinsic desirability, the main distinction between them concerns their stipulated role in the investigator's theoretical model of how treatment works.

Treatment mechanisms lend themselves to multi-level integrated assessment and analyses. For instance, if one were to assume that a treatment diminishes appetitive responses to drug cues (i.e., responses that reflect a disposition to approach; e.g., Robinson & Berridge, 1993; Zinser, Fiore, Davidson, & Baker, 1999), then one might use imaging assays to assess activity in the nucleus accumbens (Breiter et al., 1997), cortical electrophysiological measures of cerebral asymmetry (e.g., Zinser et al., 1999), behavioral and electromyographic measures of motor response, and attitudinal/self-report measures of intention and affect. Moreover, one might use both neuropharmacologic models and human information processing models to generate predictions about how responses should be integrated (e.g., Baker, Morse, & Sherman, 1987; Kramer & Goldman, 2003; Robinson & Berridge, 1993).

Examples of possible mechanism types and associated measures are presented in Table 1.

Table 1. Treatment mechanisms and related measure

Type of mechanism	Candidate measure
Biological/physiological	Neuroimaging Neurochemistry Pharmacodynamics Coping skill quality
Behavioral	Coping skill quantity Exercise level
Cognitive/information processing	Implicit attitudes Automaticity
Interpersonal	Interaction patterns Social networks
Societal/cultural	Media coverage Price/taxation measures Cessation benefits coverage

A proximal outcome is an effect of treatment that can be measured shortly after treatment and that has intrinsic significance. That is, without reference to its relationship with other outcomes or consequences, it is clearly desirable or undesirable (e.g., a side effect) from the perspective of treatment evaluation. As noted above, the distinction between mechanisms and proximal outcomes is dependent on the goals and model of the researcher. For instance, it is possible that one investigator might conceptualize withdrawal symptoms as a proximal outcome—that is, that it is intrinsically desirable that withdrawal symptoms be reduced by treatment. This investigator might also conceptualize withdrawal symptoms as a mediator/mechanism of treatment outcomes—that is, that reducing withdrawal is what allows individuals to become and remain abstinent. Another investigator—say, one who believes that relapse is caused by incentive properties of drugs (e.g., Robinson & Berridge, 1993; Stewart, Lemaire, Roache, & Meisch, 1994)—might view withdrawal symptoms as only a proximal outcome and not a mediator of treatment actions.

Typical measures of proximal outcome might include immediate abstinence, reductions in alveolar carbon monoxide levels, withdrawal symptoms/urges, adverse events, reductions in exposure to tobacco toxins (e.g., tars), and monetary savings. Of course, there is no litmus test for proximal outcomes—one investigator might see enhanced drug refusal skills as intrinsically beneficial, and another may not.

Individual differences. The interrelationships among treatments, mechanisms, and proximal outcomes offer many opportunities for moderation by individual differences. For instance, features of individual tobacco users might influence how treatments affect either mechanisms of change or proximal outcomes, or individual differences might influence the interrelationships of mechanisms and outcomes. The possible moderating influences are legion. For instance, substantial evidence suggests that gender influences

smoking cessation rates (e.g., Wetter et al., 1999) and that gender and female hormones may affect withdrawal symptomatology (Allen, Hatsukami, Christianson, & Brown, 2000; Perkins et al., 2000; Piasecki et al., 1998; Piasecki, Jorenby, Smith, Fiore, & Baker, 2003a, 2003b). One could easily surmise that smoking cessation treatments such as nicotine replacement are less effective in suppressing withdrawal symptoms in women than in men (Hatsukami et al., 1995), and that this difference, in turn, reduces women's ability to quit (cf. Perkins, 2001). Conversely, there is evidence that bupropion has equivalent efficacy in men and women (Collins et al., 2002; Smith et al., 2003). Therefore, one might posit that bupropion produces equivalent effects on withdrawal symptoms across sexes (or on affect, since research by Lerman, Roth, et al., 2002, suggests that affective status may be a more important determinant of outcomes). The particular example used is not critical. It is used merely to indicate that individual difference variables may predict differential relationships among treatments, mechanisms, and proximal outcomes, and that these moderated relationships may change from one treatment to another (say, nicotine replacement therapy vs. bupropion).

