Special Report

Transdisciplinary Tobacco Use Research Centers: Research achievements and future implications

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University of Wisconsin

Focus of the center

The University of Wisconsin Transdisciplinary Tobacco Use Research Center (TTURC) has focused on several linked topics: (a) improving our assessment and understanding of nicotine dependence, (b) exploring factors that cause or modulate relapse risk, (c) identifying genetic influences on nicotine dependence and cessation success, and (d) testing smoking cessation interventions and determining their mechanisms of action.

Key findings

Development of a new multifactorial instrument to assess nicotine dependence. This developmental research effort produced a new questionnaire that is now being widely used to assess nicotine dependence: the Wisconsin Inventory of Smoking Dependence Motives (WISDM-68), which has good psychometric properties and is appropriate for use with a broad range of smokers (men and women, ethnic minorities; Piper et al., 2004). This work also produced direct evidence that nicotine dependence is indeed multidimensional, revealing which aspects of dependence are most associated with heightened relapse risk, withdrawal severity, and heavy smoking (Piper et al.).

Insight into the nature of nicotine dependence. Research with the WISDM-68 suggests that four core features of nicotine dependence are both necessary (all groups of significantly dependent smokers have elevations on these subscales) and sufficient (some smokers who are highly dependent have elevated scores only on these subscales) for severe dependence: (a) tolerance, (b)

automaticity, (c) loss of control, and (d) craving (Piper, Bolt, et al., 2008). Unlike other dependence motives subscales, scores on these four Primary Dependence Motives subscales tend to show significant increases only after extensive experience with tobacco use and are especially predictive of dependence criteria (e.g., relapse likelihood; Piper et al., 2004). This research suggests that the dependence phenotype can be distilled into a finite set of core features: heavy smoking that is not discriminated on contextual cues; that occurs with little conscious control or mediation; and that is characterized by frequent, strong, and bothersome craving.

Insight into mechanisms via which nicotine dependence leads to relapse back to smoking. Several studies showed that nicotine withdrawal was highly variable across individuals, that it could persist or increase for several months following cessation (Piasecki, Jorenby, Smith, Fiore, & Baker, 2003a, 2003b, 2003c), and that one outcome of withdrawal was a heightened symptomatic reaction to environmental events (McCarthy, Piasecki, Fiore, & Baker, 2006). This research also showed that craving was especially related to greater likelihood of cessation failure or relapse and that different withdrawal profile dimensions predicted relapse (e.g., the slope of withdrawal, its elevation, and its variability).

The genetics of nicotine dependence. A collaboration with investigators at the University of Utah examined multiple candidate genes for nicotine dependence (Weiss et al., 2008). This research identified three haplotypes of the *CHRNA5-A3-B4* gene cluster that are associated with nicotine dependence severity (indexed by the Fagerström Test for Nicotine Dependence). Further, there is evidence of a gene $\times$ environment interaction in which associations between dependence severity and genetic variation are seen in early-onset smokers (daily smoking

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before age 17) but not in late-onset smokers. This finding has implications for public health measures such as excise taxation that can reduce youth access to and use of tobacco. The research shows that *CHRNA5-A3-B4* variants are more highly related to the WISDM-68 Primary Dependence Motives than to other motives, and these variants also predict cessation success.

Characterizing smoking treatment effectiveness. The effectiveness of multiple interventions for tobacco dependence was explored via several major clinical trials that characterized the effects of counseling and pharmacotherapy (McCarthy et al., 2008; Piper, Federman, et al., 2008; Piper et al., 2004). These showed only modest, transitory effects of counseling, and, although bupropion increased cessation rates, these increases did not persist into long-term follow-up (e.g., 1 year). Moreover, the data suggested that bupropion efficacy was not enhanced by adjunctive nicotine gum. These results underscore the need to develop new and more effective pharmacotherapy and counseling treatment strategies.

How cessation treatments work. One of the major stumbling blocks to improving cessation interventions and to matching interventions with types of patients is the lack of understanding of how such interventions work. Several papers characterized the significant short-term effects of cessation medications and identified which of these short-term effects are significantly related to long-term outcomes (McCarthy, Bolt, & Baker, 2007; McCarthy et al., 2008; M. E. Piper, E. B. Federman et al., 2008). This research used sophisticated mediational methods, including multilevel and structural equation models to control error and evaluate effects across multiple tests of the compound mediational hypothesis. Results showed that the effects of cessation medication (bupropion) that were most responsible for its long-term benefit were suppression of craving and general withdrawal symptoms and an increase in positive affect. Also, intriguing evidence indicated that the effects of bupropion on quitting motivation and self-efficacy accounted for some of its long-term benefit, suggesting that medication may yield benefit through mechanisms outside of withdrawal suppression.

Implications

One *raison d'être* for transdisciplinary (TD) research is to link observations at different levels of analysis via integrative explanatory mechanisms. The research described here attempts to yield new insights into the nature of nicotine dependence and use them as an integrative mechanism that links data on genetics, relapse vulnerability, and treatment. The research shows that nicotine dependence has core, necessary, and sufficient features consisting of heavy smoking that is not discriminated on contextual cues; that occurs with little conscious control or mediation; and that is characterized by frequent, strong, and bothersome craving. These features are linked to *CHRNA5-A3-B4* gene cluster variants, and they predict high self-administration rates, severe withdrawal, and relapse vulnerability. Moreover, pharmacological treatments work, in part, by their ability to suppress elements of the tobacco withdrawal syndrome, a manifestation of this core dependence factor.

Future plans

Future research efforts will explore further the links among genetics, dependence, and treatment response and will use this

information along with treatment research to devise new approaches to the treatment of nicotine dependence.

Roswell Park Cancer Institute

Focus of the center

The Roswell Park TTURC is an international research collaborative conducting studies on the psychosocial, behavioral, and product-related impact of the tobacco-control policies of the World Health Organization's Framework Convention on Tobacco Control (FCTC). The Roswell Park TTURC is one of the principal arms of the International Tobacco Control Policy Evaluation Collaborative (referred to subsequently as the ITC Project). The strength of the ITC Project has been its unique design, utilizing multiple driven mediational models to test hypotheses about the anticipated effects of a given tobacco control policy, when implemented in a country compared with other countries where the policy has not changed (Fong, Cummings, et al., 2006; Thompson et al., 2006). The ITC Project began in 2002 with annual longitudinal surveys of 2,000 adult smokers conducted in four countries—the United States, Canada, the United Kingdom, and Australia—and has expanded to include 11 additional countries—Ireland, Thailand, Malaysia, South Korea, China, Mexico, Uruguay, New Zealand, France, Germany, and the Netherlands. In 2007–2008, progress was made toward adding India, Bangladesh, and Sudan to the ITC Project, bringing the total to 18 countries. In the 5 years since the ITC Project began, it has conducted cohort surveys of large samples of smokers (~1,000–2,500) in countries inhabited by more than 50% of the world's smokers. All surveys contained questions that addressed all the demand reduction policies of the FCTC.

Key findings

The ITC Project is the only international study that specifically evaluates the effectiveness of FCTC policies. As a result, the ITC Project has quickly become an important source of scientific data on the impact of national-level tobacco control policies. Through the application of quasiexperimental methods, the ITC Four Country Survey has established that enhancement of warning labels (Hammond et al., 2007; Hammond, Fong, McNeill, Borland, & Cummings, 2006; Thrasher, Hammond, Fong, & Arillo-Santilan, 2007; Thrasher et al., 2007), bans on advertising and promotion (Harris et al., 2006), elimination of misleading brand descriptors (Borland et al., 2008), and implementation of smoke-free policies (Borland, Yong, Cummings, et al., 2006; Borland, Yong, Siahpush, et al., 2006; Fong, Hyland, et al., 2006; Hyland et al., 2009; Hyland et al., 2008; Hyland, Travers, Dresler, Higbee, & Cummings, 2007) have resulted in favorable changes in national cohort samples of adult smokers in the countries where those policies have been implemented, compared with countries where there was no change in policy domains. However, it cannot be assumed that tobacco control policies that have been implemented in one country will automatically work the same way when implemented elsewhere. The ITC Project is just now at a point where it can begin to explore the relative consistency or inconsistency in effectiveness of policies implemented across countries with varying income levels and cultures.

Initial analyses have found that in the three Asian low- and middle-income countries (LMICs)—Malaysia, Thailand, and

China—warnings seem to be more salient and have greater potential for informing people about the harms of smoking than those in the high-income countries (HICs) of the ITC Four Country Survey—Canada, the United States, the United Kingdom, and Australia. In Malaysia and China, which have warnings that are virtually identical (in terms of prominence) to those of the United States (text only and on the side of the pack), the salience of the warnings was much greater (more than 50%) than it was in the United States (28%).

In 2004, researchers at Roswell Park began the International Tobacco Products Repository (ITPR), the first independent system for collecting and tracking tobacco products purchased in different countries. The first purchases were initiated in the United Kingdom and Czech Republic to capitalize on the implementation of the European Union's "10-1-10" tar (mg), nicotine (mg), and carbon monoxide (parts per million) yield caps (O'Connor, McNeill, Cummings, Kozlowski, & Giovino, 2006). Since then, the ITPR has grown to include 17 countries, with a goal of including at least two countries in each of the seven World Health Organization regions by 2010. Research has focused on examining how differences in tobacco blend and design features seen in different countries influence smoking behaviors and exposures (O'Connor et al., 2008). Recent studies have examined metals in tobacco blends from cigarettes purchased in different countries and found that brands purchased in China had significantly higher levels of cadmium and lead, and greater variability in levels, than those purchased in other countries. This variation is likely related to contamination of the soil in which the tobacco used in the manufacture of the cigarettes is grown. Research also has focused on using spent cigarette filters to characterize individual variation in smoking behavior and indirectly estimate exposures from smoking (O'Connor et al., 2007; O'Connor, Stitt, & Kozlowski, 2005; Paszkiewicz & Pauly, 2008; Strasser, O'Connor, Mooney, & Wileyto, 2006).

