

SYMPOSIUM

SYM1

BIOBEHAVIORAL MECHANISMS OF SEX DIFFERENCES IN NICOTINE ADDICTION: A TRANSLATIONAL PERSPECTIVE

Chair: Cora Lee Wetherington, Ph.D.¹

Presenters: Sakire Pogun², Kenneth A. Perkins³, Julie K. Staley⁵, and Caryn Lerman⁴

Discussant: Dorothy K. Hatsukami⁶

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Over recent decades the decline in smoking has been much slower in females than in males. Females are less successful than males at quitting: they have higher relapse rates, relapse more quickly, and have a poorer response to nicotine replacement therapies. The overall public health burden due to smoking is higher for women than men, especially given adverse consequences of maternal smoking both prenatally and during the early childhood years. This symposium will present an array of biobehavioral perspectives on mechanisms of sex differences in nicotine addiction with a view toward translation to sex-based prevention and treatment efforts. The session will begin with Dr. Pogun's preclinical rodent studies describing sex differences in central and behavioral effects of nicotine, including reinforcing and motivational differences, sex differences in adolescents versus adults, and the role of estrogen. Next, Dr. Perkins will present data showing sex differences in phenotype and genotype variables that moderate nicotine sensitivity in non-smokers, sex differences in the relation between the DRD4 gene and smoking reinforcement in smokers, and sex differences in modulation of nicotine patch effectiveness by use of monetary reinforcement of smoking abstinence. Then Dr. Staley will present male and female data from her study of beta²-nAChR availability using SPECT and the nicotinic agonist radiotracer [¹²³I]5-IA-85380 ([¹²³I]5-IA) in never smokers and smokers at various time points over prolonged abstinence, including data on the association between rate of receptor normalization and depression scores. Next, Dr. Lerman will present human behavioral pharmacology data showing sex differences in the relation between a functional genetic variant in the mu opioid gene (OPRM1 Asp40) and the reinforcing value of nicotine, as well as other data supporting sex by genotype interactions in smoking cessation and treatment response. And finally, Dr. Hatsukami will provide a discussion of the relationships among these findings, their contributions to understanding sex differences in nicotine addiction, and their implications for sex-based interventions and future research.

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SYM1A

BIOBEHAVIOURAL STUDIES IN RODENTS POINT TO SEX DIFFERENCES IN THE CENTRAL EFFECTS OF NICOTINE

Sakire Pogun, Ph.D.*¹, Gorkem Yazarbas, M.D., Ph.D.^{1,2}, and Tanseli Nesil, M.Sc.^{1,3}; ¹Ege University Center for Brain Research; ²Center for Drug R&D and Pharmacokinetic Applications; ³Biotechnology Dept. Institute of Science Ege University

There are sex differences in brain structure and function and there is growing evidence that these differences impact vulnerability to addictive substances. Although drug abuse has been accepted to be a male problem, and research on addiction has been primarily conducted on male subjects, many studies on smoking behavior have included sex as a factor. While the gender-specific effects of environmental factors and social pressures on smoking behavior cannot be ignored, there is growing evidence that biological factors underlie the sexual dimorphism in the central effects of nicotine that may mediate addiction. Rodent studies point to significant sex differences in the genetics, metabolism and receptors of the nicotinic cholinergic system which result in differences in the rewarding and reinforcing effects of nicotine and are reflected in self-administration, locomotor activity, stress reactivity, consummatory behavior, body weight, and cognition. Similarly, there are sex differences between male and female smokers in the initiation, maintenance and cessation of the smoking habit. Biobehavioral studies including sex as a factor will help us understand nicotine addiction better and develop more efficient therapeutic strategies for smoking cessation. Recent research from our laboratory has shown that nicotine induces conditioned place preference (CPP) in male rats, but not in females. Estrogen may underlie this sex difference since blocking estrogen receptors reinstates CPP. Another recent finding involves individual differences in oral nicotine preference. Rats were given a free choice of nicotine or water starting at adolescence in either continuous (6 wks of nicotine choice starting at adolescence, 3 months interval, and another 6 wks of nicotine exposure as adults), or interrupted (nicotine choice available continuously from adolescence throughout adulthood) experimental design. Our results show that nicotine consumption is higher during adolescence than adulthood and that adult females consume more nicotine than males especially with interrupted design. The talk will include a brief summary of literature findings and recent findings from our laboratory.

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SYM1B

FACTORS INTERACTING WITH SEX TO INFLUENCE RESPONSES TO NICOTINE OR SMOKING

Kenneth A. Perkins, Ph.D.*¹, Caryn Lerman, Ph.D.², Joshua L. Karelitz, B.S., Amy Grotenthaler, B.S.¹, Melissa Mercincavage, B.S.¹, and Carolyn A. Fonte, R.N.¹; ¹University of Pittsburgh; ²University of Pennsylvania

We have found that smoking reward and reinforcement in women, compared to men, tend to be influenced less by nicotine and more by nonpharmacological factors in smoking. This presentation will draw largely on studies from our laboratory to identify characteristics that may moderate acute responses to nicotine or smoking in women. We assessed responses in nonsmokers and in smokers to examine factors that may be involved in dependence onset and persistence, respectively. In nonsmokers, several individual difference characteristics moderate nicotine sensitivity, but primarily in men and not in women. These include impulsivity, history of marijuana use, and DRD2 and DRD4 genotypes. Thus, few factors may alter nicotine responses in women prior to onset of dependence. In smokers, however, a variant in the DRD4 gene may enhance the increase in smoking reinforcement due to negative mood in women, but not in men. Clinically, raising quit motivation via monetary reinforcement of abstinence may increase, more in women than in men, the effectiveness of nicotine versus placebo patch over the first week of quitting. Use of such incentives may be important, as clinical trials show that women tend to gain less benefit than men from the nicotine patch. These results require replication and extension in larger samples, but they may help clarify sex differences in sensitivity to nicotine and smoking effects.

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SYM1C

IMAGING SEX-SPECIFIC EFFECTS ON BETA2*-NICOTINIC ACETYLCHOLINE RECEPTOR AVAILABILITY IN MEN AND WOMEN NEVER SMOKERS AND SMOKERS

Julie K. Staley, Ph.D.*, Yale University School of Medicine & VACHS

The nature of tobacco smoking and nicotine dependence is different between women and men. Women differ from men in their urges to smoke and smoking behavior in response to mood states. Women appear to be less sensitive and more tolerant to nicotine and exhibit a poorer response to nicotine replacement therapies. These differences may be mediated through nicotine's interactions with the beta2*-containing nicotinic acetylcholine receptors (beta2*-nAChR) in brain. Beta2*-nAChR play an integral role in nicotine self-administration, conditioned place preference, discriminative stimulus, taste aversion, dopamine release, and the upregulation in high affinity nicotinic agonist binding. To determine if this critical neural substrate contributes to the sex-specific differences in tobacco smoking, we evaluated beta2*-nAChR availability using SPECT and the nicotinic agonist radiotracer [123I]5-IA-85380 ([123I]5-IA) in men and women never smokers and smokers at various time points (1, 2, 4 and 6-12 weeks) over prolonged abstinence. Interestingly, we noted differences in the metabolism and protein binding of [123I]5-IA with slower metabolism and higher protein binding which manifested in the appearance of higher brain [123I]5-IA activity in women versus men. After correction for the differences in radiotracer metabolism and protein binding, beta2*-nAChR receptor availability did not differ between men and women never smokers. Beta2*-nAChR availability was higher in recently abstinent smokers versus never smokers with no statistically significant difference between men and women. Despite the lack of significant sex-specific differences in the extent of higher beta2*-nAChR availability, over prolonged abstinence there was a difference in receptor normalization with a greater decline in women smokers as compared to men smokers. And, individuals with higher depressive scores also had a greater decline in beta2*-nAChR availability. This enhanced rate of receptor normalization may be associated with the higher incidence of subsyndromal depressive symptoms reported more commonly by women than men.

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SYM1D

SEX DIFFERENCES IN THE NICOTINE-OPIOID SYSTEM INTERACTIONS

Caryn Lerman, Ph.D.*¹, Riju Ray, M.B.S.S., Ph.D.¹, Robert A. Schnoll, Ph.D.¹, Kenneth A. Perkins, Ph.D.², and Julie A. Blendy, Ph.D.¹; ¹University of Pennsylvania; ²University of Pittsburgh

Preclinical and clinical investigations support a role for the endogenous opioid system in nicotine reward. Additionally, there is evidence that estrogen modulates the activity mu opioid receptors (MORs). Accordingly, MOR antagonists appear to have greater effects on smoking behavior in female compared to male smokers. Human genetic studies have examined associations of a functional genetic variant in the MOR gene (OPRM1 Asp40) with smoking cessation. Data from two independent trials suggest that female carriers of the reduced function Asp40 allele of OPRM1 may have a greater ability to quit smoking. While evidence from the clinical studies is tentative and requires replication in larger studies, additional evidence for sex by OPRM1 interactions is provided in a human behavioral pharmacology study. Specifically, carriers of the OPRM1 Asp40 allele reported reduced nicotine reward; in a nicotine cigarette choice paradigm, there was a significant sex by genotype interaction suggesting a stronger genetic association with the reinforcing value of nicotine in females. These data will be presented in the context of additional studies supporting sex by genotype interactions in smoking cessation and treatment response, and directions for future research will be discussed.

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SYM2

SMOKELESS TOBACCO FOR SMOKERS: SCIENCE AND FUTURE DIRECTIONS

Chair: Dorothy Hatsukami, Ph.D.*¹
 Presenters: Lois Biener, Ph.D.*², Vaughan Rees, Ph.D.³, and Rich O'Connor, Ph.D.⁴
 Discussant: Ann McNeil*⁵
¹University of Minnesota; ²University of Massachusetts; ³Harvard University; ⁴Roswell Park Cancer Institute; ⁵University of Nottingham

In the U.S., major cigarette companies have been acquiring smokeless tobacco companies, and manufacturing smokeless tobacco products or snus. The snus products are targeted towards the cigarette smoker as a method for dealing with smoke-free environments and may consequently undermine some smokers' motivation for cessation. While the prevalence of smoking has been declining in the U.S., the smokeless tobacco market and use has been increasing. In spite of these trends, little research to date has been conducted on understanding the motive of the tobacco companies in introducing these novel smokeless tobacco products for the smoker, the consumer perception of these products, whether these products are preferred over medicinal nicotine and the effects of these products on cessation. Progress in these areas is necessary to circumvent any potential harm to public health. This symposium will present new research in these areas. Dr. Vaughn Rees will be presenting industry acquisition, sales, marketing and media data and toxicant analysis to determine the intent of current smokeless tobacco marketing efforts. Dr. Lois Biener will present data from a population survey that describes the receptivity of the population to snus products, how the consumer perceives them and predictors of snus uptake. Dr. Richard O'Connor will be presenting data from a trial that examines product choice behaviors across various nicotine containing products (e.g., medicinal nicotine, oral tobacco lozenge and snus), after receiving information about the harms of these products relative to cigarettes. Dr. Dorothy Hatsukami will describe her studies on toxicant uptake across various products and the results from her recent study examining the effects of snus products with relatively low and high nicotine levels versus medicinal nicotine on cessation. Dr. Ann McNeill, the discussant, will describe the implications from these studies and future directions.

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SYM2A

IMPLICATIONS OF CIGARETTE MANUFACTURERS ENTRY INTO THE SMOKELESS TOBACCO MARKET

Vaughan Rees, Ph.D.*¹, and Greg Connolly, D.M.D., M.P.H., School of Public Health, Harvard University

Problem/Objective: Major US cigarette companies have recently moved into the smokeless tobacco (SLT) market, traditionally the purview of non-cigarette manufacturers. The top four US cigarette manufacturers each have produced new "reduced exposure" snus products, and Reynolds and Philip Morris have recently purchased major smokeless tobacco companies. Possible motivations may include preservation of market share by capitalizing on recent SLT market growth, promotion of combined SLT and cigarette use, and enhancement of public image and reduction of exposure to litigation by offering potentially safer products.

Methods: Industry acquisition data, SLT and cigarette sales, marketing strategies and media reports were analyzed to assess cigarette companies' intentions for promoting SLT products. Nicotine and nitrosamine analyses were conducted on Camel Snus (Reynolds), Taboka and Marlboro Snus (PM), and compared with popular moist snuff products to develop a basis for understanding their addictive and toxic potential.

Results: Industry and media sources indicated that increased market share and the public relations benefits of being associated with less harmful products are primary reasons for involvement in the SLT market. Low nicotine levels of PM snus products raise questions about maintenance of use without concurrent use of cigarettes.

Conclusions: Advertising and sales data indicate an expanding moist snuff market, providing a profit motive for cigarette company acquisitions. Aggressive marketing and low nicotine levels appear intended to promote combined snus and cigarette use, rather than encouraging smokers to switch to SLT to reduce harm. The results demonstrate the need for continued surveillance of the SLT market and emphasize the need for government regulation of SLT products.