Recently, a great deal of research attention has focused on genetic factors that contribute to smoking behavior. Twin studies have documented a significant contribution of heritable factors to smoking initiation and nicotine dependence (Sullivan & Kendler, 1999). Molecular genetic approaches are being used to identify the specific genetic variants that contribute to various smoking-related phenotypes. Attention has focused on genetic variants in neurotransmitter pathways that regulate reward processes and affect (e.g., dopamine, serotonin), as well as nicotine-specific pathways (e.g., nicotinic receptors, nicotine metabolism; for a review, see Lerman & Berrettini, 2003). Studies of smoking treatment may provide an optimal research context for genetics research, since the phenotype of smoking cessation (and its proximal outcomes) can be well defined (Lerman & Niaura, 2002). Such research has the potential to lead to the tailoring of treatment modality and dose to individual differences in genotype (Evans & Relling, 1999).

A brief list of some of the individual differences that might moderate interrelationships could include gender, particular genotypes, temperament (e.g., impulsivity or negative affectivity), age, socioeconomic status, ethnicity, psychiatric status, nicotine dependence, coping style (e.g., problem focused vs. ineffective escapist), and so on. These variables are suggested by evidence that they are related to treatment efficacy or to change in potential process measures/mechanisms.

The University of Pennsylvania TTURC is investigating how individual differences in genotype moderate the effectiveness of different pharmacotherapies

for smoking cessation (e.g., bupropion, NRTs). Recent data from this center suggest that smokers with a decreased activity variant of *CYP2B6* experience greater cravings following cessation and have a higher likelihood of relapse. This effect is moderated by an individual difference variable. Among females, bupropion appears to attenuate the effects of genetic predisposition on relapse (Lerman, Roth, et al., 2002).

Reciprocal effects. As Figure 1 denotes, we are assuming the possibility of reciprocal relations (mutual influences) between mechanisms and proximal outcomes. For instance, execution of coping responses (a mechanism of treatment) might be responsible for early tobacco cessation, but once an individual begins to relapse (a proximal outcome) he or she may forgo further coping, perhaps because of abstinence violation effect—the tendency to “give up” after an initial setback (Marlatt & Gordon, 1980).

Similarly, a treatment might be thought to work by reducing tobacco withdrawal symptoms. Reduced withdrawal symptoms would constitute the mechanism through which treatment enhances short-term abstinence (the proximal outcome). A transdisciplinary approach would assess withdrawal symptoms across various response channels: self-report of affect, responding for nonpharmacologic incentives (Harrison et al., 2001), and information processing efficiency. While withdrawal symptoms, as measured by these indices, might influence the likelihood of tobacco use, these indices in turn might also reflect the impacts of tobacco use.

In considering such relations, it is important to keep in mind that treatments may exert their actions via multiple mechanisms and that each mechanism may operate via sets of overlapping and unique processes. These considerations reveal the obstacles to capturing the complex change processes via unidimensional assessments. Moreover, response systems may exert additive or interactive effects, both within and across evaluation facets (e.g., mechanisms/proximal outcomes). Finally, it is important to note that all of these relations may be affected by both individual differences and contextual factors.

The TTURCs target a wider range of measures to tap mechanisms and proximal outcomes. Moreover, the studies explore how impacts on such measures may be moderated by individual differences and contextual factors.