Finally, members of the research team conducted several studies of cigarette prices and smoking behavior and how the availability of lower-priced products may modify this association (Ciecierski, 2007; Hyland et al., 2005; Hyland et al., 2006). Data from these studies indicate that a sizeable fraction of smokers in a four-country study report purchasing cigarettes from low or untaxed sources and that this behavior decreases the likelihood of making a quit attempt. The data also indicate that the self-reported prevalence rates of low or untaxed purchases were much lower in LMICs than in HICs. The rates of low or untaxed purchases were 1.6% in Mexico, 0.1% in Malaysia, and 2.5% in Thailand at their respective baseline surveys.

Future plans

The Roswell Park TTURC plans to expand cross-country comparisons further to include additional LMICs so that it can more critically explore the generality of FCTC policy effects across a wide range of countries. Building and sustaining cohorts in countries with a range of socioeconomic conditions and cultural traditions, with enough similar countries to allow the effects of policies to be separated from sociocultural factors, are an enormous strength of the ITC Project and provides a paradigm for understanding the impact of population-based approaches for disease prevention, which are also likely to have value in global health domains other than tobacco use.

University of Minnesota

Focus of the center

The primary focus of the University of Minnesota TTURC is to examine the concept of tobacco harm reduction among smokers who continue to use tobacco products. More specifically, the aims are (a) to develop methods and measures (particularly biomarkers) to evaluate tobacco products; (b) to use these measures to assess potential reduced exposure products, and, through these assessments; (c) to determine future directions in policies and programs for tobacco harm reduction.

Key findings

The Biomarker Core of the TTURC developed highly sensitive assays for total 4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanol (NNAL) (NNAL plus its glucuronides, metabolites of the tobacco-specific lung carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone [NNK]); 1-hydroxypyrene (1-HOP), a biomarker for uptake of carcinogenic polycyclic aromatic hydrocarbons; and a series of mercapturic acids of benzene, acrolein, and other volatile cigarette smoke carcinogens and toxicants (Hecht, 2002). Some of the selected biomarkers were found to show a linear increase with cigarettes per day but demonstrated a plateau and greater variability at higher frequencies of smoking (Joseph et al., 2005). A recently completed study demonstrated that total NNAL was significantly related to lung cancer incidence, after correction for intensity and duration of smoking, in the National Cancer Institute-sponsored Prostate, Lung, Colon, and Ovarian Screening Trial, comparing prediagnostic urine samples from 100 controls and 100 smokers of at least 10 cigarettes/day. These results show that total NNAL is not only an exposure biomarker for the lung carcinogen NNK but also a risk biomarker for lung cancer (Church et al., 2008).

Some of these biomarkers were used to assess the role of cigarette reduction as a potential method to reduce tobacco toxicant exposure and perhaps disease risk (Hatsukami et al., 2005; Hecht, Carmella, et al., 2004; Hecht, Murphy, et al., 2004). Smokers were recruited and asked to systematically decrease their cigarette intake by 75%; levels of total NNAL and 1-HOP and cardiovascular risk factors were measured. Statistically significant reductions in lung carcinogen uptake and cardiovascular risk factors were observed with cigarette reduction. However, the observed decreases were generally modest, due to compensatory smoking, and sometimes transient. In animal studies, compensatory nicotine self-administration (NSA) was observed when duration of access to nicotine or nicotine dose was reduced (Harris, Burroughs, Pentel, & LeSage, 2008), and lower baseline self-administration was a strong predictor of greater compensation.

In a clinical trial that compared cigarette reduction and cessation among smokers who had cardiovascular disease but were not interested in quitting, smoking reduction failed to improve clinical and biological markers of cardiac disease (Joseph et al., 2008). These results suggest that cigarette reduction does no harm but is not likely to provide any health benefits or may not necessarily lead to greater cessation than a simple message to quit.

Other studies examined whether modified cigarettes or smokeless tobacco (ST) or switching cigarette smokers to ST

would lead to significant reductions in toxicant exposure compared with medicinal nicotine products. These studies showed (a) no difference in levels of total NNAL, 1-HOP, and cotinine in smokers of regular, light, and ultra-light cigarettes, respectively, which is consistent with epidemiological studies showing that these cigarettes do not lead to reduced risk for cancer (Hecht et al., 2005); (b) significant but only modest reductions in carcinogen exposure when smokers switched from conventional to modified reduced carcinogen cigarettes (Hatsukami et al., 2004); (c) a significant reduction in carcinogens when ST users switched from a conventional U.S. product to Swedish snus (Hatsukami et al.) and when smokers switched to Swedish snus or tobacco lozenge (Mendoza-Baumgart et al., 2007); and (d) the greatest reductions occurring with medicinal nicotine products. These studies support the concept of a continuum of risk associated with different types of nicotine-containing products (Hatsukami et al., 2007).

ST products may hold some promise for tobacco harm reduction, although medicinal nicotine products clearly lead to less toxicant exposure. New and conventional ST products marketed to cigarette smokers were analyzed for carcinogens and nicotine. The results showed lower levels of carcinogens in the newer ST products compared with conventional ST products, with varying levels of free nicotine (Stepanov, Jensen, Hatsukami, & Hecht, 2008). Total NNAL levels were similar in ST users of conventional products and smokers, and levels in ST users increased significantly with duration of use (Hecht et al., 2008; Hecht et al., 2007). These results demonstrate the potential hazards when smokers switch to conventional ST products with higher tobacco-specific nitrosamines (TSNAs), particularly if they continue to use these products.

Cigarette products that may hold promise for harm reduction are those with reduced nicotine content. Tobacco harm would be reduced by way of reducing the addiction to tobacco and possibly facilitating abstinence. TTURC research showed reduction in toxicant exposure, reduction in dependence, and similar rates of abstinence among those who smoked 0.05 mg nicotine cigarettes and used medicinal nicotine products (Hatsukami, 2008). Animal studies will examine individual differences in the threshold reinforcing dose for acquisition of NSA in adolescents and for sustaining NSA over the course of dose reduction in adults, providing models of smoking contexts (initiation vs. maintenance) and populations (adolescents vs. adults) in which reduced nicotine cigarettes would be used.

Implications

The study results have both program and policy implications. Although smoking reduction may be a method to facilitate a quit attempt in smokers who are not interested in quitting, it will not result in significant reductions in toxicant exposure nor is it necessarily a better approach than advice to quit. The products and strategies that hold the most promise for tobacco harm reduction are switching smokers completely to lower TSNA ST products or reduced nicotine cigarettes. Medicinal products hold the greatest promise among those who need continued use of nicotine. These are three approaches that should be examined more rigorously.

University of Southern California/Claremont Graduate University

Focus of the center

The University of Southern California/Claremont Graduate University TTURC investigated how social circumstance, cultural setting, dispositional phenotype, and genes might influence the course of tobacco and alcohol use trajectories in youth, and how they moderate (improve or diminish) the effectiveness of programs for tobacco and alcohol abuse prevention. The research evolved to explore neurocognitive mechanisms that mediate these relationships.

Key findings

Socially and genetically acquired influences on smoking and alcohol abuse. Research of adolescent twins aged 11–19 years in eastern China revealed heritable influences to be more pronounced for alcohol use than cigarette smoking (Leshov-Schlaggar et al., 2006). No heritable effects were found for depression and aggression, dispositional characteristics often found to be associated with cigarette smoking and alcohol use. Modest heritability was found for anxiety. Hostility was relatively more heritable in girls than boys. Bivariate associations between substance use and psychological measures could be attributed to a combination of common genetic and environmental factors. Among Chinese adolescents, experimentation with tobacco is familial and experimentation with alcohol is heritable. The genetic and environmental architecture of hostility differs by gender. Consistency of univariate results with western adolescent samples appears limited to the alcohol use measures.

Prevention relative to cultural composition of the community. Research in multiethnic southern California communities suggests that prevention program effectiveness can be influenced by the cultural setting. A community-based prevention trial found that youth in mixed-culture schools were more influenced by a program designed to emphasize individualist, self-enhancement prevention objectives and strategies, whereas students in predominantly Hispanic/Latino schools were more influenced by a collectivist family-oriented program that emphasized the well-being of the family and community (Johnson et al., 2005). This finding suggests that the fit of program to the sociocultural setting may be one reason that community-based prevention programs sometimes succeed and sometimes fail.

Dispositional characteristics of the individual. Findings from a trial carried out in central China indicated that depression–smoking comorbidity determined the effectiveness of a prevention program in influencing an adolescent’s smoking trajectory. Boys who tested high on depression and who had previously engaged in at least some cigarette smoking had flattened smoking trajectories; that is, after participating in a smoking prevention program, they were less likely to continue smoking or progress in smoking frequency than were those without the comorbidity (Sun et al., 2007). These findings suggest that the fit between program and individual dispositional characteristics is another reason that prevention programs sometimes succeed and sometimes fail.