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SYM2B

POPULATION RECEPTIVITY AND PERCEPTIONS OF SNUS IN A US TEST MARKET

Lois Biener, Ph.D.^{*1}, Karen Bogen, Ph.D.¹, Miranda Spitznagle, M.P.H.², and Katelyn Ryan, M.A.²; ¹University of Massachusetts Boston; ²Indiana Tobacco Prevention and Cessation Program

There is agreement in the public health community that low-nitrosamine smokeless tobacco is less harmful than cigarettes, but there is controversy about whether to disseminate information about the harm reduction potential of snus. Many feel that to do so would result in a net increase in harm to the population. Although there are strong feelings among professionals on each side of the question, there is virtually no evidence about the population response to the test marketing of the products. This paper provides such evidence by analyzing data from a telephone survey of Indiana adults. Indianapolis was the only test market for Philip Morris's first snus product, Taboka (introduced in August 2006) and is also a test market for Camel Snus (as of March 2007). Questions about awareness and trial of the new products were included on the 2006 and 2007 Indiana Adult Tobacco Survey, a population-based survey of the Indiana population. Analyses of the 3544 respondents were conducted to assess the level of awareness and trial of the two products among various subgroups, perceptions of the harmfulness of smokeless tobacco relative to cigarettes, and factors that predicted awareness and trial of snus. Over 80% of respondents believed that smokeless tobacco was at least as harmful as cigarettes. Statewide, 20% of respondents had heard of one of the products but fewer than 2% had tried snus. There were major subgroup differences in trial of snus, with 20% of male smokers in Central Indiana (the counties surrounding and including Indianapolis) reporting having tried Taboka or Camel Snus. Multivariate analyses indicated that awareness of either Taboka or Camel Snus was significantly higher in Central Indiana than in the rest of the state (OR: 2.80), among smokers rather than nonsmokers (OR: 4.44), and among those who received tobacco promotions in the mail (OR: 2.04). Trial of snus was significantly higher among Central Indiana males who received promotional mailings and who perceived smokeless tobacco to be safer than cigarettes. These analyses demonstrate that direct mail marketing and perceptions of relative safety are important predictors of snus uptake.

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SYM2C

HOW DO SMOKERS REACT TO INFORMATION ABOUT AND TRIAL OF ORAL NICOTINE SOURCES?

Richard J. O'Connor, Ph.D.^{*1}, Kaila J. Norton, B.S.¹, K. Michael Cummings, Ph.D., M.P.H.¹, and Ron Borland, Ph.D.²; ¹Roswell Park Cancer Institute; ²Cancer Council Victoria

Both pharmaceuticals and tobacco products have been introduced into the market that deliver nicotine orally and are marketed to smokers as temporary substitutes for cigarettes, cessation aids, or smoking alternatives. We examined the effects of offering smokers not currently interested in quitting (N=27) the opportunity to try various oral nicotine products (Commit 4mg Lozenge, Stonewall Hard Snuff, Camel Snus, Marlboro Snus), after providing credible information about harms relative to cigarettes. At first, participants were provided one container of each product to sample over one week. Then, participants could elect to use one of those products in addition to or instead of cigarettes for one week. Participants showed significant reaction to the relative risk information. At baseline 15% believed smokeless tobacco and 42% believed medicinal nicotine were less harmful than cigarettes; both increased to 67% one week later. When participants sampled products, Commit was most frequently nominated the most-liked product (55%) while Camel Snus was most commonly nominated as least-liked (45%). After the sampling phase, most participants (63%) chose Commit to use for one week while 5% declined to continue use of any products. Substitution did not occur on a large scale — on average, smokers used .125 units of their preferred product for each cigarette smoked per day (i.e., for every 8 cigarettes smoked, 1 oral product was used). Consumption of the preferred product decreased during the week, although cigarette use also tended to decrease over the week. Participants showed a statistically significant decrease in exhaled CO after the one week trial (19.5ppm vs. 16.4ppm, p=.011). The majority of smokers reported interest in future use of their preferred product, generally to aid in reducing or eliminating cigarettes smoked per day — 60% reported they would be very likely or somewhat likely to use preferred product instead of or in addition to cigarettes. Providing credible relative risk information corrects misperceptions of tobacco product harms, at least in the short term. Implications of these findings for tobacco harm reduction will be discussed.

Roswell Park Transdisciplinary Tobacco Use Research Center (via National Cancer Institute CA111236). All products were purchased on the open market.

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SYM2D

SMOKELESS TOBACCO PRODUCTS: TOXICITY, TOXICANT EXPOSURE AND SMOKING CESSATION TOOL

Dorothy K. Hatsukami, Ph.D.^{*}, Louise Hertsgaard, Irina Stepanov, Joni A. Jensen, M.P.H., and Stephen S. Hecht, Ph.D., University of Minnesota

The public health community has engaged in a debate of whether smokers should use lower tobacco-specific nitrosamine (TSNA) smokeless tobacco products as a way to quit smoking among those who have been previously unsuccessful in quitting. Concurrently, tobacco companies have been manufacturing and marketing smokeless tobacco products that have been aimed at the cigarette smoker. Few studies have been conducted that examine the toxicity and nicotine yields of these products, the uptake of toxicants across different tobacco products and whether smokeless tobacco use can lead to successful cessation. To date, our research has demonstrated the lower TSNA products vary in nicotine content. Furthermore, the toxicant exposure when using these products is significantly lower than when smoking cigarettes. In light of these results, a pilot clinical trial was conducted to examine the effects of lower TSNA smokeless tobacco products with varying levels of nicotine vs. medicinal nicotine. Smokers interested in quitting were randomized to either: 1) Camel Snus (low TSNA, moderate nicotine; n=46); 2) Taboka (low TSNA, low nicotine, n=46); and 3) 4 mg nicotine lozenge (n=24). Subjects underwent a 1-week sampling period of the different flavors of the products to which they were assigned. They were then asked to use the assigned product of the flavor of their choice for 4 weeks. After the end of the 4 weeks, they were asked to abstain from all tobacco products. The rate of dropouts was high across all conditions (37%-41%). To date, the rate of abstinence at 12 weeks post-treatment has been: Camel Snus 23.9%; Taboka 19.6%; nicotine lozenge 29.2%. These results suggest that medicinal nicotine does just as well as an oral tobacco with higher and lower levels of nicotine.

This study was funded by the University of Minnesota TTURC DA13333. All products were purchased at retail stores.

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SYM3

TOBACCO USE, CESSATION, AND RELAPSE IN CANCER PATIENTS

Chair: Vani Nath Simmons, Ph.D.^{*1}
 Presenters: Sonia A. Duffy, Ph.D., R.N.², Jamie Ostroff, Ph.D.³, and Michelle Cororve Fingeret, Ph.D.⁴
 Discussant: Ellen Gritz, Ph.D.^{*4}
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The relationship between smoking and cancer is well established. Cigarette smoking accounts for 85% of head and neck cancers and 90% of lung cancer cases. In addition to the evidence that smoking causes cancer, continued smoking after an individual has been diagnosed with cancer is related to a myriad of detrimental health effects (e.g., risk of developing a second primary cancer or other smoking related diseases). Research suggests that cancer patients are highly motivated to quit smoking; thus efforts aimed at increasing tobacco cessation and maintaining smoking abstinence among this population could have a significant public health impact. The goal of this symposium is to present new findings with the cancer patient population that further elucidates the critical need for effective smoking interventions and suggests unique targets and forms of cessation and relapse interventions for cancer patients. Dr. Sonia Duffy will present recent data from a large (N = 811) longitudinal study with head and neck cancer patients examining the impact of smoking on medical outcomes and quality of life. She will also discuss novel findings regarding the interrelationship between smoking and other co-occurring health behaviors on outcomes. Dr. Michelle Cororve Fingeret will present work examining the relationship between smoking and body image among surgically treated oral cancer patients. She will describe data on the varied patterns of body image concerns for smokers vs. non-smokers as a potentially important consideration in developing future smoking cessation treatments with oral cancer patients. Dr. Jamie Ostroff will present outcome data from a pre-surgical, randomized, smoking cessation trial with newly diagnosed cancer patients comparing enhanced usual care (EUC) and EUC + Scheduled Reduced Smoking. Dr. Vani Simmons will present qualitative and quantitative data from a study on smoking relapse among lung cancer and head/neck cancer patients including patient and provider perspectives on smoking relapse and rates and predictors of smoking relapse post-surgery. Dr. Ellen Gritz, a leading expert on smoking cessation in cancer patients, will serve as the discussant.

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SYM3A

SHORT-TERM EFFECT OF A PRE-SURGICAL SMOKING CESSATION INTERVENTION FOR NEWLY DIAGNOSED CANCER PATIENTS

Jamie Ostroff, Ph.D.^{*1}, Jack Burkhalter, Ph.D.¹, Yuelin Li, Ph.D.¹, Mariya Shiyko, M.A.¹, Susan Holland, M.P.H.¹, and Paul Cinciripini, Ph.D.²; ¹Memorial Sloan-Kettering Cancer Center; ²M.D. Anderson Cancer Center

Smoking cessation reduces the risk of peri-operative complications, disease progression and second primary malignancies in tobacco dependent cancer patients. Given high rates of smoking relapse post-treatment, development and evaluation of acceptable and efficacious interventions is needed for this special population. Eligible smokers newly diagnosed with mixed cancers (n= 185) scheduled for surgery were randomized to either enhanced usual care (EUC: physician advice, behavioral counseling, NRT), or EUC+SRS (Scheduled Reduced Smoking) delivered by a handheld computer (PDA). Smokers in the EUC+SRS condition chose a pre-surgery quit date. The PDA used an algorithm to taper the number of cigarettes smoked up to hospitalization, prompted smokers to smoke on the prescribed schedule, and assessed psychosocial variables in real time. Trial acceptance was high (87%). Biochemically verified point abstinence was assessed at hospitalization and 3 and 6 months following hospitalization. Participants were 53% female (mean age 56 years). The median baseline smoking rate was 20 cpd, and 36% reported heavy nicotine dependence. Randomization ensured that the two groups had comparable baseline characteristics in sociodemographic, psychosocial, and medical variables. Retention of patients in the trial was high, with 92% retention at hospitalization and 79% retention at 3-month follow-up. Smoking cessation outcomes at the earliest time point, hospitalization, were 50% for SRS patients (n=96) and 56.7% for EUC (n = 89) (p = 0.38, n.s. by Fisher's test). Neither patient demographics (age, gender, education, and employment status), nor baseline cessation variables (nicotine dependence, motivation to quit, quitting self-efficacy) predicted abstinence at hospitalization. Subsequent analyses will examine mediators and moderators of pre-surgical smoking abstinence as well as post-hospitalization rates of smoking relapse. Clinical implications and future directions will be discussed.

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SYM3B

BODY IMAGE CONCERNS AMONG SURGICALLY TREATED ORAL CANCER PATIENTS: A POTENTIAL TARGET FOR SMOKING CESSATION TREATMENT

Michelle Cororve Fingeret, Ph.D.^{*}, Gregory Reece, M.D., Ann Gillenwater, M.D., Yisheng Li, Ph.D., Shana Palla, M.S., and Ellen Gritz, Ph.D., University of Texas M.D. Anderson Cancer Center

Knowledge of the relationship between smoking and body image in patients with oral cancer has the potential to guide smoking cessation treatment in this population, which can ultimately prolong survival, enhance quality of life, and reduce the risk of second primary tumors. To the extent that body image contributes to smoking behaviors, patients with oral cancer who continue to smoke may benefit from intervention components specifically targeted to treat body image disturbance. Although body image issues involving post-cessation weight gain have been implicated as deterrents to smoking cessation in the general population, the nature of appearance concerns in patients with oral cancer are likely to extend well beyond body shape and size and involve aspects of outward physical appearance related to disease site and treatment outcome. Patients with oral cancer who continue to smoke postoperatively are particularly vulnerable to experiencing facial disfigurement as smoking is known to increase the risk of wound infection and poor wound healing. The purpose of this study was to obtain much needed information about the nature and extent of body image concerns among surgically treated oral cancer patients and to evaluate the relationship between smoking and body image in this patient group. Participants (N=75) completed self-report questionnaires and a breath carbon monoxide test prior to surgical intervention, 1 month and 6 months following surgical intervention. At baseline, significantly higher body image concerns were found for current smokers compared to non-smokers on two separate instruments. Generalized linear models with repeated measures indicated that the pattern of body image scores over time varied significantly between smoking status groups. Current smokers had a more consistent increase in body image concerns over time while non-smokers scores increased sharply at 1 month but decreased slightly after 6 months. These findings indicate that body image concerns are associated with smoking behaviors in oral cancer patients, and are a potential target for treatment to assist with smoking cessation throughout the active phase of cancer treatment.