One line of the Yale University TTURC research starts with the premise that relapse is caused, in part, by the priming of brain incentive systems, an effect that is partially opioid in nature. Priming may be occasioned by exposure to either tobacco or tobacco cues. In addition, researchers have noted that relapse often occurs in the context of alcohol use (Burton &

Tiffany, 1997; Dick et al., 2001; Drobles et al., 2000; Istvan & Matarazzo, 1984; Shiffman et al., 1994; Zimmerman, Warheit, Ulbrich, & Auth, 1990). Yale researchers, therefore, hypothesized that naltrexone might be an efficacious tobacco treatment, since it both antagonizes opiate effects and reduces alcohol intake (King & Meyer, 2000; O'Malley et al., 1992, O'Malley, Krishnan-Sarin, Farren, Sinha, & Kreek, 2002; O'Malley & Froehlich, 2003; Volpicelli, Alterman, Hayashida, & O'Brien, 1992). Thus, this research explores the mediation of naltrexone effects via two different routes or mechanisms: (1) slips back to tobacco use will not result in full relapse because naltrexone will antagonize tobacco-induced priming; (2) reduced alcohol use will translate into higher tobacco abstinence rates because of naltrexone's suppression of alcohol intake. The latter mechanism will be specific to alcohol users and is another example of a mechanism that is moderated by an individual difference.

TTURC research provides many other examples of mechanism and proximal outcome measures. For instance, the Minnesota TTURC will assess proximal outcomes thought to index tobacco toxin exposure (e.g., NNAL, NNAL-Gluc, 4-aminobiphenyl hemoglobin adducts, F2 isoprostanes). The Yale TTURC will assess hormone levels, changes in weight, abstinence rates, and cost-benefit outcomes (McLellan, Lewis, O'Brien, & Kleber, 2000). The University of Pennsylvania TTURC will assess changes in affect and cravings (Lerman, Roth, et al., 2002b), as well as other neurobehavioral measures, such as neurocognitive performance. Many of these effects will be examined with respect to individual differences and micro and macro contextual features.

Ultimate outcomes

As with other elements of the conceptual model presented in Figure 1, ultimate outcomes is a fuzzy set—it has no clear demarcations, and its boundaries therefore are somewhat arbitrary. For instance, postcessation abstinence could be considered either a proximal or ultimate outcome, depending on when it is measured and the goals of the researcher. In general, ultimate outcomes may be thought of as variables measured when they have achieved a stable state or when the downstream, distal effects of treatment (and consequential increased cessation) have had an opportunity to exert effects through a wide range of relevant systems (physical, societal, economic, and so on).

We emphasize the importance of ultimate outcomes because they are vital but little studied. Ultimate outcomes might include consequences of treatment/cessation such as long-term changes in healthcare use, morbidity/mortality, changes in physical activity, psychiatric status, work productivity, social networks,

tobacco use by other family members, demoralization and reduced likelihood of subsequent quit attempts, weight status, and so on. One might also include treatment impacts that don't directly involve the treated individual. For instance, interventions with broad dissemination, such as statewide quit lines, may raise awareness of tobacco use and create ripple effects that influence institutional and governmental policy. Moreover, the eventual impacts of treatment on the remaining population of tobacco users could be construed as an ultimate outcome (e.g., widespread availability of over-the-counter nicotine replacement therapy could affect the nature of the population of remaining smokers). This listing of exemplars underscores again that a comprehensive evaluation of treatments demands a multifaceted approach to conceptualization and assessment.

Finally, as Figure 1 makes clear: (1) ultimate outcomes may be influenced both by mechanisms activated by treatment and by proximal outcomes (in which case the proximal outcomes may be construed as mediators/mechanisms of ultimate outcomes); (2) individual differences may moderate interrelations among mechanisms, proximal outcomes, and ultimate outcomes; and (3) all these relations occur within micro/macro contexts that conditionalize them (e.g., reduction of lung cancer may be moderated by environmental air quality, costs moderated by nature of health care available).

Consistent with the nature of most tobacco research, TTURC researchers have focused on proximal outcomes. However, some TTURC research does focus on ultimate outcomes. For instance, Minnesota TTURC researchers will track long-term morbidity and mortality rates. These researchers have obtained permission to access subjects' medical records over the course of each individual's lifetime.