Cultural environment by disposition by program interactions ($E \times P \times E$). Findings from a prevention trial carried out in multiethnic southern California indicate the potential for complex cultural environment by dispositional phenotype by program interactions (Johnson et al., 2007). In predominantly Latino schools, larger program effects were observed for highly depressed and highly hostile youth in both the collectivist- and individualist-framed programs. In culturally mixed schools, prevention effects were greatest for low depressed and low hostile youth, especially in the individualist-framed program. These findings suggest a third reason why prevention programs may sometimes succeed and sometimes fail. The impact of social context on program effects may be particularly heightened for people with certain dispositional characteristics or particularly weakened for those with other characteristics.

Genes, abuse trajectories, and prevention. The multistep nature of tobacco use progression—from initiation, to episodic use, to dependence—provides several opportunities for risk factors to act. The TTURC's research indicates that the efficacy of an intervention program depends on dispositional attributes such as hostility and depression. Within their social networks, adolescents make behavioral choices about tobacco use—choices that depend on individuals' dispositional attributes as influenced by biological, cognitive, and emotional changes. Thus, genetic and environmental exposures that influence brain biology are potential risk factors that affect tobacco use and the efficacy of intervention programs. To this end, researchers genotyped four variable number of tandem repeat polymorphisms (SLC6A4, SLC6A3, DRD4, and the MAO A promoter), as well as 1,295 single nucleotide polymorphisms (SNPs) in 58 genes within the neuronal nicotinic receptor and dopamine systems among the Wuhan (China) Prevention Trial cohort. Results were equivocal when examining main effects of each polymorphism. This finding was somewhat expected given the complex nature of smoking initiation. However, since previous association and functional data pointed to a major role for the MAO A promoter polymorphism, examination of effect modification for this functional polymorphism by all genotyped SNPs showed substantial effects. The most significant result was for a modification effect of MAO A by an SNP within the *DRD1IP* gene. This effect is seen in both males and females. In females, the *p* value after adjustment for multiple correlated tests was .0001 for the interaction effect. Specifically, within females carrying the minor allele (AA or AG) for *DRD1IP*, the four repeat polymorphisms increased risk for initiating smoking substantially ($OR = 8.7$). In males carrying the *DRD1IP* minor allele, the effect of MAO A was 3.3. However, for both females and males, there was no observed effect for MAO A in individuals with the wild-type genotype (GG; D. Li, J. Liu, W. Lee, X. Jiang, D. Van Den Berg, A. Bergen, S. London, P. Gallaher, C.-P. Chou, J. Shih, J. Unger, C. A. Johnson, & D. V. Conti, in preparation). Ongoing analysis is examining smoking progression, interactions with prevention, and alcohol abuse.

Emotional decision capacity and tobacco-alcohol abuse trajectories. The research indicates that individual capacity for decisions under emotional arousal profoundly influences tobacco and alcohol abuse trajectories. Using a widely accepted behavioral assessment of emotional decision capacity developed by the Iowa Gambling Task, TTURC researchers found that adolescents who binge drink showed greater emotional decision dysfunction than did those who do not (Johnson et al.,

2008). This effect was independent of one's intellectual capacity, as indicated by working memory and academic performance. Similar findings were observed for daily cigarette smoking (Xiao et al., 2008). In a prospective study, nondrinkers who exhibited emotional decision deficits were more likely to progress to binge drinking over a year's time than were those without deficits, supporting the conclusion that emotional decision capacity is a critical determinant of substance abuse vulnerability (Xiao et al., 2009). Functional magnetic resonance imaging studies have provided support for the role of candidate orbitofrontal cortex and midbrain region involvement in the observed behavioral deficits, and these differences in brain function predict daily smoking and binge drinking (L. Xiao, A. Bechara, P. Palmer, & C. A. Johnson, in preparation).

Implications

The research strongly suggests that advancement on smoking and alcohol use trajectories is multiply and interactively determined by individual, biological, and behavioral characteristics and the social environment. Strategies for prevention of tobacco and alcohol abuse should take into account the separate and potentially interactive influences. It is scientifically and logically fallacious to conclude that "prevention does not work" or equally that "prevention works." Some prevention programs can and do work, conditional upon circumstance and constitution. The role of prevention science should be to identify catalytic and inhibitory agents in the biobehavioral and environmental realms and test ways to take advantage of these so as to produce more reliable, profound, and sustainable prevention effects.

Future research

Current and planned research pursues potential catalysts and inhibitors of program effects. An ongoing trial is designed to elucidate underlying processes in the observed dispositional phenotype $\times$ program effects interactions and to test cognitive and behavioral strategies for addressing critical characteristics. One critically hypothesized construct is social competence and/or the autism spectrum. Deficits in capacity for social perception and action, akin to emotional decision processes, may be a key ingredient. The current trial intervenes both individually and through environmental manipulations, some mediated by new technologies, to enhance students' social decision and behavioral capacity and assesses the success and effects of these interventions on tobacco and alcohol abuse trajectories. In an attempt to clarify the underlying genetic basis for program by dispositional phenotype interactions, the TTURC plans to genotype an additional 44,000 SNPs in 750 male students from the Wuhan Prevention Trial. These SNPs include 3,713 tag SNPs in 348 candidate genes, including several nicotinic receptors and other genes involved in the addictive process. In addition, more than 40,000 SNPs are implicated in a genome-wide scan of nicotine dependence by the NICSNP consortium (Bierut et al., 2007). The TTURC expects to finish the genotyping and analysis of these SNPs by summer 2009. This additional genotyping will expand the investigation into the underlying genetics by more thoroughly covering potential candidate pathways and suspected regions in smoking-related phenotypes.

Societal impact

Findings from the research have been fed back with recommendations to participating community agencies via annual

reports, workshops, conferences, and trainings to inform participating public health and educational systems in the United States and China. Two international conferences have brought together scientists and public health and education leaders from the United States, China, and other parts of the world. A third conference is scheduled for Bangkok in fall 2009. An international network, now supported by the National Institutes of Health Fogarty Center, has been developed for promulgation of research findings through prevention curriculum development and dissemination in schools of public health and medicine. Numerous leaders from the scientific and public agency communities have been trained in workshops and certificate and degree programs for translation and implementation of the research findings. The continued substantial financial and institutional support of this program of action research by participating community agencies attests to their appreciation for and commitment to the value of the research for their public health and educational missions.

University of Pennsylvania

Focus of the center

Nicotine dependence has a complex multifactorial etiology, underscoring the value of applying a TD research model. The mission of the University of Pennsylvania TTURC is to translate discoveries in basic neuroscience, pharmacology, genetics, and behavioral science to improve the treatment of nicotine dependence.

Key findings

A key focus of the TTURC is translational research to elucidate the biobehavioral basis of nicotine dependence and identify novel targets for the development of new medications. One line of research in this area is investigating the role of the endogenous opioid system in nicotine reward and reinforcement. An initial finding in a pharmacogenetic trial of nicotine dependence treatment pointed to the role of genetic variation in the mu opioid receptor (*OPRM1* gene) in a smoker's ability to quit and maintain abstinence (Lerman et al., 2004). To clarify the underlying biobehavioral mechanisms of this association, parallel laboratory studies were performed in mice and humans. The mouse experiments (Walters, Cleck, Kuo, & Blendy, 2005) determined that the transcription factor cAMP response element binding (CREB) and the mu opioid receptor are involved in the rewarding, but not aversive, properties of nicotine. The human experiment (Ray et al., 2006) showed that a reduced function allele of the *OPRM1* gene (Asp40) was associated with reduced nicotine reward and reinforcement. Interacting effects of the human *CREB1* and *OPRM1* genes in nicotine reward also were identified (Ray et al., 2007), consistent with the preclinical data. Extending this line of research, one of the TTURC laboratories has developed a knockin mouse that possesses the mouse equivalent of the human Asp40 variant (Asp38 in mouse).

Abstinence-induced cognitive deficits that promote relapse are another key target in the area of medication development. Preclinical studies show that nicotine withdrawal impairs learning and suggest that relapse after smoking withdrawal may occur as an attempt to ameliorate learning-related deficits (Davis, James, Siegel, & Gould, 2005). Atomoxetine, used

in the treatment of attention-deficit/hyperactivity disorder, reversed nicotine withdrawal-induced deficits in learning in the mouse contextual fear conditioning model (Davis & Gould, 2007). Although atomoxetine did not alter abstinence-induced cognitive deficits in human smokers, it reduced subjective withdrawal symptoms and cravings to smoke in a subset of smokers (Ray et al., 2009). New data also suggest that varenicline, an $\alpha 4\beta 2$ nicotinic acetylcholine receptor (nAChR) antagonist, blocks withdrawal-associated cognitive deficits in mice (Raybuck, Portugal, Lerman, & Gould, 2008). Consistent with this finding, varenicline enhances cognitive performance in abstinent smokers, an effect that may contribute to its efficacy in relapse prevention (Patterson et al., 2009). Other TTURC work has documented effects of nicotine and medications to treat nicotine dependence in a mouse event-related potential (ERP) paradigm (Metzger, Maxwell, Liang, & Siegel, 2007; Siegel et al., 2005). This work is being extended to human ERP models.

Developing and validating new models for nicotine dependence medication development is a key goal of the TTURC. Some research focuses on improving models for early human screening (Perkins, Stitzer, & Lerman, 2006). A recent experiment tested the sensitivity of a within-subject model of medication effects on abstinence and found that intrinsic, but not extrinsic, quit motivation of participants may enhance the validity of brief tests of medication efficacy for smoking cessation (Perkins et al., 2008). Additional studies are exploring the utility of neuroimaging as a tool for identifying smokers at high risk for abstinence-induced craving and to screen new medications for nicotine dependence (Wang et al., 2007).