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SYM3C

THE INTERRELATIONSHIP BETWEEN SMOKING, OTHER HEALTH BEHAVIORS, BIOMARKERS AND OUTCOMES AMONG HEAD AND NECK CANCER PATIENTS

Sonia A. Duffy, Ph.D., R.N.^{*1,2}, Jeffrey E. Terrell, M.D.¹, David L. Ronis, Ph.D.¹, Stephen B. Gruber, M.D.¹, Jeremy M.G. Taylor, Ph.D.¹, Theodoros N. Teknos, M.D.¹, Gregory T. Wolf, M.D.¹, Mumtaz Khan, M.D.³, Scott McLean, M.D.³, and Karen E. Fowler, M.P.H.²; ¹University of Michigan; ²Veterans Affairs Center for Clinical Management Research; ³Henry Ford Health System

Prior studies have provided varied information about the association between health behaviors (particularly smoking), biomarkers and outcomes among head and neck cancer patients. However, none of the studies have prospectively assessed the nature, relative strength, and interrelationships of these factors together as predictors of recurrence, survival, and quality of life. Hence, the specific aim of this study is to determine if smoking, other health behaviors (alcohol use, nutrition, physical activity, and sleep), clinical characteristics, and molecular markers interleukin-6 (IL-6) and human papillomavirus-16 (HPV-16) are major predictors of recurrence, survival, and quality of life among head and neck cancer patients. This was an observational, longitudinal study that enrolled patients (N=811) from three hospitals. Information on health behaviors, clinical characteristics, and demographics were collected through surveys and hospital records. Serum was collected every 3 months and tumor tissue was collected at time of initial tumor biopsy or tumor resection. Smoking and problem drinking were highly associated (p<.01) and both were associated with lower body mass index (BMI) (p<.01). Moreover, physical activity and sleep were associated with each other (p<.01). Low sleep scores were common and highly associated with depression (p<.01) and smoking (p<.01). Baseline smoking was the strongest predictor of survival in this population with both current and former smokers having 2.5 times the hazard of death compared to never smokers (p<.01). Smoking was associated with IL-6 (p<.001) and IL-6 is a predictor of poor survival (p<.01). However, smoking status was inversely associated with HPV-16 positive tumors (p<.01). The major predictors of changes in QOL during year 1 were smoking (p<.05) and treatment factors (p<.05). These data suggest that smoking and other health behaviors are interrelated and are associated with prognostic biomarkers and cancer recurrence, survival and quality of life. Interventions to improve health behaviors, particularly smoking, may improve outcomes among head and neck cancer patients.

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SYM3D

SMOKING RELAPSE AMONG LUNG CANCER AND HEAD AND NECK CANCER PATIENTS: QUALITATIVE AND QUANTITATIVE FINDINGS

Vani Nath Simmons, Ph.D.^{*}, Erika B. Litvin, M.A., Riddhi Patel, B.S., Paul B. Jacobsen, Ph.D., Judith McCaffrey, M.D., Gerold Bepler, M.D., Ph.D., and Thomas H. Brandon, Ph.D., Moffitt Cancer Center and University of South Florida

Continued smoking among cancer patients is related to adverse health outcomes including a reduction in treatment efficacy and poorer survival. Many patients will quit smoking after diagnosis, offering a unique window of opportunity to provide a relapse-prevention intervention. However, there is little information regarding relapse in this population, and no relapse interventions tailored to cancer patients have been developed. The goal of this study is to acquire knowledge needed to develop a smoking relapse intervention for cancer patients. The aim of Phase I was to identify patient and provider perspectives on smoking cessation and relapse and to elicit preferences for intervention content and modality. We interviewed 20 lung and head/neck cancer patients who had made a quit attempt since their diagnosis and 11 providers who work directly with patients. Transcripts were coded for key themes. The general theme that emerged was that stress and fear associated with diagnosis provided strong motivation to quit. Patients reported similar relapse triggers found in studies using general population samples, however protective factors unique to this population included fear of cancer recurrence and feeling sick or in pain. Patients and providers suggested that interventions should include information about the benefits of quitting and the risks of continued smoking specific to cancer patients, and cessation treatments. These qualitative findings are being further examined in Phase II, an ongoing, longitudinal, quantitative study examining emotional, cognitive, and physical predictors of relapse in lung and head/neck cancer patients. Follow-up data is collected at 2, 4, 6, and 12 months post-surgery. Preliminary results regarding the precipitating events and predictors of relapse will be presented. Empirically and theory based relapse risk factors (e.g., negative affect, motivation), as well as cancer specific risk factors (e.g., pain, fear of reoccurrence, fatigue), will be examined. Findings will guide the development of a future smoking relapse intervention for cancer patients.

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SYM4

**THE NEXT GENERATION OF INVESTIGATORS:
 NOVEL APPROACHES TO AN OLD PROBLEM**

Chair: Robert E. Sorge*¹
 Presenters: Sean P. Barrett², Anne-Noël Samaha³, Paul J. Kenny⁴, Matthew I. Palmatier⁵, and Darlene H. Brunzell⁶
 Discussant: Robert E. Sorge¹
¹McGill University; ²Dalhousie University; ³University of Montreal; ⁴Scripps Institute; ⁵Kansas State University; ⁶Virginia Commonwealth University

Smoking is a highly pervasive addiction in society, but there is still much to learn about the mechanisms through which nicotine contributes to smoking addiction. This symposium will be presented by emerging young investigators whose work is starting to have an impact on thinking about how nicotine contributes to tobacco addiction. The speakers will offer new findings about the rewarding effects of nicotine and will present evidence concerning a role for nicotine and nicotinic receptors in motivation. Sean Barrett (Dalhousie University) will begin by discussing the role of nicotine and non-nicotine factors in the self-administration and subjective effects of cigarettes in human smokers. Dr. Anna-Noël Samaha (University of Montreal) will describe how the speed of nicotine delivery is critical to the development of behavioural sensitisation to nicotine in animals, and also to the neurochemical effects of these infusions. Paul Kenny (Scripps Institute) will then present data regarding the nature of orexin transmission within the insula of the rat brain and the possible ways in which disruption of the orexin system could affect the rewarding effects of nicotine. Matthew Palmatier (Kansas State University) will begin the next component of this symposium by presenting new data suggesting that nicotine increases the motivation to obtain sucrose without altering sucrose palatability in rats. Darlene Brunzell (Virginia Commonwealth University) will then speak on the contributions of the nicotinic receptor subunits to an addiction phenotype. Finally, the discussant, Robert Sorge (McGill University), will briefly summarize research questions addressed and lead a discussion about the questions to be addressed in the future.

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SYM4A

**THE EFFECTS OF NICOTINE PHARMACOLOGY VS.
 NICOTINE EXPECTANCY ON TOBACCO-RELATED
 REINFORCEMENT**

Sean P. Barrett*^{1,2}, Christine Darredeau¹, Kirsten Temporale², and Sherry H. Stewart^{1,2}; ¹Dept. of Psychiatry, Dalhousie University, Halifax, Canada; ²Dept. of Psychology, Dalhousie University, Halifax, Canada

One factor that has confounded previous investigations into the reinforcing effects of nicotine in humans is that a lack of adequate blinding has often made it difficult to distinguish between the actual pharmacological effects of nicotine and placebo effects associated with the belief that one has received nicotine. The current study examined the respective roles of nicotine pharmacology and expectancy on behavioural (i.e., self-administration) and subjective (i.e., incentive motivation and withdrawal relief as measured by the Questionnaire of Smoking Urges-Brief) indices of tobacco-related reinforcement, using a mixed within/between-subjects design. 52 adult smokers (28 male; 24 female) completed two laboratory sessions in which they were required to sample three puffs of a cigarette and then permitted to earn additional puffs using a progressive ratio task. Participants were randomly assigned to receive either nicotine-containing (Quest 1) or denicotinized (Quest 3) cigarettes during both sessions but were led to believe they received nicotine-containing cigarettes during one session and denicotinized cigarettes during the other. Participants self-administered more cigarette puffs when told the cigarettes contained nicotine than when told the cigarettes contained no nicotine (p=0.017), while the actual nicotine content of the cigarettes did not affect self-administration (p=0.508). In addition, the expectation (but not the actual receipt) of denicotinized tobacco led to a decrease in subjective incentive motivation following cigarette sampling (p=0.011), whereas the receipt (but not the expectation) of nicotine tended to be associated with greater subjective withdrawal relief (p=0.055). Findings suggest that both pharmacological and psychological factors influence the reinforcing effects of smoking, but pharmacological effects of nicotine do not appear to be critical for either incentive motivation or self-administration. These results call into question the hypothesis that tobacco-related reinforcement can be solely attributed to the reinforcing effects of nicotine per se.

This research was supported by grants from the Canadian Tobacco Control Research Initiative (CD) and the Dalhousie Department of Psychiatry Research Fund (CD).

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SYM4B

**RAPID DELIVERY OF NICOTINE PROMOTES
 PSYCHOMOTOR SENSITIZATION AND ALTERS
 ITS NEUROBIOLOGICAL IMPACT**

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Nicotine is highly addictive when it is inhaled in tobacco smoke but much less addictive when it is delivered orally or through the skin. This is thought to involve the more rapid delivery of nicotine to the brain when it is smoked. However, it is not known why rapidly delivered nicotine might be more addictive. The development of addiction is thought to involve the ability of drugs to produce sensitization-related changes in the mesocorticolimbic system. One behavioural manifestation of these changes is psychomotor sensitization. We hypothesized, therefore, that the rapid delivery of nicotine might promote psychomotor sensitization. We found that rats treated with rapid intravenous injections of nicotine (delivered over 5 vs. 25-100 s) were more likely to develop psychomotor sensitization. We then examined the cells engaged by nicotine as a function of the speed of injection using c-fos and arc mRNAs as markers of cellular activity. The faster nicotine was injected, the greater its ability to induce c-fos and arc mRNA expression and this effect was specific to mesocorticolimbic regions (e.g., the caudate-putamen, nucleus accumbens shell and medial prefrontal cortex). The rate of nicotine delivery also influenced changes in gene regulation with repeated exposure to the drug. In the caudate-putamen, repeated exposure to rapid nicotine injections decreased the c-fos and arc response to a subsequent nicotine injection. In contrast, repeated exposure to slower nicotine injections either enhanced (in the case of c-fos) or did not affect (in the case of arc) drug-induced gene expression. Thus, rapidly administered nicotine increases susceptibility to sensitization and more readily engages the mesocorticolimbic system. We propose that rapidly administered nicotine might be more addictive because it more readily induces the changes in the brain that lead to addiction. As such, by rapidly delivering nicotine to the brain, the nicotine delivery system itself (i.e., cigarettes) might contribute to making cigarette smoking one of the hardest addictions to break.

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SYM4C

**INSULAR OREXIN (HYPOCRETIN)
 TRANSMISSION REGULATES NICOTINE REWARD**

Paul J. Kenny, Laboratory of Behavioral and Molecular Neuroscience, Department of Molecular Therapeutics, The Scripps Research Institute

Damage to the insular cortex can profoundly disrupt tobacco addiction in human smokers, reflected in spontaneous cessation of the tobacco habit and persistently decreased urge to smoke. Little is known concerning the neurobiological mechanisms through which the insula may control the maintenance of the tobacco habit. Emerging evidence suggests that orexin (hypocretin) transmission may play an important role in drug reinforcement processes, but its role in the rewarding actions of nicotine, considered the key addictive component of tobacco smoke, remains largely unexplored. Here I will present data demonstrating that blockade of orexin transmission at orexin-1 (OX1; hypocretin-1) receptors decreases intravenous nicotine self-administration in rats tested under fixed and progressive ratio schedules of reinforcement. Blockade of OX1 receptors also abolished the stimulatory effects of nicotine on brain reward circuitries, as measured by reversal of nicotine-induced lowering of intracranial self-stimulation (ICSS) thresholds in rats. In addition, I will show data highlighting the innervation by orexin-containing fibers into the insula, and show that OX1 receptors are located on insular cells. Furthermore, I will also show that blockade of OX1 receptors in the insula but not in the adjacent somatosensory cortex decreases nicotine self-administration in rats. These data support the hypothesis that insular orexin transmission plays a permissive role in the motivational properties of nicotine, and therefore may be a key neurobiological substrate necessary for maintaining tobacco addiction in human smokers.

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SYM4D

CHRONIC EXPOSURE TO NICOTINE INCREASES THE MOTIVATION TO OBTAIN SUCROSE REINFORCEMENT BUT DOES NOT ALTER THE PALATABILITY OF SUCROSE IN RATS

Matthew I. Palmatier*, Laura Dare, Melanie J. Hall, and Devi Bluvan, Department of Psychology, Kansas State University

Recent studies have demonstrated that nicotine (NIC) can increase operant behaviors that lead to the delivery of other non-drug reinforcers. This latter effect of NIC has been established with unconditioned or intrinsically reinforcing visual stimuli (i.e., "sensory" reinforcers) and visual/auditory stimuli that have acquired value as the result of pairing with primary rewards (i.e., conditioned reinforcers). However, the hedonic properties of these stimuli cannot be directly measured. The present studies investigated whether NIC could increase the motivation to obtain a reinforcer (sucrose solution) and whether this increased motivation reflected an increase in the hedonic properties of the reward. Naive rats were shaped to respond for 30% (w/v) sucrose under a progressively increasing ratio (PR) schedule of reinforcement. Breaking points (BPs) were operationally defined as the final ratio completed before a 20 min period in which no reward was earned. Once stable BPs were established, rats were randomly assigned to one of two groups NIC (0.4 mg/kg base) or SAL (n=8 per group). Each group was injected with its assigned solution 15 min before all subsequent testing sessions. NIC increased BPs for 30% sucrose, but did not alter responding on a separate, inactive lever. Stable BPs were then established for the following concentrations of sucrose: 60, 30, 20, 10, 5, 2.5, and 0%. For both groups, BPs increased with sucrose concentration. NIC increased BPs for all concentrations, including water (0%). In follow-up tests NIC and SAL rats were given 20-min of free access to 0, 1, 2.5, 5, 10, 30, and 60% sucrose via sipper-tube in the operant conditioning chambers. Sucrose intake followed an inverted U-shape; intake was highest from 2.5-10% and NIC pre-treatment decreased intake at these concentrations. All rats were then instrumented with intra-oral fistulae and tested for reactivity to 0, 5, and 20% sucrose. Pretreatment with NIC did not alter the frequency of ingestive or aversive responses to any solution. These preliminary findings suggest that the reinforcement enhancing effects of NIC are not based on increased valence of the primary reinforcer.