Theoretic integration

A transdisciplinary approach demands more than just a broad, multifaceted assessment plan. As noted earlier, it requires integration such that *concepts* and *theories* from one discipline are melded with concepts and theories from other disciplines, resulting in novel approaches or hypotheses. Thus, an emergent property of transdisciplinarity is the generation of research questions and approaches that otherwise would not occur.

How might such integration look? Examples might be that certain personality types or constructs would suggest gene loci to investigate for associations with dependence, and, conversely, genetic correlates of dependence might suggest the further investigation of particular personality traits, such as extraversion or sensation-seeking (Sabol et al., 1999). Such associations might suggest novel risk factors for tobacco use that could be addressed via novel psychosocial

treatments. Alternatively, the role of heritable influences on the success or likelihood of tobacco cessation might vary with respect to particular environmental contexts, suggesting new models of gene-environment correlation or interaction that could be used to guide treatment development and evaluation (Dick et al., 2001). In addition, there is emerging evidence that neurocognitive traits associated with use of nicotine and other substances have a significant heritable component (Bates & Malhotra, 2002). Research that elucidates the mediating role of such traits in the development and maintenance of nicotine dependence could point to novel pharmacologic and behavioral approaches for smoking prevention and treatment (Lerman & Berrettini, 2003).

The above are just a few examples of how transdisciplinarity might affect treatment development and evaluation. Additional exciting developments should follow when current models are integrated, both theoretically and in the laboratory. For instance, behavioral economic findings on temporal discounting (Bickel, Odum, & Madden, 1999) might be integrated with research on neuropharmacologic substrata of disinhibition (Shaham, Erb, & Stewart, 2000), and the result, in turn, could be related to genotypes influencing impulsivity.

Another sort of integration that was not addressed directly in our treatment model concerns the integration of developmental perspectives, an overarching or metadiscipline, with other disciplines of tobacco treatment research. The TTURCs that focus on treatment research, no doubt, will benefit from work being done by centers that focus on the development of nicotine addiction. An appreciation of factors that contribute to the transition of nonusers to users of tobacco should suggest new targets for treatment (needs that are being met by tobacco use), and such knowledge may provide better methods for treatment matching. In this light, most of the discussion in this paper has focused on the treatment of *dependent* tobacco users. However, intervention could occur at many points across the development of dependent tobacco users. Tobacco use may be influenced by different factors or motives across its development. For example, contextual and social factors (cultural messages, promotion, cost, peer and family influences) may play a significant role during the onset of tobacco use. However, these factors may play a lesser role in the maintenance of chronic tobacco use when physiological dependence and heritability for maintenance assume more dominant roles. In sum, theories and data generated by a developmental perspective have the potential to complement the contributions of other disciplines in enhancing tobacco treatment research.

The TTURCs provide numerous examples of the integration of diverse disciplines and levels of analysis. The University of Pennsylvania TTURC integrates

theoretical perspectives from psychology, genetics, and ethics/policy. The Minnesota TTURC integrates biochemistry, pharmacology, psychology, and medicine. The Wisconsin TTURC integrates psychology, internal medicine, engineering, and cognitive neurosciences. These examples capture integration from a global, remote perspective. A closer examination, focused, for example, on the Yale TTURC, reveals the integration of learned-helplessness models, nicotinic and opioid neuropharmacology, and clinical trials. This brief overview provides just a glimpse of the broad perspective that may be gained on the treatment of tobacco use by integrating research findings within and across the TTURC projects.

Summary

A comparison of the evaluation model presented in this paper (Figure 1) and the transdisciplinary research undertaken at the participating TTURCs reveals that transdisciplinary treatment research, while in an early stage of development, has been markedly enhanced by the NIH TTURC program. Moreover, we believe that the model reveals the potential worth of a broad, inclusive approach to tobacco treatment research. Of course, transdisciplinary tobacco research is in its infancy, and thus the benefits are as yet unproven. Therefore, future research should evaluate the relative cost-effectiveness of transdisciplinary research efforts compared with more traditional research strategies. Moreover, it is important for the reader to bear in mind that the TTURC research programs described above are fledgling and by no means capture the potential of mature transdisciplinary research efforts. Finally, we hope the research perspective we have outlined will serve as a guide to future efforts to understand how treatments work and how they can be improved.