In addition to developing novel treatment approaches and screening models, research at the TTURC seeks to improve the efficacy of existing therapies by identifying likely responders and nonresponders based on genotype. Collaborative pharmacogenetic trials have identified genetic factors predicting treatment outcome, including drug-metabolizing enzymes (Lee et al., 2007; Malaiyandi et al., 2006; F. Patterson, R. A. Schnoll et al., 2008), genes involved in dopaminergic signaling (Colilla et al., 2005; Lerman et al., 2006), and nAChRs (Conti et al., 2008). In addition, novel genes, including those coding for cell adhesion molecules, were identified in a genome-wide association (GWA) study of smoking cessation (Uhl et al., 2008).

To facilitate the translation of these findings into improved smoking outcomes and improved population health, attention must be paid simultaneously to emerging social, political, and ethical issues. A broad range of research activities have focused on translation of pharmacogenetics research on nicotine dependence to clinical practice. These issues are addressed at various points along the "research to practice" continuum, ranging from research practices themselves (e.g., the use of race constructs in genetics research) to clinical integration (e.g., the preparedness of primary care physicians to incorporate pharmacogenetic treatment approaches into clinical practice, and patients' willingness to undergo genetic testing) and to develop the capacity to monitor the diffusion of new, efficacious pharmacogenetic treatment approaches throughout the health care system (A. Shields, Lerman, & Sullivan, 2004; A. E. Shields et al., 2005; A. E. Shields & Lerman, 2008).

Summary

The TD model provides an optimal framework for research to facilitate the development and delivery of new treatments for nicotine dependence. The TTURC's research illustrates the value of a multipronged approach that incorporates cross-species validation of effects of genetic and/or pharmacological manipulations of multiple neurotransmitter systems on a variety of nicotine dependence phenotypes. These include, but are not limited to, nicotine reward; reinforcement; cognitive enhancement; and alleviation of physical, cognitive, and affective symptoms of nicotine withdrawal. Preclinical data on the neurobiology of nicotine's rewarding effects or effects of pharmacological manipulation can identify novel biological targets and move medications forward through the clinical development pipeline. Likewise, clinical data supporting the efficacy of a novel pharmacotherapy or individual differences in therapeutic response can, in turn, guide the development of preclinical research to examine underlying neurobiological mechanisms, as illustrated in the example of reduced nicotine reward in obesity.

Clearly, nicotine dependence treatment must move beyond the prescription of a one-size-fits-all approach toward a more individualized approach using genetic and other individual difference variables to guide the choice of the optimal drug, dose, and duration of treatment to maximize efficacy. While initial findings in this area are promising, replication of these findings and consideration of the social, policy, and ethical issues in the use of pharmacogenetic approaches are warranted before these findings can be translated into clinical practice.

Brown University

Focus of the center

The overarching theme of the Brown University TTURC is to identify familial, early childhood, and lifetime biopsychosocial pathways that determine lifetime patterns of smoking uptake, use, and cessation and the associated patterns of dependence. To accomplish this, the TTURC, in the first phase of study, (a) implemented a prospective, three-generation family study (New England Family Study [NEFS]) to examine the lifetime pathways to nicotine dependence; (b) developed and validated promising new lifetime tobacco use and dependence phenotypic assessments; (c) assessed measures of comorbidity (with lower screening thresholds to include subclinical pathology) such as alcohol, psychiatric disorder, and temperament; (d) prospectively examined the efficacy and cost-effectiveness of a sustained comprehensive cessation intervention; and (e) collected blood and saliva specimens to inform future genetic-related research. Using families and individuals ascertained during the first phase of the NEFS, the TTURC is currently conducting (a) a two-generation family study of genetic/familial influences on lifetime patterns of tobacco use phenotypes and comorbid psychiatric disorders; (b) an endophenotypic study of sibling pairs discordant for these tobacco use phenotypes, involving functional magnetic resonance imaging with nicotine challenge; and (c) a study examining mediation and moderation of the influence of contextual (e.g., school, family, and neighborhood) factors on the progression of tobacco use, alcohol, and other drug use in adolescents and young adults.

Key findings and implications

Researchers investigated whether maternal smoking during pregnancy is associated with an increased risk of nicotine dependence among adult offspring (Buka, Shenassa, & Niaura, 2003). Prospective data from two samples of offspring in the National Collaborative Perinatal Project were combined. Maternal smoking during pregnancy was assessed during each prenatal visit. Offspring whose mothers reported smoking a pack or more of cigarettes during their pregnancy were significantly more likely to meet *Diagnostic and Statistical Manual* criteria for lifetime tobacco dependence than offspring of mothers who reported that they never smoked during pregnancy. Offspring of mothers who smoked a pack or more of cigarettes during pregnancy are at elevated risk of developing nicotine dependence.

Considerable debate remains regarding the effects of maternal smoking during pregnancy on children's growth and development. The TTURC investigated the relation between maternal smoking during pregnancy and 14 developmental outcomes of children from birth through age 7 years, using data from the Collaborative Perinatal Project (Gilman, Gardener, & Buka, 2008). In addition to adjusting for potential confounders measured contemporaneously with maternal smoking, the authors fitted conditional fixed-effects models among siblings that controlled for unmeasured confounders. Results from the conditional analyses indicated that birth weight and odds of being overweight at age 7 were influenced by maternal smoking. However, the associations between maternal smoking and 12 other outcomes studied (Apgar score, intelligence, academic achievement, conduct problems, and asthma) were entirely eliminated after adjustment for measured and unmeasured confounders. The hypothesized effects of maternal smoking during pregnancy on these outcomes either were not present or were not distinguishable from a broader range of familial factors associated with maternal smoking.

Despite evidence that lower education is associated with a higher risk of smoking, whether the association is causal has not been established convincingly. The association between education and lifetime smoking patterns was examined in the NEFS birth cohort (Gilman, Martin, et al., 2008), controlling for a wide range of potential confounders that were measured prior to school entry, and estimating sibling fixed-effects models to control for unmeasured familial vulnerability to smoking. In the full sample of participants, regression analyses adjusting for multiple childhood factors indicated that the number of pack-years smoked was higher among individuals with less than high school education. The effects of education on quitting smoking were attenuated in the sibling fixed-effects models that controlled for familial vulnerability to smoking. A substantial portion of the education differential in smoking that has been observed repeatedly is attributable to factors shared by siblings that contribute to shortened educational careers and to lifetime smoking trajectories. Reducing disparities in cigarette smoking, including educational disparities, may therefore require approaches that focus on factors early in life that influence smoking risk over the adult life span.

Detailed information about the characteristics of smokers who do and do not participate in smoking cessation treatment is needed to improve efforts to reach, motivate, and treat smokers (Graham et al., 2008). Eligible smokers were recruited from the

NEFS. Participants and nonparticipants were compared on a broad range of sociodemographics, smoking, psychiatric and substance abuse disorders, personality, and prospective measures from early childhood. Few differences were observed, most of which were statistically significant but not clinically meaningful. Compared with nonparticipants, participants were more likely to be single, have lower income, be more nicotine dependent and motivated to quit, and have higher levels of depressed mood and stress. The encouraging conclusion is that smokers who enroll in cessation trials may not differ much from nonparticipants. Information about treatment participants can inform the development of recruitment strategies, improve the tailoring of treatment to individual smoker profiles, help to estimate potential selection bias, and improve estimates of population impact.

The interaction of the serotonin transporter gene (*5-HTT* or *SCL6A4*) with measures of environment from childhood also was examined among 452 NEFS males and females who reported trying cigarettes at least once (J. McCaffery, G. D. Papandonatos, S. Santangelo, M. Lyons, R. Niaura, D. B. Abrams, M. Tsuang, S. L. Buka, under review). Results suggested that both housing density and maternal age of less than 18 years interacted with the promoter polymorphism to predict daily and current smoking. In each case, the effects of the environmental variable were most pronounced among those carrying at least one long, or “l,” allele, with little to no effect in those carrying two copies of the “s” allele. The results suggest that the effects of early childhood environment on risk of smoking initiation and progression may be moderated by genetic variation related to the serotonin transporter gene.

The TTURC sought, first, to identify replicated genes that facilitate smokers’ ability to achieve and sustain abstinence from smoking found in more than two GWA studies of successful versus unsuccessful abstainers and, second, to nominate genes for selective involvement in smoking cessation success with bupropion hydrochloride versus nicotine replacement therapy (NRT; Uhl et al., 2008). Researchers studied White smokers who successfully versus unsuccessfully abstained from smoking with biochemical confirmation in a smoking cessation trial using NRT, bupropion, or placebo ($N = 550$). They identified variants in quit-success genes that are likely to alter cell adhesion; enzymatic; transcriptional; structural; and DNA, RNA, and/or protein-handling functions. These genes displayed modest overlap with genes identified in GWA studies of dependence on addictive substances and memory. These results support polygenic genetics for success in abstaining from smoking, overlap with genetics of substance dependence and memory, and nominate gene variants for selective influences on therapeutic responses to bupropion versus NRT.

