Research Findings
Vol. 20, No. 6 (July 2006)

Sensory Aspects May Drive Addiction in Obese Smokers

Obesity appears to reduce nicotine's rewarding effect in mice and humans.

By Patick Zickler, *NIDA NOTES* Contributing Writer

For obese smokers, the taste and smell of a lit cigarette may play as powerful a part in addiction as does the nicotine buzz. For these smokers, nicotine replacement therapies that also replace some of the sensory aspects of smoking—lozenges, gum, or nasal spray—may be more effective than a patch, according to researchers at the University of Pennsylvania's Transdisciplinary Tobacco Use Research Center (TTURC).

Lead investigator Dr. Caryn Lerman and TTURC colleagues asked 37 smokers to describe the experiences of smoking two "brands" of cigarettes; although the smokers did not know it, one brand contained nicotine and the other did not. Obese smokers rated the two nearly equal, while nonobese smokers gave higher marks to the conventional cigarettes. When allowed to choose freely, nonobese smokers preferred conventional cigarettes, while obese smokers were equally likely to choose either type.

To validate these observations and investigate their physiological basis, Dr. Julie Blendy and colleagues tested nicotine's rewarding effect in mice. Given access to two chambers, nonobese mice gravitated to the one in which researchers had dosed them with nicotine, whereas mice made obese by a high-fat diet showed no preference. These results suggest that the nicotine provided the nonobese mice, but not the obese mice, with an experience they wanted to repeat. When the researchers examined the brains of the mice, they found that the obese animals, compared with those fed a normal diet, had reduced levels of opioid receptors, which have been implicated in nicotine addiction.

"For obese smokers, sensory cues such as sights and smells and taste may be at least as rewarding as the pharmacological reward of nicotine," says Dr. Lerman. "The mouse experiment suggests a possible biological mechanism for the observation in human smokers. Diet may influence nicotine reward through effects on the opioid system," Dr. Blendy adds.

OBESITY AND HUMAN RESPONSE TO NICOTINE

The research team recruited 17 obese and 20 nonobese men and women who were regular smokers. The obese and nonobese study participants' average body mass indexes were 39.1 (range, 31.0 to 59.4) and 23.0 (range, 18.3 to 26.3), respectively. In the first part of the study, the participants smoked one cigarette from each of two color-coded sets, one that contained nicotine and one that was nicotine-free, without being informed about the difference. Participants rated the two smokes on a scale ranging from 0 (none) to 7 (complete)—for "satisfaction," "liking," and "psychological relief." On average, obese smokers gave the conventional and nicotine-free cigarettes almost identical ratings for satisfaction (3.0 for nicotine versus 2.9 for nicotine-free), liking (2.9 versus 2.8), and psychological relief (1.4 versus 1.2). Nonobese smokers gave the conventional cigarettes higher ratings for satisfaction (3.4 versus 2.1) and liking (3.7 versus 2.3) and showed no significant preference in psychological relief (1.7 versus 1.5).

OBESE SMOKERS DERIVE LESS PLEASURE FROM NICOTINE THAN OTHER SMOKERS Obese smokers rated regular and nicotine-free cigarettes very similarly.

Item/Scale	Cigarette	Mean

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		Nonobese (n=20)	Obese (n=17)
Satisfaction	Nicotine-Free	2.1	2.9
	Nicotine	3.4	3.0
Psychological relief	Nicotine-Free	1.5	1.2
	Nicotine	1.7	1.4
Liking	Nicotine-Free	2.3	2.8
	Nicotine	3.7	2.9

Next, the smokers were allowed to smoke cigarettes from either color-coded set in four sessions, spaced 30 minutes apart, but limited to four puffs per session. On average, obese smokers took as many puffs on the conventional (48 percent) as the nicotine-free (52 percent) cigarettes. Nonobese smokers took 70 percent of their puffs from the conventional cigarettes.

"Tobacco addiction involves an interplay of physiological influences, such as the effects of nicotine or other components of tobacco, with sensory influences associated with taste or aroma, the physical manipulation of cigarettes and lighters, or the sight of smoke," Dr. Lerman says. "It appears that for obese smokers, non-nicotine factors play a considerable part in maintaining addiction and therefore need to be considered in developing a treatment to help obese smokers quit. Obesity and smoking are both serious health risks, and some research suggests they act synergistically to create an even greater risk. If so, helping obese smokers to quit may have a greater impact on public health than an equivalent cessation among nonobese smokers."