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References

Allen, S. S., Hatsukami, D., Christianson, D., & Brown, S. (2000). Effects of transdermal nicotine on craving, withdrawal and premenstrual symptomatology in short-term smoking abstinence during different phases of the menstrual cycle. *Nicotine & Tobacco Research*, 2, 231–241.

Baker, T. B., Morse, E., & Sherman, J. E. (1987). The motivation to use drugs: A psychobiological analysis of urges. In P. C. Rivers (Ed.), *The Nebraska Symposium on Motivation: Alcohol Use and Abuse* (pp.257–323). Lincoln, NE: University of Nebraska Press.

Bates, J. A., & Malhotra, A. K. (2002). Genetic factors and neurocognitive traits. *CNS Spectrums*, 7, 274–284.

Bickel, W. K., Odum, A. L., & Madden, G. J. (1999). Impulsivity and cigarette smoking: Delay discounting in current, never, and ex-smokers. *Psychopharmacology*, 146, 447–454.

Breiter, H. C., Gollub, R. L., Weisskoff, R. M., Kennedy, D. N., Makris, N., Berke, J. D., Goodman, J. M., Kantor, H. L., Gastfried, D. R., Riorden, J. P., Mathew, R. T., Rosen, B. R., & Hyman, S. E. (1997). Acute effects of cocaine on human brain activity and emotion. *Neuron*, 19, 591–611.

Burton, S. M., & Tiffany, S. T. (1997). The effect of alcohol consumption on craving to smoke. *Addiction*, 92, 15–26.

Centers for Disease Control. (2000). Use of FDA-approved pharmacologic treatments for tobacco dependence—United States, 1984–1998. *Morbidity and Mortality Weekly*, 49, 665–668.

Collins, B. N., Niaura, R., Wileyto, E. P., Patterson, F., Brown, R. A., Audrain, J., Hawk, L., Epstein, L., & Lerman, C. (2002, March). Gender differences in smoking relapse in a behavioral counseling + placebo-controlled bupropion trial. Paper presented at the 8th Annual Meeting of the Society for Research on Nicotine and Tobacco, Savannah, GA.

Comings, D. E., Gade, R., Wu, S., Chiu, C., Dietz, G., Muhleman, D., Saucier, G., Ferry, L., Rosenthal, R. J., Lesieur, H. R., Rugle, L. J., & MacMurray, P. (1997). Studies of the potential role of the dopamine D1 receptor gene in addictive behaviors. *Molecular Psychiatry*, 2, 44–56.

Dick, D. M., Rose, R. J., Viken, R. J., Kaprio, J., & Koskenvuo, M. (2001). Exploring gene-environment interactions: Socioregional moderation of alcohol use. *Journal of Abnormal Psychology*, 110, 625–632.

Drobes, D. J., Beylotte, F., Scott, M., Saladin, M. E., Randell, C. L., & Anton, R. F. (2000). Cross-reactivity to alcohol and smoking cues. *Alcoholism: Clinical and Experimental Research*, 24, 147a.

El-Sheikh, M. (2001). Parental drinking problems and children's adjustment: Vagal regulation and emotional reactivity as pathways and moderators of risk. *Journal of Abnormal Psychology*, 110, 499–515.

Evans, W. E., & Relling, M. V. (1999). Pharmacogenomics: translating functional genomics into rational therapeutics. *Science*, 286, 487–491.

Fiore, M. C., Bailey, W. C., Cohen, S. J., Dorfman, S. F., Goldstein, M. G., Gritz, E. F., Heyman, R. B., Jaén, C. R., Kottke, T. E., Lando, H. A., Meckleburg, R. E., Mullen, P. D., Nett, L. M., Robinson, R., Stitzer, M. L., Tommasello, A. C., Villejo, L., & Wewers, M. E. (2000). *Treating tobacco use and dependence. A clinical practice Guideline*. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service.

