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Helping Smokers Quit Through Pharmacogenetics

Editor's note: Recently, the Food and Drug Administration approved a new drug, varenicline, to help people quit smoking. It is the first new smoking cessation drug in nearly a decade, and joins just two other pharmacotherapy approaches [nicotine replacement therapies (NRTs) and bupropion] that have been proven effective for the treatment of tobacco dependence. However, even the most effective treatments help just one in four smokers quit long-term. Smoking is the single most preventable cause of death in the U.S., killing nearly 440,000 Americans each year. Nearly 45 million Americans smoke, and about 32 million of them would like to quit. Evolving knowledge about the human genome and the neurobiology of nicotine addiction holds great potential for improving smoking cessation treatments. This Issue Brief reviews ongoing work at Penn's Transdisciplinary Tobacco Use Research Center (TTURC) to unravel the genetic factors that might affect smoking cessation and to develop more effective treatment strategies.

Individualizing smoking cessation treatments may improve quit rates

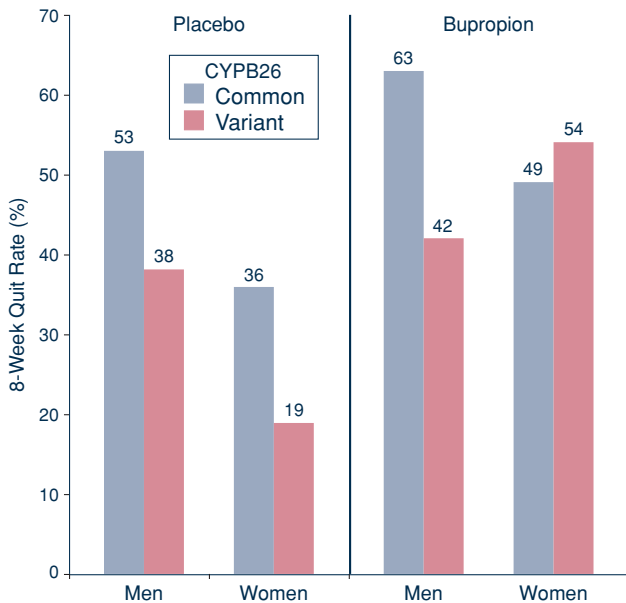
Smoking is a complex behavior with physiologic and psychological manifestations. The most effective approach for treating nicotine dependence combines behavioral counseling with drug therapy. But smoking is a hard habit to break, and only a small fraction of smokers are able to quit with current treatments.

- Rather than concluding that currently available treatments are weak or ineffective, it is possible that they are very effective in some smokers, but not in others. The challenge is to identify the smokers for whom each treatment is most effective, and to select the best drug, dose, and duration of treatment for that person.
- The emerging field of pharmacogenetics may help individualize treatments and improve quit rates. Genetic differences in drug metabolism or in the targets of a drug (e.g., brain receptors) may play a role in how a smoker responds to a treatment; understanding the role of genetic variation in therapeutic response may help practitioners select the most effective treatment for each smoker.
- To identify the genes with the greatest potential for improving clinical practice, Lerman and colleagues used new information from human studies and animal models of nicotine addiction. They studied genes that affect different biological pathways: genes that influence how nicotine is processed in the body, and genes involved in the brain's dopamine and opioid pathways that contribute to addiction.

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Genetic variation in how women process nicotine may predict response to bupropion

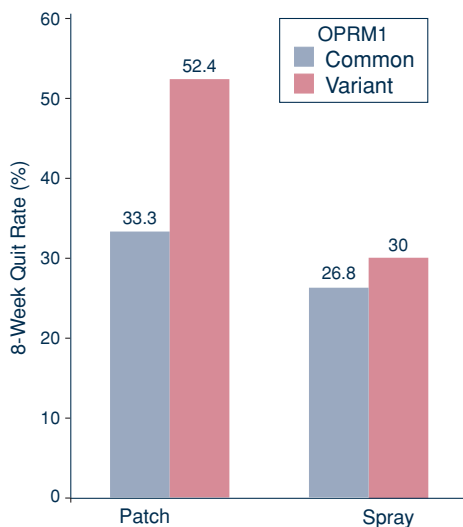
Bupropion (Zyban©) is an antidepressant that was approved as a smoking cessation treatment in 1997. Lerman and colleagues focused on an enzyme that breaks down nicotine in the brain (into an inactive form called cotinine) and also helps process bupropion. The amount of the enzyme has a genetic basis; about 70% of people of European ancestry have a form of a gene (known as CYP2B6) that produces more enzyme, while the remaining 30% have a genetic variant that makes less enzyme (and is thought to slow the rate of inactivation of nicotine in the brain). In a randomized controlled trial of bupropion, the researchers analyzed the effect of this genetic variant on cravings and smoking relapse.