NIH DA 024801.

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SYM4E

NICOTINIC SUBUNIT CONTRIBUTIONS TO ADDICTION PHENOTYPE

Darlene H. Brunzell, Ph.D.*¹, Elizabeth S. Hendrick, M.S.¹, Patrick M. Beardsley, Ph.D.¹ and J. Michael McIntosh, Ph.D.², ¹Virginia Commonwealth University, Richmond, Virginia; ²University of Utah, Salt Lake City, Utah

The beta 2 nicotinic acetylcholine receptors (beta2*nAChRs; * denotes assembly with other subunits) are critical for nicotine self-administration, nicotine conditioned place preference, and acquisition of a new response with a conditioned reinforcer. Little is known regarding which subunits in combination with beta 2 are responsible for nicotine reward and the control that cues associated with reward have over behavior. One method of classifying beta2*nAChRs is based on sensitivity to alpha conotoxin MII (MII) antagonism. alpha6beta2*nAChRs are primarily expressed in catecholaminergic nuclei and have high affinity for MII. The more ubiquitously expressed alpha4beta2*nAChRs are chiefly insensitive to MII antagonism. These studies determined whether infusion of MII into the nucleus accumbens shell (NAc) of Long Evans rats dose-dependently blocks progressive ratio (PR) responding for nicotine plus light/ tone cues. Rats were trained under an FR 1 schedule of reinforcement with 20-s timeout; responding on an active lever resulted in i.v. delivery of 0.03 mg/kg nicotine plus light/ tone cues (NIC). To control for any primary reinforcing effects of the cues, active lever responding in a separate group of rats (CUE) resulted in presentation of the light/ tone alone. Depressions on an inactive lever had no consequence. Following 14 days of training, the schedule was changed to PR so that animals had to give an increasing number of responses for each infusion and/or cue delivery. Prior to each day of PR, animals received micro-infusions of MII interspersed with days in which they received vehicle infusions into the NAc shell (2 min 0.5-1 uL of 0, 1, or 10 pmols/side MII followed by a 2-min wait period). There was no effect of infusion on inactive lever responding or on active lever responding in CUE animals. Preliminary data, however, showed a dose-dependent decrease in number of infusions and break points for NIC animals. These data suggest that alpha6beta2*nAChRs on accumbens dopamine terminals may regulate either primary nicotine reinforcement or the conditioned reinforcing properties of the light/ tone by virtue of their association with nicotine.

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SYM5

SMOKERS WITH SERIOUS MENTAL ILLNESS: A FOCUS ON MECHANISMS AND MODELS

Chair: Jennifer W. Tidey, Ph.D.*¹

Presenters: Jennifer W. Tidey, Ph.D.¹, Jill M. Williams, M.D.², Andrea H. Weinberger, Ph.D.³, and A. Eden Evins, M.D.⁴

Discussant: Saul Shiffman Ph.D.*⁵

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⁵University of Pittsburgh

Rates of smoking in people with serious mental illness (SMI) are two to three times higher than smoking rates in the general population. Smoking treatments are less effective for smokers with SMI than for non-psychiatric smokers, even among those who are motivated to quit and who enroll in combined pharmacological and psychosocial treatment programs. The overarching viewpoint of this symposium is that a better understanding of the unique biological and environmental mechanisms that contribute to smoking in people with SMI is critical and necessary for the development of effective treatments for smokers with SMI. Hypotheses concerning the high smoking rates in smokers with SMI focus on the idea that smoking improves psychiatric symptoms and cognitive dysfunction or that nicotine may be more reinforcing for these smokers due to the neuropathology associated with their illnesses. This symposium will highlight findings from novel studies that investigate these hypotheses by comparing, under controlled behavioral laboratory conditions, the effects of biological and environmental variables in people with and without SMI. The symposium chair will provide a brief overview of the elevated smoking rates and treatment results in people with SMI. Dr. Williams will present results of a comparison of smoking topography and nicotine intake in smokers with bipolar disorder, smokers with schizophrenia and smokers with no psychiatric illness. Dr. Weinberger will discuss subjective responses to smoking cues in smokers with and without a history of major depressive disorder. Dr. Tidey will compare the effects of high-dose nicotine replacement and sensorimotor smoking replacement in smokers with schizophrenia and those without psychiatric illness. Dr. Evins will compare nicotine's effects on reward responsiveness and cognitive performance in non-smokers with and without schizophrenia. Finally, Dr. Shiffman will discuss the implications of these findings for the development of novel, effective smoking treatments for smokers with serious mental illness.

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SYM5A

NICOTINE INTAKE IN SMOKERS WITH SCHIZOPHRENIA AND BIPOLAR DISORDER

Jill M. Williams, M.D.*^{1,2}, Kunal K. Gandhi, M.B.B.S., M.P.H.^{1,2}, Magdalena Galazyn, M.A.¹, Supriya Kumar, B.A.^{1,2}, and Shou-En Lu, Ph.D.²; ¹UMDNJ-Robert Wood Johnson Medical School; ²UMDNJ-School of Public Health

The exact parameters of increased nicotine intake in schizophrenia have not been well studied. Since studies also show high smoking rates in bipolar disorder (suggesting similarities to schizophrenia) we now include them in our studies. One hundred twenty six subjects (31 schizophrenia; SCZ; 44 bipolar, BPD and 51 controls; CON) were assessed in a single day, ad libitum smoking topography session using the CRESSmicro device to measure smoking behavior. The following smoking topography variables were measured: time to first puff, number of cigarettes smoked, puffs per cigarette, puff volume, puff duration, IPI (inter-puff interval), peak flow, and average flow. Mean values of repeatedly measured topography variables were estimated and compared using a three-level nested linear model analysis to model the differences in SCZ, BPD and CON subjects and in the double nested structure of data (puffs within cigarettes and cigarettes within subjects). Smokers were not different in baseline characteristics including gender, cigarettes per day, expired carbon monoxide, or total FTND score. Smokers with SCZ smoked significantly more puffs per cigarette compared to CON (16.1 vs. 11.9, p<0.001). Smokers with SCZ also took significantly more puffs per cigarette compared to BPD (16.1 vs. 13.3, p<0.05). IPI was also significantly shorter among smokers with SCZ compared to CON (13.1 vs. 24.2, p<0.001) and BPD (13.1 vs. BPD 22.8, p=0.001) but there was no significant difference between IPI in BPD and CON. All subjects had blood draws for nicotine and cotinine. Serum nicotine levels were higher in SCZ compared to both CON (37.9 vs. 30.5, p=0.014) and BPD (37.9 vs.29.9, p=0.009) but there was no significant difference between in BPD and CON. Serum cotinine values were also higher in SCZ compared to CON (459.6 vs. 285.6, p<0.001) and BPD (459.6 vs. 292.6, p<0.001) despite smoking a similar number of cigarettes per day. Intermediary values in BPD may be due to effects of medications or symptom levels that warrant further study. Understanding cigarette puffing parameters that determine nicotine intake will be crucial to developing effective pharmacotherapy for this group.

This work was supported by a grant from the National Institute of Mental Health (R01-MH076672-01A1) to JMW.

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SYM5B

CUE REACTIVITY IN SMOKERS WITH AND WITHOUT DEPRESSION

Andrea H. Weinberger, Ph.D.*¹, and Tony P. George, M.D., F.R.C.P.C.²; ¹Yale University School of Medicine; ²University of Toronto

The prevalence of smoking for adults with major depression is much higher than the general population. In addition, smokers with a history of depression appear to have more difficulty with smoking cessation and require more attempts to quit. Little is known about the specific ways that smokers with depression differ from other smokers. Gaining a better understanding of differences between these groups of smokers will aid the creation of novel interventions and tailoring of current treatments to be more efficacious with this difficult-to-treat population. Reactivity to smoking cues may be one useful way to examine differences between smokers with and without depression. Previous studies have examined cue reactivity in smokers with schizophrenia, but not smokers with depression. The purpose of this pilot study was to examine differences in cravings and affect elicited by smoking-related cues in smokers with and without a history of major depressive disorder (MDD). Participants were nicotine dependent smokers with either no history of MDD (MDD-; n=23) or a history of MDD and no current treatment (MDD+Tx; n=12). Participants completed two cue reactivity sessions: the first session after smoking one of their cigarettes, and the second session after an hour of smoking deprivation. Smoking groups were similar on baseline smoking and nicotine dependence while MDD+Tx- reported higher symptoms of depression and cognitive impulsivity. Cue-induced cravings for cigarettes increased for all smokers suggesting that smokers with depression responded similarly to smokers without depression to smoking cues. Negative and positive affect during the cue reactivity sessions differed based on history of depression and smokers with a history of depression showed a greater increase in urges to smoke related to negative reinforcement during the laboratory session. The cue reactivity paradigm may be a useful method to examine responsiveness of smokers with depression to smoking cessation treatments in comparison to non-depressed smokers.

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SYM5C

SENSORIMOTOR AND NICOTINE REPLACEMENT IN SMOKERS WITH AND WITHOUT SCHIZOPHRENIA

Jennifer W. Tidey, Ph.D.*¹, Damaris J. Rohsenow, Ph.D.^{1,2}, Gary B. Kaplan, M.D.³, and Robert M. Swift, M.D.^{1,2}; ¹Center for Alcohol and Addiction Studies, Brown University; ²Providence VA Medical Center; ³VA Boston Healthcare System/Boston University School of Medicine

Smoking rates are very high, and cessation rates are extremely low in smokers with schizophrenia (SWS). Nicotine replacement appears to be less effective at reducing smoking urges and smoking behavior in SWS compared to equally heavy smokers without schizophrenia, suggesting that alternative or complementary strategies may be needed to reduce their smoking. In this laboratory study we are investigating whether sensorimotor replacement for smoking will boost the effects of nicotine replacement for reducing smoking urges, withdrawal symptoms and smoking behavior in SWS. Smokers with schizophrenia (current n = 24; 68% male; M = 30.7 cigarettes per day) and equally heavy smokers without psychiatric illness (CON; n = 14, 70% male, M = 25.4 cigarettes per day) undergo laboratory sessions in which they receive transdermal nicotine replacement (42 mg or placebo) alone or in combination with sensorimotor replacement for smoking (denicotinized cigarettes or no cigarettes). Outcome measures include smoking urge, nicotine withdrawal and smoking behavior. Preliminary results from this ongoing study indicate that SWS smoked more total puffs and had larger session puff volumes than CON (p's < .05). Sensorimotor replacement, but not nicotine replacement decreased smoking urges, nicotine withdrawal symptoms and smoking behavior (total puffs, total session smoke volume, CO boost) in both groups (all p's < .05). Overall, preliminary findings from this study indicate that sensorimotor replacement for smoking is as or more effective at reducing smoking behavior than high-dose nicotine replacement, at least in acute studies. Smoking treatments that include sensorimotor replacement may improve quit rates in this population.

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SYM5D

EFFECTS OF NICOTINE ON REWARD RESPONSIVENESS AND COGNITIVE PERFORMANCE IN NON-SMOKERS WITH AND WITHOUT SCHIZOPHRENIA

Ruth S. Barr, M.D.¹, Melissa Culhane, M.P.H.², Lindsay Jubelt², and A. Eden Evins, M.D.*^{2,3}; ¹Queens University, Belfast, Northern Ireland, UK; ²Massachusetts General Hospital, Boston, MA; ³Harvard Medical School

Background: Tobacco smoking, driven by the addictive properties of nicotine, is the most prevalent preventable cause of death in the Western World. Accumulated evidence suggests that nicotine may increase appetitive responding for non-drug incentives in the environment and may improve cognitive performance, particularly in those with psychiatric disorders such as schizophrenia for which the prevalence of tobacco use is especially high.

Methods: To test this hypothesis, we conducted a randomized, double-blind, placebo-controlled, crossover study of the effect of a single dose of transdermal nicotine on reward responsiveness and cognitive performance in 60 healthy non-smokers with and without schizophrenia. A novel signal detection task in which correct responses were differentially rewarded in a 3:1 ratio was used to assess the extent to which participants modulated their behavior as a function of reward. Attention was assessed with the Continuous Performance Test Identical Pairs Version (CPT-IP) and memory assessed with an episodic memory task.