OBESE MICE AND NICOTINE

In the animal component of their investigation, the researchers simulated human obesity in mice by feeding them a high-fat diet (45 percent fat, 35 percent carbohydrates, 20 percent protein) for 15 weeks. A control group of mice received a normal laboratory diet (12 percent fat, 60 percent carbohydrates, 28 percent protein). The researchers injected each animal with nicotine while confining it to one compartment of a two-compartment test chamber daily for 8 days. Subsequently, they placed each mouse in the test chamber and allowed it free access to either compartment for 15 minutes. Nonobese mice spent most of this time in the compartment where they received the drug, indicating that the nicotine injections had given them pleasure they would like to repeat. However, obese mice showed no preference for the side associated with the drug.

The investigators next examined the brains of the mice and found evidence that the animals maintained on a high-fat diet had less precursor associated with structures called mu-opioid receptors on cells in the ventral tegmental area (VTA) of the brain. The VTA is where nicotine acts to increase the availability of dopamine, a chemical that causes the pleasurable sensations associated with many drugs of abuse. Other animal research has implicated mu-opioid receptors in neurochemical processes that lead to nicotine addiction, and the finding that fewer of these receptors are activated in the brains of the high-fat-diet mice could in part explain their blunted response to nicotine's rewarding effect.

"In this mouse study, the animals could not control their diet. But humans choose what and when to eat," says Dr. Allison Chausmer of NIDA's Division of Basic Neuroscience and Behavioral Research. "The observations made in these mice suggest a fascinating chain of events leading from a behavior, selecting what to eat, to a measurable biochemical change in the brain and altered response to an addictive drug. They illustrate the complexity of factors that contribute to the powerful addictive grip of tobacco and—conversely—can potentially be manipulated to improve the effectiveness of treatments that help smokers quit."

SOURCE

Blendy, J.A., et al. Reduced nicotine reward in obesity: Cross-comparison in human and mouse. *Psychopharmacology* 180(2):306-315, 2005. [Abstract]

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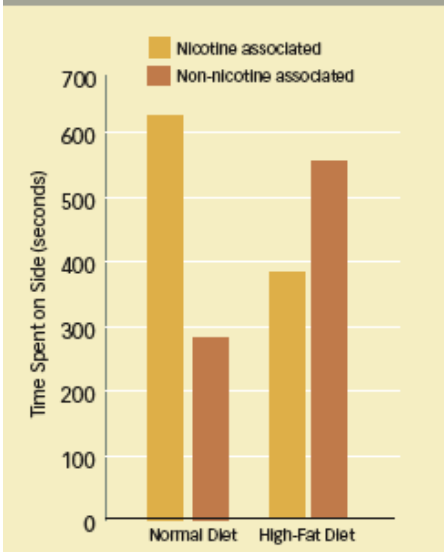
MICE RAISED ON A HIGH-FAT DIET HAVE DIMINISHED RESPONSE TO NICOTINE Mice fed a normal diet spent most of a 15-minute test period on the side of a cage in which they had been given nicotine, whereas mice fed a high-fat diet showed no such preference.



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Research Findings
Vol. 20, No. 5 (April 2006)

Bupropion Helps People With Schizophrenia Quit Smoking

Data address physicians' concerns about prescribing the medication for smokers with schizophrenia.

By Lori Whitten, *NIDA NOTES* Staff Writer

The smoking-cessation aid bupropion is safe and effective for people with schizophrenia, researchers at Massachusetts General Hospital and Harvard Medical School have found. In a NIDA-funded study of smokers with schizophrenia, those who took sustained-release bupropion were more likely to stop smoking by their quit date and to achieve continuous abstinence for a month than those who received placebo, and they also remained abstinent longer. The researchers did not observe any adverse interactions with the patients' antipsychotic medications or exacerbation of psychiatric symptoms.

The U.S. Food and Drug Administration (FDA) approved sustained-release bupropion as a treatment for depression in 1996 and as a smoking-cessation aid in 1997, but physicians have been reluctant to prescribe the medication for patients with schizophrenia. "Although 75 to 85 percent of people with schizophrenia smoke, we have lacked data on treatments for nicotine addiction in this population, resulting in many not receiving advice to quit," says Dr. A. Eden Evins, lead investigator of the study.