Yale University

Focus of the center

Rates of smoking and nicotine dependence continue to be high in individuals with psychiatric disorders (Grant, Hasin, Chou, Stinson, & Dawson, 2004), and women are less likely than men to quit smoking (Schnoll, Patterson, & Lerman, 2007). Studying subgroups of smokers who are less successful in treatment is critical because reversibility of smoking-related disease is related to duration of smoking (Hughes, 1996; Peto, 1996). Further, some risk factors, such as heavy alcohol use, are associated with

greater cancer risk (Ringborg, 1998). Given that most smokers try to quit smoking only once every 3–4 years (U.S. Department of Health and Human Services, 1990), the development of earlier *effective* interventions for these subgroups is desirable. To pursue the investigation of treatment-resistant smokers, the Yale TTURC incorporates a continuum of research from molecular genetics, neuroimaging, human laboratory paradigms, behavioral and pharmacological trials, and policy research.

Key findings

Depression. Current depression predicts poorer smoking cessation outcomes (Anda et al., 1990), suggesting that understanding the effect of nicotine on mood is essential. Using preclinical models, Caldarone et al. (2004) identified that (a) endogenous nAChRs modulate circuits related to mood; (b) the antidepressant response of the tricyclic antidepressant amitriptyline depends on the presence of high-affinity nAChRs; and (c) changes in signaling pathways occur following chronic, but not acute nicotine treatment, identifying candidate pathways involved in the transition from nicotine use to dependence (Addy et al., 2007; Steiner, Heath, & Picciotto, 2007). Surprisingly, antagonism of nAChRs using mecamylamine resulted in antidepressant effects (Caldarone et al., 2004; Rabenstein, Caldarone, & Picciotto, 2006). Subsequently, George, Sacco, Vessicchio, Weinberger, and Shytle (2008) demonstrated that mecamylamine has antidepressant effects in treatment-refractory smokers and nonsmokers with major depression. Picciotto, Addy, Mineur, and Brunzell (2008) have synthesized what is known about the contribution of activation and desensitization of nAChRs to behaviors related to nicotine and mood.

Alcohol use. Alcohol consumption and tobacco use are also highly associated. Using a nationally representative sample, McKee, Falba, O’Malley, Sindelar, and O’Connor (2007) demonstrated that occasional and daily smoking were highly associated with hazardous levels of drinking and alcohol diagnoses. To understand potential mechanisms, Löf et al. (2007) investigated the role of the nAChR system in ethanol reinforcement and ethanol consumption. In rodents, presentation of an ethanol-associated conditioned stimulus induced elevations in nucleus accumbens dopamine and acted as a conditioned reinforcer. Both these effects were blocked by systemic injection of nicotinic antagonists. These data support the critical role of nicotinic receptors in conditioned reinforcement to alcohol cues and suggest that pharmacological manipulations of nAChRs may be a strategy to prevent cue-induced relapse. Other TTURC researchers are testing the potential value of mecamylamine, a nicotine antagonist, in the treatment of alcohol drinking. McKee, Krishnan-Sarin, Shi, Mase, and O’Malley (2006) are examining whether varenicline, a partial agonist, attenuates the adverse effect of alcohol on ability to resist smoking using a laboratory model developed in the TTURC and whether varenicline reduces alcohol drinking among heavy-drinking smokers using a paradigm in which beneficial effects of NRT were demonstrated (McKee, O’Malley, Shi, Mase, & Krishnan-Sarin, 2008).

Beyond interventions targeted to individuals, the Yale and Roswell Park TTURCs collaborated on an analysis of the effects of smoking bans in indoor public places on alcohol drinking (McKee et al., 2009). Adult smokers and nonsmokers from Scotland were compared with individuals in the rest of the United Kingdom, which did not have smoke-free policies. Reduced

drinking in pubs and bars among moderate- and heavy-drinking smokers occurred in Scotland without an increase in home drinking, suggesting that smoke-free policies may have additional alcohol-related public health benefits. Future research will investigate how tobacco policies and taxation influence drinking and alcohol use disorders in other countries.

Female gender. Although more men smoke, women are less likely than men to quit smoking (Schnoll et al., 2007). Yale research has identified sex differences that might explain this finding as follows: (a) the association between depression, alcohol, and drug use disorders and smoking is stronger in women (Husky, Paliwal, Mazure, & McKee, 2007, 2008); (b) women report higher perceived risks of cessation, and the perception of risk is associated with lower motivation and poorer treatment outcome (McKee, O'Malley, Salovey, Krishnan-Sarin, & Mazure, 2005); and (c) stressful life events contribute more to smoking relapse in women than in men (McKee, Maciejewski, Falba, & Mazure, 2003). Nonsmoking women and men, however, do not differ in the availability of β_2 -nAChRs implicated in nicotine reinforcement (Cosgrove et al., 2007), as measured using a SPECT radiotracer developed in part through the TTURC (Staley et al., 2005). Ongoing research will determine whether upregulation of these receptors seen in smokers (Staley et al., 2006) normalizes at different rates in women and men and how this relates to the expression of depression and anxiety.

Women are concerned about weight gain from smoking cessation and value potential treatments that reduce weight gain (Busch et al., 2004). Naltrexone was shown to reduce weight gain in combination with nicotine patch (O'Malley et al., 2006) and bupropion (Toll, Leary, et al., 2008). Although naltrexone did not improve quit rates, reduction of weight gain might encourage weight-concerned smokers to make a quit attempt. Basic research has identified interactions between nicotine and feeding pathways that may lead to the development of other treatments (Abizaid et al., 2006; Fornari, Pedrazzi, Picciotto, Zoli, & Zini, 2007). Behavioral interventions emphasizing the benefits of quitting rather than the risks of continued smoking appear to be effective for women with low perception of quitting risks (Toll, Salovey, et al., 2008).

Future directions

In addition to the research described previously, Yale TTURC investigators are contributing expertise on nicotine and tobacco to other initiatives at Yale, including the Interdisciplinary Research Consortium on Stress, Self-Control and Addiction; the Psychotherapy Development Center; the Center for Translational Neuroscience of Alcoholism; and the Clinical and Translational Science Award.

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Declaration of Interests

None declared.

Note

A review of the Special Report on the following page was run in issue 11(5), pp. 467–474, “Bridging basic and clinical science with policy studies: The Partners with Transdisciplinary Tobacco Use Research Centers experience,” by Kimberly Kobus and Robin Mermelstein. The review should have been published alongside this report, but due to an oversight, it was published separately. Readers' attention is drawn to this review.

References

University of Wisconsin

McCarthy, D. E., Bolt, D. M., & Baker, T. B. (2007). The importance of how: A call for mechanistic research in tobacco dependence treatment studies. In T. B., Baker, R., Bootzin and T. A., Treat (Eds.), *Psychological clinical science: Recent advances in theory and practice: Integrative perspectives in honor of Richard M. McFall* (pp. 133–163), New York: Lawrence Earlbaum Associates.

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.

McCarthy, D. E., Piasecki, T. M., Lawrence, D. L., Jorenby, D. E., Shiffman, S., Fiore, M. C., et al. (2008). A Randomized Controlled Clinical Trial of Bupropion SR and Individual Smoking Cessation Counseling. *Nicotine and Tobacco Research*, 10, 717–729.

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 relations. *Journal of Abnormal Psychology*, 112, 14–27.

Piasecki, T. M., Jorenby, D. E., Smith, S. S., Fiore, M. C., & Baker, T. B. (2003c). Smoking withdrawal dynamics: III. Correlates of withdrawal heterogeneity. *Experimental and Clinical Psychopharmacology*, 11, 276–285.

Piper, M. E., Bolt, D. M., Kim, S.-Y., Japuntich, S. J., Smith, S. S., Niederdeppe, J., et al. (2008). Refining the tobacco dependence phenotype using the Wisconsin Inventory of Smoking Dependence Motives (WISDM). *Journal of Abnormal Psychology*, 117, 747–761.

Piper, M. E., Federman, E. B., McCarthy, D., Bolt, D., Smith, S. S., Fiore, M. C., et al. (2008). Using mediational models to explore the nature of tobacco motivation and tobacco treatment effects. *Journal of Abnormal Psychology*, 117, 94–105.

Piper, M. E., Federman, E. B., McCarthy, D. E., Bolt, D. M., Smith, S. S., Fiore, M. C., et al. (2008). Efficacy of bupropion alone and in combination with nicotine gum. *Nicotine and Tobacco Research*.

Piper, M. E., Piasecki, T. M., Federman, E. B., Bolt, D. M., Smith, S. S., Fiore, M. C., et al. (2004). A Multiple Motives Approach to Tobacco Dependence: The Wisconsin Inventory of Smoking Dependence Motives (WISDM-68). *Journal of Consulting and Clinical Psychology*, 72, 139–154.

Weiss, R. B., Baker, T. B., Cannon, D. S., von Niederhausen, A., Dunn, D. M., Matsunami, N., et al. (2008). A candidate gene approach identifies the CHRNA5-A3-B4 region as a risk factor for age-dependent nicotine addiction. *PLoS Genetics*, 4(7), e1000125.

Roswell Park Cancer Institute

Borland, R., Fong, G. T., Yong, H. H., Cummings, K. M., Hammond, D., King, B., et al. (2008). What happened to smokers' beliefs about light cigarettes when "light/mild" brand descriptors were banned in the UK? Findings from the International Tobacco Control (ITC) Four Country Survey. *Tobacco Control*, 17, 256–262.

Borland, R., Yong, H., Cummings, K. M., Hyland, A., Anderson, S., & Fong, G. T. (2006). Determinants and consequences of smoke-free homes: Findings from the International Tobacco Control (ITC) Four Country Survey. *Tobacco Control*, 15, iii42–iii50.

Borland, R., Yong, H., Siahpush, M., Hyland, A., Campbell, S., Cummings, K. M., et al. (2006). Support for and reported compliance with smoke-free restaurants and bars by smokers in four countries: Findings from the International Tobacco Control (ITC) Four Country Survey. *Tobacco Control*, 15, iii34–iii41.