Results: Despite expected adverse effects such as nausea, nicotine significantly increased response bias toward the more frequently rewarded condition, at the expense of accuracy, independent of effects on attention or overall vigilance in controls and in those with schizophrenia not treated with clozapine, and improved attention and memory in both groups, with a greater effect in those with schizophrenia.

Conclusions: In summary, a single dose of transdermal nicotine enhanced response to non-drug-related rewards in the environment, and improved attention and memory performance in both groups and was associated with greater improvements in inhibition of impulsive responses and novelty detection in non-smokers with schizophrenia compared with controls. These effects may contribute to reinforcement of early smoking behavior and development of nicotine dependence in patients and controls. Nicotinic agonists may prove to be particularly effective nicotine dependence treatments for those with schizophrenia if they are shown to have a lasting effect to ameliorate some attention and memory deficits associated with the disorder.

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SYM6

WHAT ROLE DOES MAO INHIBITION PLAY IN SMOKING AND SMOKING CESSATION?

Chair: Paul B.S. Clarke, Ph.D.⁵
 Presenters: Paul Cumming, Ph.D.⁶, Karine Guillem, Ph.D.², Frances Leslie, Ph.D.*³, and Tony George, M.D.⁴
 Discussant: Paul B.S. Clarke, Ph.D.⁵

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Nicotine is widely considered to be a weak reinforcer possessing strong abuse liability. One possible explanation is that in smokers, nicotine's reinforcing effects are potentiated by inhibition of brain monoamine oxidase (MAO). Thus, MAO activity is inhibited in tobacco smokers, and MAO-inhibiting drugs can dramatically increase nicotine intake in laboratory animals. Paradoxically, MAO is also attracting interest as a target for smoking cessation pharmacotherapy. This session will attempt to integrate recent findings from animal and human studies. Paul Cumming will describe several MAO-inhibiting chemicals in tobacco smoke, including harman and norharman. He will suggest that some of these chemicals attain pharmacologically significant levels in smokers, with potential effects on the mesolimbic dopamine system. Karine Guillem will describe how chronic treatment with MAO-inhibitors both increased the motivation to self-administer nicotine and prolonged the aversive state associated with nicotine withdrawal in rats. Frances Leslie will also report MAO inhibitor-induced potentiation of nicotine self-administration in rats, and will propose neural mechanisms underlying this potentiation. Tony George will describe the effects of MAO inhibitors in smoking cessation. In particular, he will present the results of a recently completed Phase II double-blind, randomized placebo-controlled clinical trial of the MAO-B inhibitor selegiline hydrochloride for treatment of tobacco dependence in nicotine dependent community-dwelling cigarette smokers. Finally, Paul Clarke (discussant) will lead a critical discussion of the following issues. Can existing animal models adequately capture the effects of MAO-A and MAO-B inhibition in smokers? Would the mild MAO inhibition seen in smokers be sufficient to potentiate nicotine reinforcement? Can MAO inhibitors in smoke exert antidepressant effects? Lastly, how may MAO inhibition both motivate tobacco smoking and facilitate quitting?

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SYM6A

MAO INHIBITION DOES NOT POTENTIATE AMPHETAMINE-INDUCED DOPAMINE RELEASE IN THE [11C]raclopride-PET COMPETITION MODEL

Paul Cumming, Ph.D., Department of Nuclear Medicine, Ludwig-Maximilian's Universität of Munich, Munich, Germany

Beta-carbolines in tobacco smoke are the likely cause of inhibition of MAO in brain of smokers, as has been revealed by PET studies with MAO-radioligands. It is a matter of some interest to determine whether this MAO inhibition contributes to the psychopharmacology of tobacco abuse, or is an epiphenomenon without functional consequences. Acute administration of beta-carbolines increases interstitial dopamine concentrations in rat nucleus accumbens (Iurlo et al., 2001), whereas MAO-blockade can potentiate the amphetamine-evoked release of dopamine (Butcher et al., 1988). It might be supposed that MAO inhibition due to smoking, by potentiation the action of psychostimulants, constitutes a generalization of the Ayahuasca effect, in which the action of a weak hallucinogen is potentiated by co-administration of a harmine, a beta-carboline MAO inhibitor. In order to test this claim, we carried out microPET studies with [11C]raclopride and amphetamine challenge (Pedersen et al., 2006); pre-treatment with pargyline (5 or 20 mg/kg) tended to increase the availability of dopamine D2 sites in rat striatum, suggesting a paradoxical reduction in dopamine tonus. Challenge with amphetamine sulphate (1 mg/kg) evoked the expected 20% decline in [11C]raclopride binding throughout the rat striatum, indicating a near doubling of the competition from endogenous dopamine. However, the pargyline pre-treatment did not potentiate this effect. In other PET studies, pargyline (6 mg/kg) totally occluded the specific binding of the beta-carboline [11C]harmine throughout the brain of anesthetized pigs (Jensen et al., 2006). Acute challenge with amphetamine sulphate (1 mg/kg) evoked a 20% decline in striatal [11C]raclopride binding, just as in the rat. Likewise, the pargyline pre-treatment had no systematic effect on the magnitude of the amphetamine-induced [11C]raclopride binding changes in pig striatum. Together, these results seem to exclude important effects of acute MAO inhibition of amphetamine-induced dopamine release, as measured by the PET competition model. It remains to be determined if MAO inhibition can modulate the apparent dopamine release evoked by natural reinforcers, nicotine, or the conditioned release of dopamine.

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SYM6B

CHRONIC MAO-INHIBITORS TREATMENT INCREASED THE MOTIVATION TO SELF-ADMINISTER NICOTINE AND PROLONGED THE AVERSIVE STATE ASSOCIATED WITH NICOTINE WITHDRAWAL IN RATS

Karine Guillem, Ph.D., Dept. of Psychiatry, Univ. of Pennsylvania, Philadelphia, PA

The weak reinforcing effects of nicotine do not readily account for the intense addictive properties of tobacco. It is known that current smokers have decreased monoamine oxidase activities (MAO-A and MAO-B), and that cigarette smoke contains MAO inhibitors (MAOI-A and B). Thus, we propose that decreased MAO activity could be involved in the addictive properties of smoking. We study here the possibility of a synergic interaction between nicotine and two MAOI, on both the reinforcing and motivational properties of nicotine self-administration, and the aversive state associated with nicotine withdrawal in rats. The reinforcing and motivational properties of nicotine were examined using nicotine self-administration (0.03 mg base/kg/infusion) in rats following chronic administration of either saline, tranylcypromine (MAOI-A/B) or phenelzine (MAOI-A/B). We show that animals pretreated with MAOIs self-administered more nicotine and worked more to obtain the drug, indicating that chronic MAOI-A/B treatment enhances the reinforcing, as well as the motivational properties of nicotine in rats. Although the primary reinforcing properties of nicotine trigger the initiation of drug consumption, the negative consequences of drug abstinence might motivate the continued administration of drug. Therefore, we study the effects of chronic MAOI pretreatment (saline, tranylcypromine and phenelzine) on the aversive motivational component of nicotine withdrawal in rats rendered dependent on nicotine by subcutaneous implantation of osmotic minipumps (vehicle or nicotine base 3.2 mg/kg/day). We show that MAOI treatment induced a long-lasting (up to 8 months) conditioned place aversion selectively in nicotine-abstinent rats. Such a long-lasting motivational effect might serve as a powerful negative stimulus motivating the continued administration of nicotine or relapse after abstinence. Together, these results suggest that the inhibition of MAO activity by compounds present in tobacco smoke may combine with nicotine and contribute, at least in part, to both the intense addictive properties of tobacco and the persistence of tobacco habits that characterize smoking addiction.

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SYM6C

POSITIVE EFFECTS OF MONOAMINE OXIDASE INHIBITORS ON THE ACQUISITION OF NICOTINE SELF-ADMINISTRATION IN RATS

Frances M. Leslie*, James D. Belluzzi, Shahrdad Lotfipour, Monica Arnold, and Anne-Sophie Villégier, Department of Pharmacology, University of California, Irvine

Although it is well established that tobacco contains monoamine oxidase inhibitors (MAOIs), there has been little research into the effects of MAO inhibition on the rewarding effect of nicotine. We have therefore examined the effect of pre-treatment with tranylcypromine (TCP), a non-selective, irreversible inhibitor of MAO-A and -B, on acquisition of nicotine self-administration in adult and adolescent rats, aged postnatal day (P)90 and 28, respectively. Pretreatment with racemic TCP (3 mg/kg), one hour prior to behavioral testing, significantly increased nicotine self-administration at both ages and substantially decreased the optimally effective dose of drug. In female rats, it also increased responding for visual cues in the absence of nicotine. Mechanistic studies, using different pretreatment intervals and stereoisomers of TCP, showed that MAO inhibition alone is not responsible for enhancement of nicotine reinforcement. Acute effects of TCP, such as monoamine release, interact with MAO inhibition to enhance both nicotine self-administration and nicotine-induced DA overflow in the nucleus accumbens. Whereas the plus isomer of TCP increased self-administration via activation of nicotinic receptors, the negative TCP isomer increased the salience of associated cues via a serotonergic mechanism. Even though TCP produced long-lasting inhibition of MAO, substitution of acute MAOI pretreatment with saline significantly reduced nicotine self-administration. Reinforced responding was sustained, however, in animals in which TCP pretreatment was replaced with norharmane, a natural tobacco constituent which also inhibits MAO activity and induces acute monoamine release. Furthermore, addition of norharmane (0.25 microg/kg/inj) to the intravenous administration solution supported acquisition and maintenance of self-administration of a low dose of nicotine (7.5 microg/kg/inj) in naive, adult males. These findings provide substantial evidence that the addictive properties of tobacco may result from the combined actions of nicotine and other smoke constituents.

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SYM6D

MONOAMINE OXIDASE INHIBITION AS A STRATEGY FOR TOBACCO PHARMACOTHERAPY

Tony P. George, M.D., F.R.C.P.C., University of Toronto and Yale University, Toronto, ON, Canada

Tobacco dependence is a treatable disorder for which we have three classes of approved medications (NRTs, bupropion and varenicline). However, not all tobacco smokers respond to these approved pharmacotherapies. Thus, the development of novel and more effective tobacco medications is of considerable public health importance. Cigarette smoke is known to contain non-nicotine components (eg the alkaloids harman and norharman), which inhibit monoamine oxidase (MAO) isoforms (A and B). Several lines of evidence from pre-clinical, translational human and clinical trials in smokers suggest the potential utility of using MAO inhibitors as tobacco pharmacotherapies (see George and Weinberger, Clinical Pharmacologies and Therapeutics, 2008). Dr. George will describe translation human studies, which have explored potential mechanisms of the efficacy of this pharmacological strategy, and proof of concept clinical trials. In particular, he will present the results of a full Phase II double-blind, randomized, placebo-controlled parallel groups controlled trial in N=102 community dwelling treatment-seeking cigarette smokers which clearly suggests the safety and efficacy of the MAO-B inhibitor selegiline (Deprenyl; 10 mg/d orally) for smoking cessation. Data presented suggest that MAO inhibition is a novel, safe and efficacious approach for pharmacotherapy development, which is garnering increasing interest and support from the academic and pharmaceutical research communities.

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SYM7

CRAVING TO SMOKE: NEW LABORATORY AND FIELD STUDIES

Chair: Reuven Dar, Ph.D.^{*4}

Presenters: Alvaro Pascual-Leone, M.D., Ph.D.¹, Neal Doran, Ph.D.², Saul Shiffman, Ph.D.³, and Reuven Dar, Ph.D.^{*4}

Discussant: Raymond Niaura, Ph.D.⁵

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⁵Warren Alpert Medical School of Brown University

Craving is one of the hallmarks of regular smoking and is considered a primary factor in maintaining smoking and in leading to relapse in smokers attempting to quit. The symposium puts together four studies that examine various aspects of craving using diverse methodologies. The presentations includes two field studies, in which smokers provided ratings of craving in natural settings, and two laboratory studies, one examining the effects of cue exposure on craving and its interaction with impulsivity and the other employing non-invasive brain stimulation to reduce craving. Together, these studies address central questions in regard to craving, including the relationship of craving to smoking and to smoking withdrawal, the interaction of craving with personality factors, and the brain structures which may mediate craving.

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SYM7B

CRAVING TO SMOKE IN FLIGHT ATTENDANTS: RELATIONSHIPS WITH FLIGHT DURATION, TIME SINCE LAST CIGARETTE AND OPPORTUNITY TO SMOKE

Reuven Dar, Ph.D.^{*}, Nurit Rosen, M.A., Department of Psychology, Tel Aviv University, Israel

This study aimed to replicate and extend the findings of a previous study by our group, which suggested that craving to smoke was strongly determined by habits and expectations and had little relationship to smoking withdrawal. Participants were 53 flight attendants who were light to heavy smokers and were not permitted to smoke during the flight due to airline regulations. Each participant rated his or her craving to smoke on a 1-7 scale at pre-determined time points during a 2-way flight (each leg 3-5.5 hours long) and a one-way flight (8-13 hours long). The results indicate that craving to smoke was related to the time remaining to the end of the flight rather than to the time that has elapsed since the last cigarette. In both short and long flights, craving began to increase toward the end of the flight. Craving at the last measurement point was equal in short and long flights (approximately 4.5 on 1-7 scale). Craving levels at the final assessment point in the two short flights was much higher than craving levels at the parallel time point in the long flight (4.55 vs. 2.36, respectively, $t(52) = 8.76, p < .001$). In the two-legged flights, craving levels at the beginning of the second leg were lower than those at the end of the first leg, regardless of whether participants were able to smoke during the break between legs. These results corroborate the view that craving to smoke is primarily determined by cues and expectations and has relatively little relationship to smoking deprivation.