Dr. Evins and her colleagues treated 53 patients, aged 24 to 66, for nicotine dependence. When they began treatment, the patients smoked 30 cigarettes a day, on average, and typically had made two previous quit attempts. During the 12-week study, each participated in weekly sessions of group cognitive-behavioral therapy (CBT) and received either 300 milligrams a day of sustained-release bupropion or placebo. The CBT program was adapted for patients with schizophrenia from standard smoking-cessation therapy. Each patient visited the clinic once a week for evaluations of smoking (self-report confirmed by expired air carbon monoxide measurements), changes in psychiatric symptoms, medication compliance, and side effects.

Therapists encouraged all patients to set a quit date before the 4th week of treatment, and 36 percent of those taking bupropion—compared with 7 percent of those on placebo—achieved this goal, demonstrating abstinence at the 4-week assessment. Sixteen percent of patients in the bupropion group, but none taking placebo, achieved abstinence throughout the last month of treatment. Among patients who were not abstinent at the end of the study, those in the bupropion group reduced the average number of cigarettes smoked daily from 34 to 9, compared with a drop from 25 to 15 in the placebo group.

Bupropion was generally well tolerated and did not exacerbate the symptoms of schizophrenia. Depression and flat affect, as well as cognitive function, tended to improve among patients taking the medication. Common side effects experienced by people taking antipsychotic medications, such as muscle stiffness and shuffling gait, were not worsened by nicotine abstinence or bupropion. About 80 percent of patients in both the medication and placebo groups kept to their regimens throughout the study.

The findings confirm promising results from several smaller studies. Dr. Evins points out that the relapse rate was high after treatment discontinuation—75 percent of those who were abstinent at week 12 had relapsed to smoking at the 3-month followup. Only about 4 percent of patients in either group were abstinent in the week before the 3-month followup. Other studies of bupropion in the general population have shown that about half of patients tend to relapse after treatment

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discontinuation. "Patients with schizophrenia may need a longer course of bupropion with CBT or a combination of bupropion and nicotine replacement therapy to avoid relapse," says Dr. Evins.

Source

Evins, A.E., et al. A double-blind placebo-controlled trial of bupropion sustained-release for smoking cessation in schizophrenia. *Journal of Clinical Psychopharmacology* 25(3):218-225, 2005. [Abstract]

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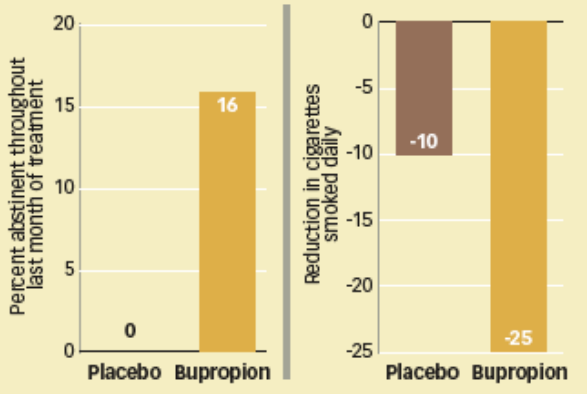
BUPROPION ENHANCES OUTCOME OF COGNITIVE-BEHAVIORAL THERAPY Patients with schizophrenia who participated in weekly group cognitive-behavioral therapy for smoking cessation were more likely to remain abstinent throughout the last month of a 12-week study if they also took bupropion. Among patients still smoking at study's end, those receiving bupropion smoked fewer cigarettes daily than those on placebo.



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Genetic Predisposition and Depression Both Influence Teen Smoking

Research Findings
Vol. 20, No. 4 (March 2006)

By Patrick Zickler, *NIDA NOTES* Staff Writer

NIDA-supported scientists have found that a gene, called *DRD2*, partly determines whether an adolescent who takes a first puff on a cigarette will progress to regular smoking. Adolescents who carry one of the two known forms of the gene (*A1*) are more likely than those with the other variant (*A2*) to become daily smokers. If the teen also suffers from depression, the genetic effect is amplified, further increasing the likelihood of smoking escalation, according to Dr. Janet Audrain-McGovern and colleagues at the University of Pennsylvania Transdisciplinary Tobacco Use Research Center (TTURC).

The new findings result from a large-scale study that Dr. Audrain-McGovern and her research group undertook to clarify outstanding issues surrounding *DRD2* and smoking. Scientists have suspected for some time that variations in *DRD2* might influence people's responses to tobacco, based on the gene's function: It helps guide construction of sites where the neurotransmitter dopamine—which plays a key role in producing the pleasurable effects of nicotine—attaches to brain cells. Some previous studies have found that, indeed, men and women who smoked or were nicotine-dependent were more likely to have the *A1* *DRD2* variant than the *A2*. However, other studies did not confirm the link.