Ciecierski, C. T. (2007). *The market for legal and illegal cigarettes in Poland: A closer look at demand and supply-side characteristics* (IDRC Working Paper Series/ITEN Working Paper Series No 1), from http://www.idrc.ca/en/ev-84071-201-1-DO_TOPIC.html

Fong, G. T., Cummings, K. M., Borland, R., Hastings, G., Hyland, A., Giovino, G. A., et al. (2006). The conceptual framework of the International Tobacco Control (ITC) Policy Evaluation Project. *Tobacco Control*, 15, iii3–iii11.

Fong, G. T., Hyland, A., Borland, R., Hammond, D., Hastings, G., McNeill, A., et al. (2006). Reductions in tobacco smoke pollution and increases in support for smoke-free public places following the implementation of comprehensive smoke-free workplace legislation in the Republic of Ireland: Findings from the ITC Ireland/UK Survey. *Tobacco Control*, 15, iii51–iii58.

Hammond, D., Fong, G., Borland, R., Cummings, K. M., McNeill, A., & Driezen, P. (2007). Text and graphic warnings on cigarette packages: Findings from the ITC Four Country Survey. *American Journal of Preventive Medicine*, 32, 202–209.

Hammond, D., Fong, G., McNeill, A., Borland, R., & Cummings, K. M. (2006). Effectiveness of cigarette warning labels in

informing smokers about the risks of smoking: Findings from the International Tobacco Control (ITC) Four Country Survey. *Tobacco Control*, 15, iii26–iii30.

Harris, F., McNeill, A., Anderson, S., Hastings, G., Borland, R., Fong, G. T., et al. (2006). Effects of the 2003 advertising/promotion ban in the United Kingdom on awareness of tobacco marketing: Findings from the International Tobacco Control (ITC) Four Country Survey. *Tobacco Control*, 15, iii26–iii33.

Hyland, A., Higbee, C., Borland, R., Travers, M., Hastings, G., Fong, G. T., et al. (2009). Attitudes and beliefs about secondhand smoke and smoke-free policies in four countries: Findings from the International Tobacco Control Four Country Survey. *Nicotine and Tobacco Research*, 11, 642–649.

Hyland, A., Higbee, C., Hassan, L., Fong, G. T., Borland, R., Cummings, K. M., et al. (2008). Does smoke-free Ireland have more smoking inside the home and less in pubs than the United Kingdom? Findings from the International Tobacco Control Policy Evaluation Project. *European Journal of Public Health*, 18, 63–65.

Hyland, A., Higbee, C., Li, Q., Bauer, J. E., Giovino, G. A., Alford, T., & Cummings, K. M. (2005). Access to low taxed cigarettes deters smoking cessation attempts. *American Journal of Public Health*, 95, 994–995.

Hyland, A., Laux, F., Higbee, C., Hastings, G., Ross, H., Chaloupka, F., et al. (2006). Cigarette purchase patterns in four countries and the relationship with cessation: Findings from the International Tobacco Control (ITC) Four Country Survey. *Tobacco Control*, 15, iii59–iii64.

Hyland, A., Travers, M., Dresler, C., Higbee, C., & Cummings, K. M. (2007). A 32-country comparison of tobacco smoke derived particle levels in indoor public places. *Tobacco Control*, 15, 159–165.

O'Connor, R. J., Hammond, D., McNeill, A., King, B., Kozlowski, L. T., Giovino, G. A., et al. (2008). How do different cigarette design features influence standard tar yields of popular cigarette brands sold in different countries? *Tobacco Control*, 17(Suppl.1), i1–i5.

O'Connor, R. J., Kozlowski, L., Hammond, D., Vance, T. T., Stitt, J. P., & Cummings, K. M. (2007). Digital image analysis of cigarette filter staining to estimate smoke exposure. *Nicotine and Tobacco Research*, 9, 865–871.

O'Connor, R. J., McNeill, A., Cummings, K. M., Kozlowski, L. T., & Giovino, G. A. (2006). How did UK cigarette makers get their brands to 10 mg. "tar" or less? *British Medical Journal*, 332, 302.

O'Connor, R. J., Stitt, J., & Kozlowski, L. T. (2005). A digital image analysis system for identifying filter vent blocking on ultralight cigarettes. *Cancer Epidemiology, Biomarkers, and Prevention*, 14, 533–537.

Paszkievicz, G. M., & Pauly, J. L. (2008). Spectrofluorometric method for measuring tobacco smoke particulate matter on cigarette filters and Cambridge pads. *Tobacco Control*, 17(Suppl. 1), i53–i58.

Strasser, A. A., O'Connor, R., Mooney, M. E., & Wileyto, E. P. (2006). Digital image analysis of cigarette filter stains as an indicator of compensatory smoking. *Cancer Epidemiology, Biomarkers, and Prevention*, 15, 2565–2569.

Thompson, M. E., Fong, G. T., Hammond, D., Boudreau, C., Driezen, P. R., Hyland, A., et al. (2006). Methods of the International Tobacco Control (ITC) Four Country Survey. *Tobacco Control*, 15, iii12–iii18.

Thrasher, J. F., Hammond, D., Fong, G. T., & Arillo-Santilan, E. (2007). Smokers' reactions to cigarette package warnings with graphic imagery and with only text: A comparison of Mexico and Canada. *Mexican Journal of Public Health*, 49, S233–S240.

Thrasher, J. F., Rousu, M., Anaya-Ocampo, R., Reynales-Shigematsu, L., Arillo-Santillan, E., & Hernandez-Avila, M. (2007). Estimating the impact of different cigarette package warning label policies: The auction method. *Addictive Behaviors*, 32, 2916–2925.

University of Minnesota

Church, T. R., Anderson, K. E., Caporaso, N. E., Geisser, M. S., Le, C., Zhang, Y., et al. (2008, April). *Total NNAL, a serum biomarker of exposure to a tobacco-specific carcinogen, is related to lung cancer in smokers. Presentation at the American Association for Cancer Research Annual Meeting*. San Diego, CA.

Harris, A. C., Burroughs, D., Pentel, P. R., & LeSage, M. G. (2008). Compensatory nicotine self-administration in rats during reduced access to nicotine: An animal model of smoking reduction. *Experimental and Clinical Psychopharmacology*, 16, 86–97.

Hatsukami, D. K. (2008, February). *Science and future research directions for reduced nicotine content cigarettes. Presentation at the National Cancer Advisory Boarding Meeting*. Bethesda, MD.

Hatsukami, D. K., Joseph, A. M., LeSage, M. G., Jensen, J., Murphy, S. E., Pentel, P., et al. (2007). Developing the science base for reducing tobacco harm reduction. *Nicotine and Tobacco Research*, 9(Suppl. 4), S537–S553.

Hatsukami, D. K., Kotlyar, M., Allen, S., Jensen, J., Li, S., Le, C., et al. (2005). Effects of cigarette reduction on cardiovascular risk factors and subjective measures. *Chest*, 128, 2528–2537.

Hatsukami, D. K., Lemmonds, C., Zhang, Y., Murphy, S. E., Le, C., Carmella, S. G., et al. (2004). Evaluation of carcinogen exposure in people who used "reduced exposure" tobacco products. *Journal of the National Cancer Institute*, 96, 844–852.

Hecht, S. S. (2002). Human urinary carcinogen metabolites: Biomarkers for investigating tobacco and cancer. *Carcinogenesis*, 23, 907–922.

Hecht, S. S., Carmella, S. G., Edmonds, A., Murphy, S. E., Stepanov, I., Luo, X., et al. (2008). Exposure to nicotine and a tobacco-specific carcinogen increase with duration of use of smokeless tobacco. *Tobacco Control*, 17, 128–131.

Hecht, S. S., Carmella, S. G., Le, K. A., Murphy, S. E., Li, Y. S., Le, C., et al. (2004). Effects of reduced cigarette smoking on levels of 1-hydroxypyrene in urine. *Cancer Epidemiology, Biomarkers, and Prevention*, 13, 834–842.

Hecht, S. S., Carmella, S. G., Murphy, S. E., Riley, W. T., Le, C., Luo, X., et al. (2007). Similar exposure to a tobacco-specific carcinogen in smokeless tobacco users and cigarette smokers. *Cancer Epidemiology, Biomarkers, and Prevention*, 16, 1567–1572.

Hecht, S. S., Murphy, S. E., Carmella, S. G., Li, S., Jensen, J., Le, C., et al. (2005). Similar uptake of lung carcinogens by smokers of regular, light, and ultralight cigarettes. *Cancer Epidemiology, Biomarkers, and Prevention*, 14, 693–698.

Hecht, S. S., Murphy, S. E., Carmella, S. G., Zimmerman, C. L., Losey, L., Kramarczuk, I., et al. (2004). Effects of reduced cigarette smoking on the uptake of a tobacco-specific lung carcinogen. *Journal of the National Cancer Institute*, 96, 107–115.

Joseph, A. M., Hecht, S. S., Murphy, S. E., Carmella, S. G., Le, C. T., Zhang, Y., et al. (2005). Relationships between cigarette consumption and biomarkers of tobacco toxin exposure. *Cancer Epidemiology, Biomarkers, and Prevention*, 14, 2963–2968.

Joseph, A. M., Hecht, S. S., Murphy, S. E., Lando, H., Carmella, S. G., Gross, M., et al. (2008). Smoking reduction fails to improve clinical and biological markers of cardiac disease: A randomized controlled trial. *Nicotine and Tobacco Research*, 10, 471–481.