Fiore, M. C., Novotny, T. E., Pierce, J. P., Giovino, G. A., Hatzidreou, E. J., Newcomb, P. A., Surawicz, T. S., & Davis, R. M. (1990). Methods used to quit smoking in the United States: Do cessation programs help? *Journal of the American Medical Association*, 263, 2760–2765.

Fuster, V., Badimon, L., Badimon, J. J., & Chesebro, J. H. (1992). The pathogenesis of coronary artery disease and the acute coronary syndromes (1). *New England Journal of Medicine*, 326, 242–250.

Gustafson, D., Hawkins, R., Boberg, E., Pingree, S., Serlin, R., Graziano, F., & Chan, C. (1999). Impact of a patient-centered, computer-based health information/support system. *American Journal of Preventive Medicine*, 16, 1–9.

Harrison, A. A., Liem, Y. T. B., & Markou, A. (2001). Fluoxetine combined with a serotonin-1A receptor antagonist reversed reward deficits observed during nicotine and amphetamine withdrawal in rats. *Neuropsychopharmacology*, 25, 55–71.

Hatsukami, D. K., Skoog, K., Allen, S. S., & Bliss, R. (1995). Gender and the effects of different doses of nicotine gum on tobacco withdrawal symptoms. *Experimental and Clinical Psychopharmacology*, 3, 163–173.

Hays, R. D., Marshall, G. N., Wang, E. Y. I., & Sherbourne, C. D. (1994). Four-year cross-lagged associations between physical and mental health in the medical outcomes study. *Journal of Consulting and Clinical Psychology*, 62, 441–449.

Hu, T.-H., Sung, H.-Y., Keeler, T. E., & Marciniak, M. (2000). Cigarette consumption and sales of nicotine replacement products. *Tobacco Control*, 9(Suppl. 2), ii60–ii63.

Istvan, J., & Matarazzo, J. D. (1984). Tobacco, alcohol, and caffeine use: A review of their interrelationships. *Psychological Bulletin*, 95, 301–326.