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SYM7A

NON-DAILY SMOKERS' CRAVING AND WITHDRAWAL WHEN THEY ARE NOT SMOKING

Saul Shiffman, Ph.D.^{*}, Stuart Ferguson, Ph.D., Deborah Scharf, M.S., Hilary Tindle, M.D., M.P.H., and Sarah Scholl, B.A., University of Pittsburgh, Pittsburgh, PA, USA

Non-daily, intermittent smokers (ITS) constitute a substantial and growing proportion of smokers. The behavior of ITS is puzzling, in part, because it defies the more typical pattern of daily smokers, who are known to experience significant craving and withdrawal if they go as long as a day without smoking. In this study, we assessed craving and withdrawal intensity among ITS in three contexts: 1) at moments they were about to smoke; 2) on the days that they smoked, at randomly-selected times when they were not smoking; and 3) at random times on days when they did not smoke at all. Subjects were 47 ITS who reported smoking at least weekly, but not daily (56% female, average age 33.89 [SD 11.15]). Ecological momentary assessment methods were used to assess smoking and craving: subjects used a palmtop computer diary to record cigarettes for 3 weeks, and were also "beeped" at random by the computer about 5 times a day to assess craving, restlessness, and irritability (0-100 on a 33-mm VAS scale) at times when they were not smoking. This analysis is based on assessment of 1,616 smoking occasions and 1,991 random non-smoking assessments. Subjects smoked on 62% ($\pm 24\%$) of assessed days, on average. On smoking occasions, ITS reported average craving of 63.9 (± 20.4). On days when they smoked, but at times that they were not smoking, their craving intensity was much lower, averaging 27.7 (± 17.4); $p < 0.0001$. On days when they did not smoke at all, their craving was lower still ($p < 0.0001$), averaging 19.7 (± 20.0); median craving was 13.6 on the 0-100 scale. On non-smoking days, almost half (46.5%) of ITS reported average craving < 10 , which was considered essentially "no craving" (physically within 3.3 mm of 0). Moreover, restlessness and irritability were not elevated on non-smoking days or at non-smoking times. These data suggest that ITS do experience substantial momentary craving at times that they smoke, but very low (and often no) craving between cigarettes and on days when they voluntarily forego smoking, and no elevation in withdrawal symptoms when they go without smoking.

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SYM7C

IMPULSIVITY AND CRAVING FOLLOWING SMOKING CUE EXPOSURE

Neal Doran, Ph.D.^{*1}, Jessica Cook, Ph.D.², Dennis McChargue, Ph.D.³, and Bonnie Spring, Ph.D.⁴; ¹University of California, San Diego; ²University of Washington; ³University of Nebraska; ⁴Northwestern University

Current smokers may be more likely than non-smokers to possess characteristics such as impulsivity that increase their susceptibility to tobacco use and impair their ability to quit. Recent research suggests that impulsivity is a construct with multiple components that may influence tobacco use in different ways. Impulsive individuals may be particularly drawn to cigarette smoking because they are disproportionately attracted to rewarding stimuli and related environmental cues. Previous research indicates that impulsive smokers report higher levels of cigarette craving following exposure to smoking cues. The purpose of the present study was to examine whether specific components of impulsivity (sensation seeking, lack of premeditation, lack of perseverance, urgency) would predict specific aspects of cigarette craving (appetitive craving, negative affect craving) after exposure to tobacco cues in a laboratory setting. In a counterbalanced, repeated measures design, adult smokers ($n = 60$, 50% female) underwent a 5-minute exposure to a smoking cue in one session and a neutral cue in a second session. Craving was assessed immediately before and immediately after cue exposure. Smokers with high sensation seeking scores exhibited greater increases in appetitive craving [$t(118) = 2.28, p = .02$] but not negative affect craving. Those with higher scores on the urgency [$t(118) = 3.77, p < .01$] and lack of perseverance [$t(118) = 2.52, p = .01$] components of impulsivity reported greater increases in negative affect craving but not appetitive craving. Lack of premeditation was not significantly associated with either aspect of craving. These data suggest a complex relationship between impulsivity and reactivity to environmental smoking cues that varies across the multiple components of impulsivity and across different environmental contexts.

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SYM7D

REDUCING CRAVING WITH NON-INVASIVE BRAIN STIMULATION

Shirley Fecteau, Ph.D.*, Felipe Fregni, Ph.D., and Alvaro Pascual-Leone, M.D., Ph.D.

Neural correlates of drug- and food-craving include hyperactivity in reflexive areas, such as the orbitofrontal cortex, and lack of regulatory influence from lateral prefrontal (reflective) circuits. The modulation of these dysfunctional neural circuits through invasive and non-invasive brain stimulation may provide a valuable therapeutic approach. We have been investigating the potential of repetitive Transcranial Magnetic Stimulation (rTMS) or transcranial direct current stimulation (tDCS) to noninvasively modulate activity in the dorsolateral prefrontal cortex (DLPFC) and influence craving. We hypothesized that high frequency rTMS or anodal tDCS, both of which are thought to enhance activity in the targeted brain region, would increase activity in the DLPFC and thus promote reflective control onto reflexive systems, resulting in a decrease in craving. Various decision-making tasks were used to assess the cognitive impact of the intervention. DLPFC stimulation with high frequency rTMS or anodal tDCS significantly reduced craving for cocaine, nicotine, alcohol and food. The effects were greater for right- than left-sided stimulation and specific for stimulation parameters that increase activity in the targeted DLPFC. In conclusion, enhancing activity in the right DLPFC using high-frequency rTMS or anodal tDCS can reduce craving in cocaine dependent individuals, reduce nicotine craving, decrease alcohol abuse, and help control food craving. The effects may be mediated by dorsolateral prefrontal structure, but could also involve modulation of anterior insula. These results highlight the potential of noninvasive neuromodulation as a therapeutic tool for craving and substance abuse. Furthermore the findings suggest that the right DLPFC plays a crucial role in implementing reflective control (informed by cultural, moral, and societal motives) of reflexive impulsive behaviors driven by primitive, self-centered motives.

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SYM8

TARGETS FOR TREATING NICOTINE ADDICTION: NOT THE USUAL SUSPECTS

Chair: Allison C. Hoffman*, Ph.D.⁵

Presenters: Scott F. Saccone, Ph.D.¹, Olivier George, Ph.D.², Jim R. Fadel, Ph.D.³, and Athina Markou⁴

¹Washington University in Saint Louis; ²The Scripps Research Institute;

³University of South Carolina School of Medicine; ⁴University of California at San Diego; ⁵National Institute on Drug Abuse

Most of the first-line medications currently approved for treating tobacco dependence are nicotine replacement therapies. However, the neurobiological mechanisms underlying nicotine addiction are complex and have implicated a number of other receptor systems. The use of genetic tools, such as genome-wide association scans and genetic mutants, in addition to basic animal behavior research, have indicated some novel targets for treating nicotine addiction might not have otherwise been suggested. This symposium seeks to highlight some of these unanticipated targets, including the $\alpha 5$ nicotinic, CRF, orexin, and glutamate receptor systems. These presentations will take a translational approach by discussing emerging research from both animal and human studies, and how findings might affect research directions and potential for nicotine dependence treatments. Since the target audience includes both animal and human nicotine/tobacco researchers, it is hoped that these presentations will stimulate additional research into unconventional targets.

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SYM8A

THE NIDA NEUROSNP PROJECT: SUPPLEMENTING HIGH-DENSITY SNP MICROARRAYS FOR ADDITIONAL COVERAGE OF ADDICTION-RELATED GENES

Scott F. Saccone, Ph.D.*¹, Laura J. Bierut, M.D.¹, Elissa J. Chesler, Ph.D.², Peter W. Kalivas, Ph.D.³, Caryn Lerman, Ph.D.⁴, Andrew W. Bergen, Ph.D.⁵, Nancy L. Saccone, Ph.D.¹, George R. Uhl, M.D., Ph.D.⁶, Howard J. Edenberg, Ph.D.⁷, and Joni L. Rutter, Ph.D.⁸; ¹Washington University; ²Oak Ridge National Laboratory; ³Medical University of South Carolina; ⁴University of Pennsylvania; ⁵SRI International; ⁶NIDA IRP; ⁷Indiana University; ⁸National Institute on Drug Abuse

Progress in the search for human disease genes has been recently accelerated by advances in DNA technology. In the NIDA NeuroSNP project (<http://zork.wustl.edu/nida/neurosnp.html>), we assessed the coverage of several commercial SNP microarrays for genes that are biologically relevant to addiction. We have assembled a set of addiction-related genes using both expert nomination and data from mouse systems genetics. The known variation in these genes was then compared to the variation that can be detected by various commercial SNP microarrays. We found that a significant amount of variation would not be accounted for by all commercial SNP microarrays considered, including high-end models such as the Affymetrix 6.0 and Illumina Human1M arrays. We propose a solution to this problem by creating a publicly available SNP database that can be used to systematically fill these gaps. The database utilizes a biological prioritization scheme, known as a genomic information network (GIN), which permits researchers to select the most biologically relevant SNPs subject to a given budget. The GIN method incorporates SNP/gene functional properties (such as synonymy and promoters), mouse QTL mapping data and co-expression analysis, and human/mouse evolutionary conservation. This ensures high priority genomic regions are comprehensively covered in genetic studies of addiction. The GIN method can also be used to prioritize the results of a genome-wide association study (GWAS) for further study, such as replication genotyping, by highlighting SNPs with strong biological relevance. We discuss the application of this method to the NicSNP GWAS and candidate gene study of nicotine dependence. In particular, we show how, using the NicSNP data, the method highlights a SNP in CHRNA5 nicotinic receptor gene for which there is independent evidence of replication in the literature for association with nicotine dependence.

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SYM8B

THE OREXIN/HYPOCRETIN SYSTEM: A POTENTIAL NOVEL TARGET IN NICOTINE ADDICTION

Jim R. Fadel, Ph.D.*, University of South Carolina School of Medicine

The hypothalamus is a prominent central site of nicotine action but the phenotype of nicotine-sensitive neurons in this region has not been fully described. Hypothalamic orexin/hypocretin neurons are important regulators of state-dependent behavior and project to diverse brain regions such as the prefrontal cortex, insular cortex and ventral tegmental area. Recent studies point to an important role for orexin neuropeptides in the reinforcing and addictive properties of psychostimulant drugs. Here, we combined anatomical and pharmacological approaches to studying the effect of acute nicotine treatment on orexin neurons in rats. Systemic nicotine dose-dependently activated orexin neurons via an apparent $\alpha 4\beta 2$ -dependent mechanism. In vivo microdialysis experiments showed that nicotine also elevates glutamate and acetylcholine levels in the lateral hypothalamus. Furthermore, nicotine-elicited Fos expression in orexin neurons was reduced by lesions of either the prefrontal cortex or the cholinergic basal forebrain, suggesting that glutamatergic inputs from the PFC and cholinergic inputs from the basal forebrain act cooperatively to mediate the effect of acute nicotine on these cells. Tract-tracing studies indicated that a substantial portion of nicotine-sensitive orexin neurons project to forebrain regions that modulate attention and arousal, including the basal forebrain and thalamic paraventricular nucleus. We are currently studying the effect of nicotine on orexin inputs to the insular cortex, which is crucial for interoception is implicated in nicotine addiction. Collectively, these data highlight the orexin system as a prominent target of nicotine treatment and a key node participating in nicotine effects on attention and arousal. While still subject to empirical demonstration, it is tempting to speculate that orexin regulation of neural pathways mediating interoception (the organism's awareness of its physiological status) may facilitate the intense craving that underlies relapse following withdrawal from chronic nicotine. Thus, the orexin system may represent a novel therapeutic target for the treatment of nicotine addiction.

National Alliance for Research on Schizophrenia and Depression; American Federation for Aging Research.