Mendoza-Baumgart, M. I., Tulunay, O. E., Hecht, S. S., Zhang, Y., Murphy, S., Le, C., et al. (2007). Pilot study on lower nitrosamine smokeless tobacco products compared with medicinal nicotine. *Nicotine and Tobacco Research*, 9, 1309–1323.

Stepanov, I., Jensen, J., Hatsukami, D., & Hecht, S. S. (2008). New and traditional smokeless tobacco: comparison of toxicant and carcinogen levels. *Nicotine and Tobacco Research*, 10, 1773–1782.

University of Southern California/ Claremont Graduate University

Bierut, L. J., Madden, P. A., Breslau, N., Johnson, E. O., Hatsukami, D., Pomerleau, O. F., et al. (2007). Novel genes identified in a high-density genome wide association study for nicotine dependence. *Human Molecular Genetics*, 16, 4–35.

Johnson, C. A., Cen, S., Gallaher, P., Palmer, P. H., Xiao, L., Ritt-Olson, A., et al. (2007). Why smoking prevention programs sometimes fail. Does effectiveness depend on sociocultural context and individual characteristics? *Cancer Epidemiology, Biomarkers, and Prevention*, 16, 1043–1049.

Johnson, C. A., Unger, J. B., Ritt-Olson, A., Palmer, P. H., Cen, S. Y., Gallaher, P., et al. (2005). Smoking prevention for ethnically diverse adolescents: 2-year outcomes of a multicultural, school-based smoking prevention curriculum in Southern California. *Preventive Medicine*, 40, 842–852.

Johnson, C. A., Xiao, L., Palmer, P., Sun, P., Wang, Q., Wei, Y., et al. (2008). Affective decision-making deficits, linked to a dysfunctional ventromedial prefrontal cortex, revealed in 10th grade Chinese adolescent binge drinkers. *Neuropsychologia*, 46, 714–726.

Lessov-Schlaggar, C. N., Pang, Z., Swan, G. E., Guo, Q., Wang, S., Cao, W., et al. (2006). Heritability of cigarette smoking and alcohol use in Chinese male twins: The Qingdao twin registry. *International Journal of Epidemiology*, 35, 1278–1285.

Sun, P., Unger, J. B., Guo, Q., Gong, J., Ma, H., Palmer, P. H., et al. (2007). Comorbidity between depression and smoking moderates the effect of a smoking prevention program among boys in China. *Nicotine and Tobacco Research*, 9(Suppl. 4), S599–S609.

Xiao, L., Bechara, A., Cen, S., Grenard, G., Stacy, A., Gallaher, P., et al. (2008). Affective decision-making deficits, linked to a dysfunctional ventromedial prefrontal cortex, revealed in 10th grade Chinese adolescent smokers. *Nicotine and Tobacco Research*, 10, 1085–1097.

Xiao, L., Bechara, A., Grenard, L. J., Stacy, A. W., Palmer, P., Wei, Y., et al. (2009). Affective decision making predictive of Chinese adolescent drinking behaviors. *Journal of the International Neuropsychological Society*, 15, 1–11.

University of Pennsylvania

Colilla, S., Lerman, C., Shields, P. G., Jepson, C., Rukstalis, M., Berlin, J., et al. (2005). Association of catechol-O-methyltransferase with smoking cessation in two independent studies of women. *Pharmacogenetic Genomics*, 15, 393–398.

Conti, D. V., Lee, W., Li, D., Liu, J., Van Den Berg, D., Thomas, P. D., et al. (2008). Nicotinic acetylcholine receptor $\beta 2$ subunit gene implicated in a systems-based candidate gene study of smoking cessation. *Human Molecular Genetics*, 17, 2834–2848.

Davis, J. A., & Gould, T. J. (2007). Atomoxetine reverses nicotine withdrawal-associated deficits in contextual fear conditioning. *Neuropsychopharmacology*, 32, 2011–2019.

Davis, J. A., James, J. R., Siegel, S. J., & Gould, T. J. (2005). Withdrawal from chronic nicotine administration impairs contextual fear conditioning in C57BL/6 mice. *Journal of Neuroscience*, 25, 8708–8713.

Lee, A. M., Jepson, C., Hoffmann, E., Epstein, L., Hawk, L. W., Lerman, C., et al. (2007). CYP2B6 genotype alters abstinence rates in a bupropion smoking cessation trial. *Biological Psychiatry*, 62, 635–641.

Lerman, C., Jepson, C., Wileyto, E. P., Epstein, L. H., Rukstalis, M., Patterson, F., et al. (2006). Role of functional genetic variation in the dopamine D2 receptor (DRD2) in response to bupropion and nicotine replacement therapy for tobacco dependence: results of two randomized clinical trials. *Neuropsychopharmacology*, 31, 231–242.

Lerman, C., Wileyto, E. P., Patterson, F., Rukstalis, M., Audrain-McGovern, J., Restine, S., et al. (2004). The functional mu

opioid receptor (OPRM1) Asn40Asp variant predicts short-term response to nicotine replacement therapy in a clinical trial. *Pharmacogenomics Journal*, 4, 184–192.

Malaiyandi, V., Lerman, C., Benowitz, N. L., Jepson, C., Patterson, F., & Tyndale, R. F. (2006). Impact of CYP2A6 genotype on pretreatment smoking behaviour and nicotine levels from and usage of nicotine replacement therapy. *Molecular Psychiatry*, 11, 400–409.

Metzger, K. L., Maxwell, C. R., Liang, Y., & Siegel, S. J. (2007). Effects of nicotine vary across two auditory evoked potentials in the mouse. *Biological Psychiatry*, 61, 23–30.

Patterson, F., Jepson, C., Strasser, A., Loughead, J., Perkins, K., Gur, R. C., et al. (2009). Varenicline improves mood and cognition during smoking abstinence. *Biological Psychiatry*, 65, 144–149.

Patterson, F., Schnoll, R. A., Wileyto, E. P., Pinto, A., Epstein, L. H., Shields, P. G., et al. (2008). Toward personalized therapy for smoking cessation: a randomized placebo-controlled trial of bupropion. *Clinical Pharmacology and Therapeutics*, 84, 320–325.

Perkins, K. A., Lerman, C., Stitzer, M., Fonte, C. A., Briski, J. L., Scott, J. A., et al. (2008). Development of procedures for early screening of smoking cessation medications in humans. *Clinical Pharmacology and Therapeutics*, 84, 216–221.

Perkins, K. A., Stitzer, M., & Lerman, C. (2006). Medication screening for smoking cessation: A proposal for new methodologies. *Psychopharmacology (Berl)*, 184, 628–636.

Ray, R., Jepson, C., Patterson, F., Strasser, A., Rukstalis, M., Perkins, K., et al. (2006). Association of OPRM1 A118G variant with the relative reinforcing value of nicotine. *Psychopharmacology (Berl)*, 188, 355–363.

Ray, R., Jepson, C., Wileyto, P., Patterson, F., Strasser, A. A., Rukstalis, M., et al. (2007). CREB1 haplotypes and the relative reinforcing value of nicotine. *Molecular Psychiatry*, 12, 615–617.

Ray, R., Rukstalis, M., Jepson, C., Strasser, A. A., Patterson, F., Lynch, K., et al. (2009). Effects of atomoxetine on subjective and neurocognitive symptoms of nicotine abstinence. *Journal of Psychopharmacology*, 23, 168–176.

Raybuck, J. D., Portugal, G. S., Lerman, C., & Gould, T. J. (2008). Varenicline ameliorates nicotine withdrawal-induced learning deficits in C57BL/6 mice. *Behavioral Neuroscience*, 122, 1166–1171.

Shields, A., Lerman, C., & Sullivan, P. (2004). Translating emerging research on the genetics of smoking into clinical practice: ethical and social considerations. *Nicotine and Tobacco Research*, 6, 675–688.

Shields, A. E., Blumenthal, D., Weiss, K. B., Comstock, C. B., Currivan, D., & Lerman, C. (2005). Barriers to translating emerging genetic research on smoking into clinical practice. Perspectives of primary care physicians. *Journal of General Internal Medicine*, 20, 131–138.

Shields, A. E., & Lerman, C. (2008). Anticipating clinical integration of pharmacogenetic treatment strategies for addiction:

are primary care physicians ready? *Clinical Pharmacology and Therapeutics*, 83, 635–639.

Siegel, S. J., Maxwell, C. R., Majumdar, S., Trief, D. F., Lerman, C., Gur, R. E., et al. (2005). Monoamine reuptake inhibition and nicotine receptor antagonism reduce amplitude and gating of auditory evoked potentials. *Neuroscience*, 133, 729–738.

Uhl, G. R., Liu, Q. R., Drgon, T., Johnson, C., Walther, D., Rose, J. E., et al. (2008). Molecular genetics of successful smoking cessation: Convergent genome-wide association study results. *Archives of General Psychiatry*, 65, 683–693.

Walters, C. L., Cleck, J. N., Kuo, Y. C., & Blendy, J. A. (2005). Mu-opioid receptor and CREB activation are required for nicotine reward. *Neuron*, 46, 933–943.

Wang, Z., Faith, M., Patterson, F., Tang, K., Kerrin, K., Wileyto, E. P., et al. (2007). Neural substrates of abstinence-induced cigarette cravings in chronic smokers. *Journal of Neuroscience*, 27, 14035–14040.