King, A. C., & Meyer, P. J. (2000). Naltrexone alteration of acute

- smoking response in nicotine-dependent subjects. *Pharmacology, Biochemistry & Behavior*, 66, 563–572.
- Kop, W. J., Gottdiener, J. S., & Krantz, D. S. (2001). Stress and ischemia. In A. Baum, T. A. Revenson, & J. E. Singer (Eds.), *Handbook of health psychology* (pp. 669–682). Mahwah, NJ: Erlbaum.
- Kramer, D. A., & Goldman, M. S. (2003). Using a modified Stroop task to implicitly discern the cognitive organization of alcohol expectancies. *Journal of Abnormal Psychology*, 112, 171–175.
- Krishnan-Sarin, S., Meandzija, B., & O'Malley, S. (in press). Naltrexone and nicotine patch in smoking cessation: A preliminary study. *Nicotine and Tobacco Research*.
- Lemmonds, C. A., Mooney, M., Reich, B., & Hatsukami, D. (in press). Characteristics of cigarette smokers seeking treatment for cessation vs. reduction. *Addictive Behaviors*.
- Lerman, C., & Berrettini, W. (2003). Elucidating the role of genetic factors in cigarette smoking. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, 118B(1), 48–54.
- Lerman, C., & Niaura, R. (2002). Applying genetic approaches to the treatment of nicotine dependence. *Oncogene*, 21, 7412–7420.
- Lerman, C., Roth, D., Kaufmann, V., Audrain, J., Hawk, L., Liu, A., Niaura, R., & Epstein, L. (2002). Mediating mechanisms of the impact of bupropion in smoking cessation treatment. *Drug and Alcohol Dependence*, 67, 219–223.
- Lerman, C., Shields, P. G., Wileyto, E. P., Audrain, J., Pinto, A., Hawk, L., Krishnan, S., Niaura, R., & Epstein, L. (2002c). Pharmacogenetic investigation of smoking cessation treatment. *Pharmacogenetics*, 12, 627–634.
- Lichtenstein, E., & Hollis, J. (1992). Patient referral to a smoking cessation program: Who follows through? *Journal of Family Practice*, 34, 739–744.
- Lynch, J. W., Everson, S. A., Kaplan, G. A., Salonen, R., & Salonen, J. T. (1998). Does low socioeconomic status potentiate the effects of heightened cardiovascular responses to stress on the progression of carotid atherosclerosis? *American Journal of Public Health*, 88, 389–394.
- Manuck, S. B. (1994). Cardiovascular reactivity in cardiovascular disease: "Once more unto the breach." *International Journal of Behavioral Medicine*, 1, 4–31.
- Marlatt, G. A., & Gordon, J. R. (1980). Determinants of relapse: Implications for the maintenance of behavior change. In P. O. Davidson, & S. M. Davidson (Eds.), *Behavioral medicine: Changing health lifestyles* (pp. 410–452). New York: Guilford.
- McLellan, A. T., Lewis, D. C., O'Brien, C. P., & Kleber, H. D. (2000). Drug dependence, a chronic medical illness: Implications for treatment, insurance, and outcomes evaluation. *Journal of the American Medical Association*, 284, 1689–1695.
- O'Malley, S. S., & Froehlich, J. C. (2003). Advances in the use of naltrexone: An integration of preclinical and clinical findings. *Recent Developments in Alcoholism*, 16, 217–245.
- O'Malley, S. S., Jaffe, A. J., Chang, G., Schottenfeld, R. S., Meyer, R. E., & Rounsaville, B. (1992). Naltrexone and coping skills therapy for alcohol dependence. A controlled study. *Archives of General Psychiatry*, 49, 881–887.
- O'Malley, S. S., Krishnan-Sarin, S., Farren, C., Sinha, R., & Kreek, M. J. (2002). Naltrexone decreases craving and alcohol self-administration in alcohol dependent subjects and activates the hypothalamo-pituitary-adrenocortical axis. *Psychopharmacology*, 160, 19–29.
- Perkins, K. A. (2001). Smoking cessation in women. Special considerations. *CNS Drugs*, 1, 391–411.
- Perkins, K., Levine, M., Marcus, M., Shiffman, S., D'Amico, D., Miller, A., Keins, A., Ashcom, J., & Broge, M. (2000). Tobacco withdrawal in women and menstrual cycle phase. *Journal of Consulting and Clinical Psychology*, 68, 176–180.
- Piasecki, T. M., Fiore, M. C., & Baker, T. B. (1998). Profiles in discouragement: Two studies of variability in the time course of smoking withdrawal symptoms. *Journal of Abnormal Psychology*, 107, 238–251.
- Piasecki, T. M., Jorenby, D. E., Smith, S. S., Fiore, M. C., & Baker, T. B. (2003a). Smoking withdrawal dynamics: I. Abstinence distress in lapsers and abstainers. *Journal of Abnormal Psychology*, 112, 3–13.