- The study included 426 smokers. All participants received 7 group counseling sessions to quit smoking; 229 received bupropion and 197 received a placebo throughout the 10-week treatment phase. Quit rates were determined at the end of treatment and six months after the quit date.
- DNA from blood samples showed that about 30% of the smokers had the genetic variant with decreased enzyme activity (slow metabolizers). These smokers were more likely to experience cravings after they quit, and were more likely to relapse, than smokers without the variant.
- Smokers were more likely to quit with bupropion than with placebo. Slow metabolizers were less likely to quit than fast metabolizers. Treatment with bupropion particularly helped women who were slow metabolizers, increasing quit rates from 19% to 54%. These effects were mainly evident at the end of treatment, and weaker at the six-month followup.

Certain smokers may benefit from an extended dose and duration of nicotine patch

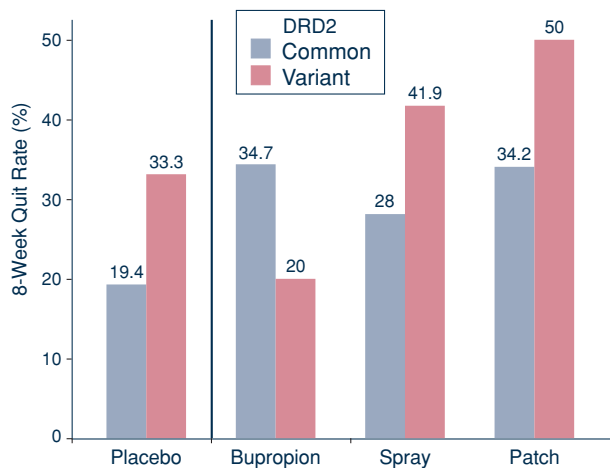
Nicotine replacement therapies, such as the patch, nasal spray, and gum, are also approved as a treatment for smoking cessation. Because the short-term administration of nicotine affects the brain's opioid system (the same system involved in responses to morphine or heroin), Lerman and colleagues focused on a specific opioid receptor gene variant (known as OPRM1 Asn40Asp). About 25%-30% of people of European ancestry have a variant that makes less protein (and therefore, probably results in less receptor activity in the brain).



- The researchers hypothesized that this genetic variant would affect how well smokers respond to different forms of nicotine replacement therapy. They compared quit rates and symptoms in an randomized study of the nicotine patch versus nicotine nasal spray in 320 smokers of European ancestry. All participants received 7 sessions of group counseling, and were randomly assigned to receive either the nicotine patch or nasal spray for 8 weeks. Quit rates were determined at 8 weeks and at six months.
- Smokers carrying the variant were significantly more likely than others to quit at the end of therapy with the nicotine patch, and reported less mood disturbance and weight gain. There was no significant difference in response to the nasal spray.
- Standard patch treatment consists of 4 weeks of a high-dose patch, tapered off in the following 4 weeks. An analysis of the patch group found that the association of the variant with quitting was greatest during the high-dose patch treatment, then reduced as treatment was tapered, and disappeared after treatment was discontinued. This suggests that extending treatment with the

patch at high dosages may improve quit rates in this group of smokers. In an ongoing randomized trial, Lerman and colleagues are now testing whether smokers with this variant have higher quit rates after 24 weeks of extended treatment, rather than the 8-week standard treatment.

Genetic differences in the brain-reward pathways of smokers may reveal whether they would benefit more from bupropion or nicotine replacement therapy



Nicotine produces increases in levels of dopamine, a chemical in the brain associated with the rewarding effects of smoking. Lerman and colleagues examined the effects of a specific variation in a dopamine receptor gene (called DRD2-141C Ins/Del). They analyzed data from both the bupropion study and the nicotine patch/nasal spray study to determine whether this variation predicts responses to either drug therapy. About 16% of the study participants had a genetic variant that is thought to reduce levels of protein for this receptor.