DRD2 Variants and Smoking Progression

Dr. Audrain-McGovern's team recruited 615 adolescents (322 girls, 293 boys) to participate in their study. Because genetic diversity would increase the difficulty of interpreting results, all the youths were of European ancestry. Analysis of DNA obtained from cheek swabs showed that the frequencies of the alternative *DRD2* forms, or alleles, were roughly the same among the participants as have been seen in general population samples of people of European stock: Two-thirds (67 percent) had inherited the *A2* allele from both parents, 30 percent had one *A1* and one *A2*, and 3 percent had two copies of the *A1*.

The researchers interviewed the teens in ninth grade, asking questions used in the Youth Risk Behavior Survey, including, "Have you ever tried or experimented with

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cigarette smoking, even a few puffs?" "Have you smoked at least one whole cigarette?" "How many cigarettes have you smoked in the last 30 days?" and "How many cigarettes have you smoked in your lifetime?" Based on their responses, the teens were categorized as never smokers, puffers (a few puffs, but never a whole cigarette), experimenters (at least one but fewer than 100 lifetime cigarettes), and current smokers (smoked in the past 30 days and 100 or more lifetime cigarettes).

The teens answered the same questions again in the fall and spring of their 10th-grade year and in the spring of their 11th-grade year. Analyzing the teens' sequential responses together with their genetic data, the researchers found no association between variation in *DRD2* alleles and the likelihood that participants who had never smoked would start, Dr. Audrain-McGovern says. "However, among adolescents who had taken at least a single puff, we found a clear association between the *A1* allele and progressing up the ladder of smoking frequency—for example, moving from puffer to experimenter, or experimenter to current smoker. Each additional copy of the *A1* allele nearly doubled the odds of progression," she says. Among teens who had at least puffed once, those with a single *A1* allele were 1.8 times as likely, and teens who had inherited *A1* alleles from both parents were 3.4 times as likely as those with two *A2* alleles to progress to heavier smoking before they finished 11th grade.

"These results clearly illustrate the important interplay between a gene and the environment," Dr. Audrain-McGovern says. "The *DRD2* variant appears to play no role in whether or not these teens took that first puff. Its effect isn't seen until there is some biological exposure. Then, we see a markedly different response to nicotine, perhaps because the *A1* allele is associated with reduced density of dopamine receptors. If individuals with this allele have lower baseline levels of dopamine activity, they might experience greater reward when nicotine triggers an enhanced dopamine release."

DRD2 and Depression

During the ninth-grade interviews, the researchers administered the Center for Epidemiological Studies Depression Scale (CES-D Scale) to the study participants. Each teen rated how frequently he or she had experienced each of 20 depression symptoms during the past week. One hundred teens (16 percent) scored 23 or higher on this scale, which indicates clinically significant depression. Of the 100, 52 had at least one *A1* allele. Teens without an *A1* allele had an average CES-D score of 12.3; those with one *A1* and one *A2* had an average score of 15.1; and those with two copies of the *A1* allele averaged 16.7. There also was a significant association between the CES-D score and smoking status at the initial interview: The average score was 12.5 for never smokers, 14.6 for puffers, 13.7 for experimenters, and 20.8 for current smokers.

Teens with high depression scale scores and the *A1* allele were at the highest risk of smoking progression. Among teens with at least one *A1* allele, 33 percent of depressed teens, compared with 25 percent of nondepressed teens, reported smoking progression within 2 years.

The interaction of the *DRD2* allele and depression on smoking progression highlights the intricate interplay of genetic, psychological, and social factors that influence adolescents' smoking behavior, observes Dr. Allison Chausmer of NIDA's Division of Basic Neuroscience and Behavioral Research. "This research group has previously shown that adolescents who have depression are more receptive than nondepressed teens to the messages contained in tobacco advertising. This is not a trivial number of potential smokers. Roughly one in five high school students has symptoms that represent clinically significant depression. Those who succumb to the appeal of tobacco manufacturers' advertising and have this particular genetic makeup may be more likely to progress to higher levels of smoking and ultimately experience consequences of reduced health and longevity."

Source

- Audrain-McGovern, J., et al. Interacting effects of genetic predisposition and depression on adolescent smoking progression. *American Journal of Psychiatry* 161(7):1224-1230, 2004. [Full Text]

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