- Piasecki, T. M., Jorenby, D. E., Smith, S. S., Fiore, M. C., & Baker, T. B. (2003b). Smoking withdrawal dynamics: II. Improved tests of withdrawal-relapse connections. *Journal of Abnormal Psychology*, 112, 14–27.
- Piper, M. E., Piasecki, T. M., Federman, E. B., Bolt, D. M., Smith, S. S., Fiore, M. C., & Baker, T. B. (in press). A multiple motives approach to tobacco dependence: The Wisconsin Inventory of Smoking Dependence Motives (WISDM-68). *Journal of Consulting and Clinical Psychology*.
- Robinson, T. E., & Berridge, K. C. (1993). The neural basis of drug craving: An incentive-sensitization theory of addiction. *Brain Research Reviews*, 18, 247–291.
- Sabol, S. Z., Nelson, M. L., Fisher, C., Gunzerath, L., Brody, C. L., Hu, S., Sirota, L. A., Marcus, S. E., Greenberg, B. D., Lucas, FR, IV, Benjamin, J., Murphy, D. L., & Hamer, D. H. (1999). A genetic association for cigarette smoking behavior. *Health Psychology*, 18, 7–13.
- Schrecker, T., Acosta, L., Somerville, M. A., & Bursztajn, H. J. (2001). The ethics of social risk reduction in the era of the biological brain. *Social Science & Medicine*, 52, 1677–1687.
- Shaham, Y., Erb, S., & Stewart, J. (2000). Stress-induced relapse to heroin and cocaine seeking in rats: a review. *Brain Research Reviews*, 33, 13–33.
- Shiffman, S., Fischer, L. A., Paty, J. A., Gnys, M., Hickcox, M., & Kassel, J. D. (1994). Drinking and smoking: A field study of their association. *Annals of Behavioral Medicine*, 16, 203–209.
- Shortell, S., Gillies, R., Anderson, D., Erickson, K. M., & Mitchell, J. B. (1996). *Remaking health care in America: Building organized delivery systems*. San Francisco: Jossey-Bass.
- Slutske, W. S., Heath, A. C., Madden, A. F., Bucholz, K. K., Statham, D. J., & Martin, N. G. (2002). Personality and genetic risk for alcohol dependence. *Journal of Abnormal Psychology*, 111, 124–133.
- 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 & Tobacco Research*, 5, 99–109.
- Smith, T. W., & Ruiz, J. M. (2002). Psychosocial influences on the development and course of coronary heart disease: Current status and implications for research and practice. *Journal of Consulting and Clinical Psychology*, 70, 548–568.
- Stewart, R. B., Lemaire, G. A., Roache, J. D., & Meisch, R. A. (1994). Establishing benzodiazepines as oral reinforcers: Midozolam and diazepam self-administration in rhesus monkeys. *Journal of Pharmacology & Experimental Therapeutics*, 271, 200–211.
- Sullivan, P. F., & Kendler, K. S. (1999). The genetic epidemiology of smoking. *Nicotine & Tobacco Research*, 1(Suppl. 2), S51–S57 & S69–S70.
- Tiffany, S. T. (1990). A cognitive model of drug urges and drug-use behavior: Role of automatic and nonautomatic processes. *Psychological Review*, 97, 147–168.
- Volpicelli, J. R., Alterman, A. I., Hayashida, M., & O'Brien, C. P. (1992). Naltrexone in the treatment of alcohol dependence. *Archives of General Psychiatry*, 49, 876–880.
- Wendel, J. S., Miklowitz, D. J., Richards, J. A., & George, E. L. (2000). Expressed emotions and attributions in the relatives of bipolar patients: An analysis of problem solving interactions. *Journal of Abnormal Psychology*, 109, 792–796.
- Wetter, D. W., Kenford, S. L., Smith, S. S., Fiore, M. C., Jorenby, D. E., & Baker, T. B. (1999). Gender differences in smoking cessation. *Journal of Consulting and Clinical Psychology*, 67, 555–562.
- Zelman, D. C., Brandon, T. H., Jorenby, D. E., & Baker, T. B. (1992). Measures of affect and nicotine dependence predict differential response to smoking cessation treatments. *Journal of Consulting and Clinical Psychology*, 60, 943–952.
- Zimmerman, R. S., Warheit, G. J., Ulbrich, P. M., & Auth, J. B. (1990). The relationship between alcohol use and attempts and success at smoking cessation. *Addictive Behaviors*, 15, 197–207.
- Zinser, M. C., Fiore, M. C., Davidson, R. J., & Baker, T. B. (1999). Manipulating smoking motivation: Impact on an electrophysiological index of approach motivation. *Journal of Abnormal Psychology*, 108, 240–254.

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