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SYM8C ROLE OF GLUTAMATE IN NICOTINE DEPENDENCE

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Several motivational forces maintain nicotine dependence, including the primary rewarding properties of nicotine, the reward enhancing effects of nicotine (i.e., enhancement of the reward value of other stimuli by nicotine), the alleviation of nicotine withdrawal symptoms through further nicotine administration, and self-medication of cognitive or reward deficits in psychiatric populations with nicotine administration. Preclinical research in animal models of these various aspects of nicotine dependence suggests a critical role of glutamate transmission, and potentially its interactions with the γ -aminobutyric acid (GABA), cholinergic and dopaminergic transmitter interactions in the ventral tegmental area, and possibly other brain sites, in the behavioral effects of nicotine. Specifically, decreasing glutamate transmission through actions at either excitatory postsynaptic ionotropic or metabotropic glutamate receptors, or inhibitory presynaptic metabotropic glutamate receptors decreased the rewarding effects of nicotine, and/or cue-induced reinstatement of nicotine-seeking. Similar decreases in nicotine self-administration were seen when a N-methyl-D-aspartate (NMDA) receptor antagonist or a metabotropic glutamate 2/3 receptor agonist was injected into the ventral tegmental area. Further, early nicotine withdrawal is characterized by decreased function of presynaptic inhibitory metabotropic glutamate 2/3 receptors, increased expression of excitatory postsynaptic NMDA receptor subunits in limbic and/or frontal brain sites, and decreased expression of the cystine-glutamate exchanger in the ventral tegmental area and the nucleus accumbens. These neuroadaptations possibly develop to counteract decreased glutamate transmission that is hypothesized to characterize early nicotine withdrawal; while protracted abstinence may be associated with increased glutamate response to stimuli previously associated with nicotine administration. In conclusion, glutamate transmission in limbic and frontal brain sites is critically involved in nicotine dependence and could be targeted to treat the various aspects of nicotine dependence, and thus assist people to quit smoking.

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SYM8D A NEUROBIOLOGICAL MECHANISM FOR THE "HOOK" IN NICOTINE DEPENDENCE

Olivier George, Ph.D.^{*}, The Scripps Research Institute

The main psychoactive ingredient responsible for tobacco addiction has long been hypothesized to be nicotine. Nicotine acutely produces modest positive reinforcing effects by activating the reward systems, including the mesolimbic dopamine system. However this mechanism is not sufficient to explain the transition from nicotine use to nicotine dependence. Nicotine dependence has been hypothesized to result from neuroadaptive changes in the brain that produces a powerful need to continue tobacco use (being "hooked"). Such neuroadaptation may involve the mechanisms responsible for the negative emotional states observed during abstinence and represent a powerful source of negative reinforcement leading to excessive drug intake. Recruitment of an anti-reward system, such as stress-regulatory extrahypothalamic corticotropin releasing factor (CRF) via activation of CRF1 receptors, may contribute significantly to the motivation for compulsive use of tobacco, defined as use driven by negative reinforcement. This talk highlights recent animal studies in our laboratory showing that activation of the extrahypothalamic CRF-CRF1 system during abstinence mediates both the anxiety-like symptoms of withdrawal and excessive nicotine intake observed after abstinence. Thus, dependent rats may increase their nicotine intake after abstinence to obtain relief from the resulting CRF-CRF1 receptor-mediated negative emotional state. This CRF1 receptor-dependent mode of negative reinforcement may explain the chronic relapsing feature of nicotine addiction and represent the neurobiological equivalent of a subject "hooked" on tobacco. The recruitment of such anti-reward systems may critically explain the transition from drug use to drug dependence and suggest new targets for non-nicotine pharmacotherapy to aid smoking and smokeless tobacco cessation.

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SYM9 SOCIOECONOMIC STATUS AND SMOKING CESSATION

Chair: David W. Wetter¹

Presenters: Mohammad Siahpush² and Lorraine R. Reitzel¹

Discussant: David B. Abrams³

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Tobacco use is a major determinant of health disparities and there is a profound socioeconomic status (SES) gradient in smoking prevalence, cessation, and related disease burden. For example, 58% of the SES gradient in U.S. male mortality is attributable to tobacco. Although the SES gradient in smoking-related outcomes has been known for decades, these disparities have become even more pronounced over time. Unfortunately, there are few data addressing the specific mechanisms that link SES with smoking-related outcomes. The goal of this symposium is to present recent research investigating the potential pathways between SES and smoking cessation. Dr. Abrams will introduce the symposium, define SES, and briefly review the evidence linking SES to smoking prevalence, cessation, and related disease burden. Dr. Siahpush will present data examining the association of financial stress with smoking cessation outcomes among smokers who participated in the International Tobacco Control Four Country Survey, a prospective cohort study of smokers in the US, Canada, UK, and Australia. Dr. Wetter will present data evaluating a model of the specific pathways and mechanisms that link SES with smoking relapse using a structural equation modeling approach in a diverse sample of smokers seeking treatment. Dr. Reitzel will present data investigating the relations between postpartum smoking relapse and subjective social status (SSS) — an individual's perception of her/his position in the social hierarchy and a potentially more comprehensive measure of social status than traditional indicators of SES — in a diverse sample of pregnant women who quit smoking because of their pregnancy. Dr. Abrams will highlight potential policy and intervention implications of the studies and lead the discussion with the audience.

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SYM9A SMOKERS WITH FINANCIAL STRESS ARE MORE LIKELY TO WANT TO QUIT BUT LESS LIKELY TO TRY OR SUCCEED: FINDINGS FROM THE INTERNATIONAL TOBACCO CONTROL (ITC) FOUR COUNTRY SURVEY

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Objective: To examine the association of financial stress with intention to quit smoking, making a quit attempt, and quit success. Design and participants: The analysis used data from 3411 daily smokers who participated in Waves 4 and 5 (2005-2007) of the International Tobacco Control (ITC) Four Country Survey, a prospective study of a cohort of smokers in the US, Canada, UK, and Australia.

Measurement: The outcomes were having an intention to quit at Wave 4, making a quit attempt, and quit success at Wave 5. The main predictor was financial stress at Wave 4: "because of a shortage of money, were you unable to pay any important bills on time, such as electricity, telephone or rent bills?" Additional sociodemographic and smoking-related covariates were also examined.

Findings: Smokers with financial stress were more likely than others to have an intention to quit at baseline (OR: 1.71; 95% CI: 1.19-2.46), but were less likely to have made a quit attempt at follow-up (OR: 0.74; 95% CI: 0.56-0.96). Among those who made a quit attempt, financial stress was associated with a lower probability of abstinence at follow-up (OR: 0.52; 95% CI: 0.31-0.87).

Conclusions: Cessation treatment efforts should consider routinely assessing the financial stress of their clients and providing additional counseling and resources for smokers who experience financial stress. Social policies that provide a safety net for people who might otherwise face severe financial problems, such as not being able to pay for rent or food, may have a favorable impact on cessation rates.

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SYM9B

MODELING THE PATHWAYS LINKING SOCIOECONOMIC STATUS AND SMOKING RELAPSE: A STRUCTURAL EQUATION MODELING APPROACH

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Although there has been a socioeconomic gradient in smoking prevalence, cessation, and disease burden for decades, these disparities have become even more pronounced over time. Unfortunately, there are few data addressing the specific pathways and mechanisms that link socioeconomic status (SES) with smoking-related outcomes. The purpose of the current study was three fold. First, previously published models of the relationship between SES and health, and of relapse, were synthesized to develop a conceptual model of the mechanisms linking SES to relapse. Hypothesized mechanisms included neighborhood disadvantage (e.g., problems, little social capital), social support, stress/negative affect, craving, and agency (e.g., self-efficacy). The primary outcome was relapse 4-weeks post-quit date. Constructs assessing SES, neighborhood disadvantage, and social support were assessed precessation, with stress/negative affect, craving, and agency measured on the quit date. Second, the conceptual model was evaluated using a latent variable modeling approach in a diverse sample of 424 smokers seeking treatment (139 Whites; 144 African Americans; 141 Latinos). Finally, a multiple group structural modeling analysis was conducted to determine if the final model was a good fit across racial/ethnic groups. As hypothesized, SES had significant direct and indirect effects on relapse. Specifically, neighborhood disadvantage, social support, stress/negative affect, craving, and agency mediate the relation between SES and smoking relapse. Importantly, the multiple group analysis indicated few differences in model pathways across racial/ethnic groups. The present study provides one of the first models illuminating the specific mechanisms that link SES and smoking relapse. Policy, community, and individual-level interventions that target low SES smokers and address the specific pathways identified in the current model could potentially attenuate the impact of SES on relapse.

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SYM9C

SUBJECTIVE SOCIAL STATUS IS ASSOCIATED WITH POSTPARTUM RELAPSE

Lorraine R. Reitzel*¹, Tracy Costello¹, Jennifer Irvin Vidrine¹, Yisheng Li¹, Patricia Dolan Mullen², Mary M. Velasquez³, Paul M. Cinciripini¹, Ludmila Cofta-Woerpel¹, Anthony Greisinger¹, and David W. Wetter¹; ¹The University of Texas, M.D. Anderson Cancer Center; ²The University of Texas-Houston, School of Public Health; ³The University of Texas-Austin; ⁴Kelsey Research Foundation

Smoking has become increasingly concentrated among those with the lowest socioeconomic status (SES). In addition to having a higher prevalence of smoking, individuals with lower SES are less successful at quitting. This SES gradient in smoking prevalence and cessation has also been demonstrated among pregnant women. Pregnancy represents a unique public health opportunity as up to half of pregnant smokers quit during their pregnancies. Unfortunately, 80% resume smoking by 1-year postpartum. Thus, it is critical to identify the risk factors and mechanisms underlying postpartum relapse. Subjective social status (SSS) reflects an individual's perception of her/his position in the social hierarchy, and is a significant predictor of health over and above traditional markers of SES such as education and income. Unlike traditional indicators of SES, SSS captures relative class standing in one's community and taps into perceptions of inequality. The goal of the current study was to examine the unique predictive ability of SSS with respect to postpartum relapse and established predictors of postpartum smoking among a diverse sample of pregnant women (35% White; 32% Black; 30% Latino) who quit smoking because of their pregnancy (N=246). SSS predicted dependence, confidence, temptations, positive and negative affect, stress, depression, and social support even after controlling for education, income, age, race/ethnicity, and partner status. SSS predicted abstinence through 26 weeks postpartum, and continued to predict even after adjusting for education, income, age, race/ethnicity, and partner status (p=.059). SSS provided unique predictive information on risk for postpartum smoking over and above the effects of demographics and objective SES. Unfortunately, women with lower SSS are likely to face significant hurdles in maintaining postpartum abstinence, highlighting the need for targeted interventions with this high-risk subgroup of pregnant women. Results also point to potential points of intervention (e.g., depression, stress, social support). To the best of our knowledge, this is the first study to explore the effects of SSS on postpartum smoking relapse.

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SYM10

TREATMENT OF SMOKING AS A CHRONIC ILLNESS IN PRIMARY CARE

Chair: Edward F. Ellerbeck, M.D., M.P.H.*¹
 Presenters: Ana-Paula Cupertino, Ph.D.¹, and Lawrence C. An, M.D.²
 Discussant: Scott Sherman, M.D.³

¹University of Kansas School of Medicine; ²University of Minnesota; ³New York University

Cigarette smoking is a chronic illness characterized by repeated cycles of quit attempts and relapse. In practice, however, most smoking cessation interventions are based on single, short-term interventions lasting only a few weeks or months. These interventions provide treatment only to smokers that are already prepared to quit and do not consistently reengage relapsed smokers in new treatment plans. New models of chronic disease care have been developed and implemented successfully for the treatment of other chronic illnesses such as diabetes, asthma, and heart failure. These models of chronic disease management may provide an alternative approach for expanding the reach and effectiveness of smoking cessation efforts. In this symposium, Dr. An will describe the results of proactive telephone outreach offering cessation services to smokers identified in a primary care clinic's electronic medical records system. Dr. Ellerbeck will describe an alternative model in which centralized case managers (counselors) work in parallel with primary care practices to promote smoking cessation. Dr. Cupertino will describe the interest of smokers in smoking cessation efforts and show the impact of cessation efforts for smokers requesting up to 4 cycles of treatment. Finally, an interactive discussion will be led by Dr. Sherman who will describe how the "medical home" model for primary care could impact the treatment of smoking cessation as a chronic disease.

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SYM10A

PROACTIVE OUTREACH TO SMOKING PATIENTS IDENTIFIED IN THE ELECTRONIC MEDICAL RECORD: A PILOT PROJECT

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Objective: To assess the feasibility of proactive telephone outreach to smoking patients identified by the electronic medical record.

Study Design: Patients identified as smokers in the electronic medical record of a large primary care clinic in the Midwest (n=1653) were proactively called by phone by a clinic nurse (RN) to offer referral to telephone counseling for smoking cessation. Three referral strategies were tested sequentially. Patients in the first phase (n=590) received a direct offer of being transferred to counseling. In the second phase (n=457), the phone script incorporated elements of motivational interviewing, and the final phase (n=606) included motivational interviewing plus an offer of full coverage for prescription stop-smoking medications for those who agreed to enroll in phone counseling.

Results: Approximately 60% of patients identified by the electronic medical record as smokers were reached by phone. Of those, 80% identified themselves as current smokers, and 57% of smokers expressed interest in quitting. Of current smokers reached by phone 24% were enrolled in phone counseling. This corresponds to 11% of all smokers identified in the medical record. There were no significant differences in the uptake of phone counseling between the three phases of this pilot program.

Conclusions: This pilot study resulted in a high percentage of contacts with current smokers. The proportion of smokers enrolled in phone counseling is significantly higher than media campaigns or fax referrals from clinicians. Proactive outreach has the potential to substantially increase use of assistance for smoking cessation in the population.