- In the group receiving bupropion, smokers with the common form of the gene were more likely to quit than those with the variant (35% versus 20%).
- In the nicotine patch/nasal spray study, the association was reversed: 46% of the smokers with the variant had quit at the end of treatment, compared to 31% of those with the common form.
- These results suggest that smokers with the common variant respond better to bupropion, and those with the less common variant respond better to nicotine replacement therapy. These effects were not significant at the six-month followup, suggesting that the genetic associations with response to treatment are most likely to be observed when smokers are still taking the drug.

Other clinical features may help identify the best type of nicotine replacement therapy for individual patients

In addition to pharmacogenetic approaches, Lerman and colleagues are also exploring clinical characteristics that might guide the choice of treatment for individual smokers. In their nicotine patch/nasal spray study, they investigated individual characteristics that were associated with the effectiveness of smoking cessation treatments.

- Although quit rates were similar at the six-month followup for the patch and nasal spray, there were differences for certain subgroups of smokers. The patch was more effective for less dependent smokers, those who were not obese, and were white. Conversely, the nasal spray was more effective for smokers who were highly dependent, obese, or members of minority groups.
- Building on the concept that nicotine metabolism affects a smoker's response to treatment, the researchers investigated the use of a pre-treatment blood test that measures the rate at which nicotine is broken down. They found that this measure predicted the effectiveness of the patch at the end of treatment and at the six-month followup, but did not predict the effectiveness of the nasal spray. The odds of quitting smoking were significantly lower for smokers who were faster metabolizers of nicotine.
- These results should be considered exploratory, and need to be confirmed through prospective studies that validate the usefulness of matching treatment to a smoker's individual characteristics.

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POLICY IMPLICATIONS

As these studies indicate, pharmacogenetic research may lead to the development of tailored treatment strategies to help people quit smoking. These results must be confirmed through larger, prospective trials before they can be translated into clinical practice, but these early results are promising.

- Even if these results are replicated, using genetic testing to tailor individual treatment raises certain clinical and ethical challenges. For example, the same genetic variants that can predict response to treatment may reveal predispositions to psychiatric disorders or other addictions.
- Additional research is needed to examine the risks, benefits, and challenges of conveying genetic information about smoking predisposition to patients, clinicians, and the public.
- The cost-effectiveness of tailoring smoking cessation treatments should be assessed through economic analyses. TTURC researchers are collecting cost information as part of their trial of the standard versus extended patch treatment, and are developing models to simulate the cost-effectiveness of different treatment alternatives.
- Many of the variations in candidate genes studied so far occur too infrequently in non-white populations to be studied effectively. Pharmacogenetic studies of common variations in non-white populations are needed to develop tailored treatment strategies for other ethnic groups.

This Issue Brief is based on the following articles: C. Lerman, R. Tyndale, F. Patterson, et al. Nicotine metabolite ratio predicts the efficacy of transdermal nicotine for smoking cessation. Clinical Pharmacology & Therapeutics, June 2006, in press; C. Lerman, C. Jepsen, E.P. Wileyto, et al. Role of functional genetic variation in the dopamine D2 receptor (DRD2) in response to bupropion and nicotine replacement therapy for tobacco dependence: results of two randomized clinical trials. Neuropsychopharmacology, January 2006, vol. 31, pp. 231-242; W.H. Berrettini, C. Lerman. Pharmacotherapy and pharmacogenetics of nicotine dependence. American Journal of Psychiatry, August 2005, vol.162, pp.1441-1451; C. Lerman, F. Patterson, W. Berrettini. Treating tobacco dependence: State of the science and new directions. Journal of Clinical Oncology, January 2005, vol. 23, pp. 311-323; A.E. Shields, C. Lerman, P.F. Sullivan. Translating emerging research on the genetics of smoking into clinical practice: Ethical and social considerations. Nicotine & Tobacco Research, August 2004, vol. 6, pp. 675-688; C. Lerman, V. Kaufmann, M. Rukstalis, et al. Individualizing nicotine replacement therapy for the treatment of tobacco dependence. Annals of Internal Medicine, March 16, 2004, vol. 140, pp. 426-433; C. Lerman, P.G. Shields, E.P. Wileyto, et al. Pharmacogenetic investigation of smoking cessation treatment. Pharmacogenetics, November 2002, vol. 12, pp. 627-634.

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