Brown University

Buka, S. L., Shenassa, E. D., & Niaura, R. (2003). Elevated risk of tobacco dependence among offspring of mothers who smoked during pregnancy: A 30-year prospective study. *American Journal of Psychiatry*, 160, 1978–1984.

Gilman, S. E., Gardener, H., & Buka, S. L. (2008). Maternal smoking during pregnancy and children's cognitive and physical development: A causal risk factor? *American Journal of Epidemiology*, 168, 522–531.

Gilman, S. E., Martin, L. T., Abrams, D. B., Kawachi, I., Kubzansky, L., Louks, E. B., et al. (2008). Educational attainment and cigarette smoking: A causal association? *International Journal of Epidemiology*, 37, 615–624.

Graham, A. L., Papandonatos, G. D., Depue, J. D., Pinto, B. M., Borrelli, B., Neighbors, C. J., et al. (2008). Lifetime characteristics of participants and non-participants in a smoking cessation trial: Implications for external validity and public health impact. *Annals of Behavioral Medicine*, 35, 295–307.

Yale University

Abizaid, A., Liu, Z.-W., Andrews, Z. B., Shanabrogh, M., Borok, E., Elsworth, J., et al. (2006). Ghrelin modulates the activity and synaptic input organization of midbrain dopamine neurons while promoting appetite. *Journal of Clinical Investigation*, 116, 3229–3239.

Addy, N. A., Fornasiero, E., Tanya, R., Stevens, T. R., Taylor, J. R., & Picciotto, M. R. (2007). Role of calcineurin in nicotine-mediated locomotor sensitization. *Journal of Neuroscience*, 27, 8571–8580.

Anda, R. F., Williamson, D. F., Escobedo, L. G., Mast, E. E., Giovino, G. A., & Remington, P. L. (1990). Depression and the dynamics of smoking: A national perspective. *Journal of the American Medical Association*, 264, 1541–1545.

Busch, S., Falba, T., Duchovny, N., Jofre-Bonet, M., O'Malley, S., & Sindelar, J. (2004). Value to smokers of improved cessation products: Evidence from a willingness-to-pay survey. *Nicotine and Tobacco Research*, 6, 631–639.

Caldarone, B. J., Harrist, A., Cleary, M. A., Beech, R. D., King, S. L., & Picciotto, M. R. (2004). High-affinity nicotinic acetylcholine receptors are required for antidepressant effects of amitriptyline on behavior and hippocampal cell proliferation. *Biological Psychiatry*, 56, 657–664.

Cosgrove, K. P., Mitsis, E. M., Bois, F., Frohlich, E., Tamagnan, G. D., Krantzler, E., et al. (2007). 123I-5-IA-85380 SPECT imaging of nicotinic acetylcholine receptor availability in nonsmokers: effects of sex and menstrual phase. *Journal of Nuclear Medicine*, 48, 1633–1640.

Fornari, A., Pedrazzi, P., Picciotto, M. R., Zoli, M., & Zini, I. (2007). Nicotine withdrawal increases body weight, neuropeptide Y and Agouti-related protein expression in the hypothalamus and decreases uncoupling protein-3 expression in the brown adipose tissue in high-fat fed overweight mice. *Neuroscience Letters*, 411, 72–76.

George, T. P., Sacco, K. A., Vessicchio, J. C., Weinberger, A. H., & Shytle, R. D. (2008). Nicotinic antagonist augmentation of selective serotonin reuptake inhibitor—refractory major depressive disorder: A preliminary study. *Journal of Clinical Psychopharmacology*, 28, 340–344.

Grant, B. F., Hasin, D. S., Chou, P. S., Stinson, F. S., & Dawson, D. A. (2004). Nicotine dependence and psychiatric disorders in the United States. *Archives of General Psychiatry*, 61, 1107–1115.

Hughes, J. R. (1996). The future of smoking cessation therapy in the United States. *Addiction*, 91, 1787–802.

Husky, M. M., Paliwal, P., Mazure, C. M., & McKee, S. A. (2007). Gender differences in associations between substance use diagnoses and smoking. *Journal of Addiction Medicine*, 1, 161–164.

Husky, M. M., Paliwal, P., Mazure, C. M., & McKee, S. A. (2008). Gender differences in the comorbidity of smoking behavior and major depression. *Drug and Alcohol Dependence*, 93, 176–179.

Löf, E., Olausson, P., deBejczy, A., Stomberg, R., McIntosh, J. M., Taylor, J. R., et al. (2007). Activation of nicotinic acetylcholine receptors in the VTA mediate the dopamine activating and reinforcing properties of ethanol-associated cues. *Psychopharmacology*, 195, 333–343.

McKee, S. A., Falba, T., O'Malley, S. S., Sindelar, J., & O'Connor, P. G. (2007). Smoking status is a clinical indicator for problematic alcohol use in US adults. *Archives of Internal Medicine*, 167, 716–721.

McKee, S., Higabee, C., O'Malley, S., Hassan, L., Borland, R., Cummings, M., et al. (2009). Longitudinal evaluation of smoke-free Scotland on pub and home drinking behavior: Findings from the International Tobacco Control Policy Evaluation Project. *Nicotine and Tobacco Research*, 11, 619–626.

- McKee, S. A., Krishnan-Sarin, S., Shi, J., Mase, S., & O'Malley, S. S. (2006). Modeling the effect of alcohol on smoking lapse behavior. *Psychopharmacology*, 189, 201–210.
- McKee, S. A., Maciejewski, P. K., Falba, T., & Mazure, C. M. (2003). Sex differences in the effects of stressful life events on changes in smoking status. *Addiction*, 98, 847–855.
- McKee, S. A., O'Malley, S., Salovey, P., Krishnan-Sarin, K., & Mazure, C. M. (2005). Perceived risks and benefits of smoking cessation: Gender-specific predictors of motivation and treatment outcome. *Addictive Behavior*, 30, 423–435.
- McKee, S. A., O'Malley, S. S., Shi, J., Mase, T., & Krishnan-Sarin, S. (2008). Transdermal nicotine replacement attenuates alcohol reactivity and reduces alcohol self-administration. *Psychopharmacology*, 196, 189–200.
- O'Malley, S. S., Cooney, J. L., Krishnan-Sarin, S., Dubin, J. A., McKee, S. A., Cooney, N. L., et al. (2006). A controlled trial of naltrexone augmentation of nicotine replacement therapy for smoking cessation. *Archives of Internal Medicine*, 166, 667–674.
- Peto, R. (1996). Influence of dose and duration of smoking on lung cancer rates. *LARC Scientific Publication*, 74, 23–33.
- Picciotto, M. R., Addy, N. A., Mineur, Y. S., & Brunzell, D. H. (2008). It is not “either/or”: Activation and desensitization of nicotinic acetylcholine receptors to behaviors related to nicotine addiction and mood. *Progress in Neurobiology*, 84, 329–342.
- Piper, M., Federman, E. B., McCarthy, D., Bolt, D., Smith, S. S., Fiore, M. C., et al. (2008). Using mediational models to explore the nature of tobacco motivation and tobacco treatment effects. *Journal of Abnormal Psychology*, 117, 94–105.
- Rabenstein, R. L., Caldarone, B. J., & Picciotto, M. R. (2006). The nicotinic antagonist mecamylamine has antidepressant-like effects in wild type 7 nicotinic acetylcholine receptor knockout mice but not beta2- or alpha7- nicotinic acetylcholine receptor subunit knockout mice. *Psychopharmacology*, 189, 395–401.
- Ringborg, U. (1998). Alcohol and risk of cancer. *Alcoholism: Clinical and Experimental Research*, 22(Suppl. 7), 323S328S.
- Schnoll, R. A., Patterson, F., & Lerman, C. (2007). Treating tobacco dependence in women. *Journal of Women's Health*, 16, 1211–1218.
- Staley, J., Dyck, C. V., Weinzimmer, D., Brenner, E., Baldwin, R., Tamagnan, G., et al. (2005). Iodine-123-5-IA-85380 SPECT measurement of nicotinic acetylcholine receptors in human brain by the constant infusion paradigm: feasibility and reproducibility. *Journal of Nuclear Medicine*, 46, 1466–1472.
- Staley, J. K., Krishnan-Sarin, S., Cosgrove, K. P., Krantzler, E., Frohlich, E., Perry, E., et al. (2006). Human tobacco smokers in early abstinence have higher levels of beta2 nicotinic acetylcholine receptors than nonsmokers. *Journal of Neuroscience*, 26, 8707–8714.
- Steiner, R. C., Heath, C. J., & Picciotto, M. R. (2007). Nicotine-induced phosphorylation of extracellular signal regulated kinase (ERK) in mouse primary cortical neurons: evidence for involvement of glutamatergic signaling and CaMKII. *Journal of Neurochemistry*, 103, 666–678.
- Toll, B. A., Leary, V., Wu, R., Salovey, P., Meandzija, B., & O'Malley, S. (2008). A preliminary investigation of naltrexone augmentation of sustained-release bupropion to stop smoking with less weight gain. *Addictive Behaviors*, 33, 173–179.
- Toll, B. A., Salovey, P., O'Malley, S. S., Mazure, C., Latimer, A., & McKee, S. A. (2008). Message framing for smoking cessation: The interaction of risk perceptions and gender. *Nicotine and Tobacco Research*, 10, 195–200.
- U.S. Department of Health and Human Services. (1990). *Tobacco use in 1986. Methods and basic tabulations from adult use of tobacco survey*. (Vol OM 90–2004). Washington, DC: U.S. Department of Health and Human Services.