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SYM10B IMPACT OF VARYING LEVELS OF DISEASE MANAGEMENT ON SMOKING CESSATION: A RANDOMIZED TRIAL

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Cigarette smoking is a chronic, relapsing illness that is inadequately addressed in primary care practice. We compared cessation rates among smokers receiving pharmacotherapy management alone or when combined with either moderate-intensity or high-intensity disease management that includes counseling and provider feedback. We identified and recruited smokers from 50 rural primary care practices and randomly assigned patients smoking > 10 cigarettes/day to one of 3 interventions: 1) free pharmacotherapy with pharmacotherapy management alone at four 6-month intervals (n = 250); 2) pharmacotherapy management supplemented with offers of up to 2 telephone counseling calls every 6 months (moderate-intensity disease management, n = 249); or 3) pharmacotherapy management supplemented with up to 6 telephone counseling calls every 6 months (high-intensity disease management, n = 251). With both moderate and high-intensity disease management, progress reports were faxed to the participants' physician every 6 months. Participants were not required to quit or utilize pharmacotherapy. Pharmacotherapy utilization was comparable across treatment groups, with 63.9%, 40.8%, 23.8%, and 24.6% requesting pharmacotherapy during the 1st, 2nd, 3rd, and 4th 6-month cycles of treatment. Abstinence rates increased throughout the 24-month study. At 12 months, 15.6%, 20.6%, and 23.9% of pharmacotherapy management, moderate-intensity, and high-intensity disease management participants, respectively, reported abstinence (p=0.04). Significant treatment group differences persisted at month 18, but by 24 months abstinence rates were similar in the three groups (23.0%, 23.5%, and 27.9% for pharmacotherapy management, moderate-intensity, and high-intensity disease management participants, respectively (p=0.43). Pharmacotherapy management costs were \$630 per successful quitter. Smokers are willing to make repeated pharmacotherapy-assisted quit attempts leading to progressively greater smoking abstinence. Although more intensive disease management can temporarily increase quit rates, pharmacotherapy management alone appears to be highly cost-effective with similar long-term outcomes.

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SYM10C CONSECUTIVE CYCLES OF SMOKING CESSATION PHARMACOTHERAPY

A. Paula Cupertino, Ph.D.^{*}, Kimber Richter, Ph.D., Laura M. Mussulman, M.A., M.P.H., Niaman Nazir, M.B.B.S., M.P.H., Jonathan D. Mahnken, Ph.D., Theresa I. Shireman, Ph.D., and Edward F. Ellerbeck, M.D., M.P.H., University of Kansas School of Medicine

Introduction: Tobacco dependence is a chronic, relapsing condition. Most treatment, however, utilizes short-term, acute care approaches. Only a few studies have examined the benefits of recycling relapsed smokers, and many insurers and smoking cessation programs restrict smokers to 1 or 2 cycles of treatment.

Objectives: The purpose of this study is to assess the effect on smoking cessation of offering repeated courses of pharmacotherapy.

Methods: Kan Quit was a population-based clinical trial of a disease-management program for smoking cessation that enrolled 750 smokers seen in rural primary care practices. Every six months (months 0, 6, 12 and 18), participants were offered a free 6-week course of 21mg/day nicotine patch or a 7-week course of bupropion 300mg/day, regardless of their interest in quitting smoking. This analysis focused on the persistent smokers who made repeated pharmacotherapy-assisted quit attempts with each offer of treatment.

Results: Of the 726 participants that completed the trial, 464 (63.9%) took medication during the first cycle of treatment. Of continuing smokers, 52.7% of 383, 45.8% of 177 and 64.7% of 68 opted for 2nd, 3rd and 4th consecutive cycles of pharmacotherapy, respectively. Following the 1st, 2nd, 3rd, and 4th cycles of pharmacotherapy, six-month quit rates were 17.4%, 12.4%, 16.0% and 15.9%, respectively. Across all four cycles of treatment, cessation rates were higher for participants making pharmacotherapy-assisted quit attempts compared to those declining pharmacotherapy.

Conclusion: Pharmacotherapy-assisted quit rates do not appear to diminish even after multiple consecutive pharmacotherapy-aided quit attempts. Providers and policymakers should support repeated cycles of pharmacotherapy among continuing smokers.

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SYM11 NICOTINE AND INFORMATION PROCESSING

Chair: Allison C. Hoffman, Ph.D.^{*5}
 Presenters: Amir Levine, M.D.¹, Evelyn K. Lambe, Ph.D.², Raad Nashmi, Ph.D.³, and Thomas J. Gould, Ph.D.⁴
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Although people smoke cigarettes because of nicotine's reinforcing effects, the central effects of nicotine are far more diverse. Of particular interest are nicotine's effects on information processing, which could play a key role in the maintenance of tobacco use and the chronic relapses associated with quit attempts. The goal of this symposium is to examine nicotine's effects on cognitive, sensory and emotional information processing. There will be four presentations. Dr. Amir Levine will discuss nicotine's effects on information processing via epigenetic mechanisms. Dr. Evelyn Lambe will discuss the cellular mechanisms underlying the ability of nicotine to perturb attention circuitry during development, focusing on an unusual subtype of nicotinic receptors (alpha4beta2alpha5) that are essential for the normal maturation of corticothalamic neurons. Dr. Raad Nashmi will discuss the effect of chronic nicotine on cell specific upregulation of functional alpha 4* nicotinic receptors in the CNS. Lastly, Dr. Thomas Gould will discuss some intriguing interactions between nicotine and learning that produce a novel pattern of MAPK gene expression. Since the target audience includes both animal and human nicotine/tobacco researchers, it is hoped that these presentations will stimulate discussion on the mechanisms that underlie nicotine's effects on information processing, and the impact that these effects may have on long-term tobacco users.

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SYM11A THE NICOTINIC ALPHA5 SUBUNIT PLAYS A KEY ROLE IN THE DEVELOPMENT OF PREFRONTAL ATTENTION CIRCUITRY

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We have recently shown robust nicotinic excitation of corticothalamic neurons during development. These neurons gate thalamic activity and, in adulthood, play a critical role in attention and information processing. The developmental sensitivity of corticothalamic neurons to nicotinic stimulation suggests a role for nicotinic receptors in the maturation and plasticity of these neurons. Moreover, the timing of this sensitivity suggests that developing corticothalamic circuitry is vulnerable to disruption by exposure to the drug nicotine. Here, we show that the developmental peak in corticothalamic nicotinic currents depends on the presence of an unusual subtype of nicotinic receptor (alpha4beta2alpha5). This subtype is expressed in a relatively few regions of the brain and is unique among the high affinity nicotinic receptors for its degree of permeability to calcium and, therefore, its potent activation of downstream signaling cascades. In experiments performed with transgenic mice deleted for the alpha5 nicotinic subunit as well as their wildtype controls, we show that the developmental peak of nicotinic sensitivity is dependent on the presence of the alpha5 nicotinic subunit. Interestingly, treatment of prefrontal brain slices with nicotine makes neurons from wildtype mice resemble those of mice lacking this alpha5 subunit. Further examination of the corticothalamic neurons in the alpha5 knockout mice reveals striking differences in their electrophysiological properties, morphology, and synaptic plasticity. These data suggest that alpha4beta2alpha5 nicotinic receptors are critical for the normal maturation of the corticothalamic neurons and suggest a cellular mechanism for the vulnerability of developing attention circuitry to nicotine.

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SYM11B CELL SPECIFIC UPREGULATION OF ALPHA4* NICOTINIC RECEPTORS WITH CHRONIC NICOTINE

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Exposure to chronic nicotine results in the upregulation of nicotinic acetylcholine receptors (nAChRs) in the brains of chronic smokers. To understand the effects of chronic nicotine we need to measure the molecular and functional changes in specific neurons and synapses. We sought to quantify $\alpha 4$ containing ($\alpha 4^*$) nAChRs in specific neuronal subtypes at subcellular resolution. Using homologous recombination, we engineered knock-in mice that express $\alpha 4$ nAChR subunits containing yellow fluorescent protein in the M3-M4 cytoplasmic loop ($\alpha 4$ YFP). Mice were implanted with mini-osmotic pumps, which delivered either saline or nicotine (2 mg/kg/hr for 10 d). Spectral confocal imaging was performed to isolate $\alpha 4$ YFP fluorescence in various brain regions. We found that chronic nicotine did not alter the number of $\alpha 4^*$ nAChRs in the neurons implicated in drug addiction and reward — the dopaminergic (DA) neurons in the ventral tegmental area (VTA) nor in the DA neurons in the substantia nigra pars compacta (SN). Instead, the receptors were selectively upregulated in GABAergic neurons in both the VTA and substantia nigra (SN). Correspondingly, in whole-cell patch-clamp recordings from midbrain slices there was higher basal firing frequencies and greater acute nicotine responsiveness in SN GABAergic neurons exposed to chronic nicotine. Meanwhile DA neurons that were exposed to chronic nicotine had lower basal firing rates and were less responsive to acute nicotine. Our second intriguing finding was that the largest upregulation of $\alpha 4$ nicotinic receptors occurred in the medial perforant path of the hippocampus. This corresponded in enhanced long-term potentiation of excitatory postsynaptic responses when upregulated receptors were activated by acute nicotine. The pattern of cell specific upregulation of $\alpha 4$ nAChRs explains two effects of chronic nicotine — tolerance of the DA reward pathway and sensitization of synaptic transmission in the forebrain.

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SYM11C NICOTINE AND LEARNING INTERACT TO PRODUCE A NOVEL PATTERN OF HIPPOCAMPAL GENE EXPRESSION THAT UNDERLIES LONG-LASTING CHANGES IN LEARNING

Thomas J. Gould, Ph.D.*, Temple University

Nicotine use results in long-lasting changes in learning and behavior; this suggests that nicotine administration can produce robust changes in synaptic plasticity. Long-lasting changes in behavior and memory are linked to changes in gene transcription. Recent work from our lab suggests that the effects of nicotine in the hippocampus are necessary and sufficient to produce changes in learning. In mice, acute intrahippocampal nicotine infusion enhanced contextual learning whereas withdrawal from chronic intrahippocampal nicotine infusion disrupted contextual learning. These effects were not present in beta2 nicotinic receptor subunit knockout mice. In a series of experiments, we tested if nicotine and learning would interact to produce a pattern of gene expression different than that found with either nicotine administration or learning alone; if inhibition of related gene products would inhibit the effects of nicotine on learning; and whether the beta2 nicotinic receptor subunit is necessary for observed gene expression changes. Using a cDNA microarray to screen for changes in gene transcription due to an interaction of nicotine and learning, the mitogen activated protein kinase (MAPK) family (with emphasis on the c-Jun N-terminal Kinase 1 (JNK1)) was targeted for further analysis. qRT-PCR indicated that JNK1 mRNA was upregulated in the hippocampus 30 minutes post training in nicotine-treated mice trained in contextual fear conditioning but downregulated 2 hours post training. This pattern of gene expression was unique to JNK1 and absent in mice trained without nicotine and untrained nicotine-treated mice. Changes in JNK1 mRNA expression were absent in beta2 nicotinic receptor subunit knockout mice. Finally, inhibition of hippocampal JNK protein 60 minutes post training blocked the enhancement of learning by nicotine. Thus, nicotine and learning interact to produce a novel pattern of gene expression in the hippocampus mediated by beta2-containing nicotinic receptors that results in a long-lasting change in learning. The ability of nicotine and learning to interact to alter gene expression, learning, and hippocampal function may contribute to nicotine addiction.

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SYM11D A MOLECULAR STUDY OF THE GATEWAY HYPOTHESIS OF STAGES IN ADOLESCENT DRUG USE

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The Gateway hypothesis describes a regular developmental sequence and stages of progression of drug consumption in which the use of cigarettes (nicotine) or alcohol precedes the use of other illicit drugs. It raises two fundamental questions that can only be addressed in animal models: (1) Is there a biological basis, separate from the affect of psychosocial factors, for the observation that the use of a specific drug predisposes to the subsequent use of another? and (2) What cellular and molecular mechanisms underlie this sequential progression of drug use? To address these issues, we designed a paradigm of sequential drug administration. We explored how nicotine, a drug used earlier in the sequence, and cocaine and other drugs that are taken later in the sequence alter the level of transcription of selected genes in the striatum. After both oral nicotine treatment (7 d and 24 hr) and acute cocaine injection, fosB expression increased. We then examined whether the increased expression of these genes following the administration of one drug was modified by pretreatment with the other drug, either cocaine or nicotine. Pre-exposure to nicotine for 7 d there was a marked increase in fosB expression in response to a cocaine injection. When the protocol was reversed (cocaine treatment first, nicotine challenge), fosB expression did not change. In electrophysiological studies, we show that nicotine priming enhances the changes in LTP that are typical to cocaine in several brain regions. Behaviorally mice exposed to 7-d nicotine have increased sensitization to cocaine and methamphetamine. We show here a molecular mechanism that underlies the progression from the use of nicotine to other drugs of abuse. We further describe changes in behavior and electrophysiological signatures of long-term synaptic plasticity that parallel epigenetic changes and changes in gene expression, which provide the neurobiological underpinnings for the Gateway hypothesis.

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