Smoking Cessation: Physicians Urged to Lead

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ORLANDO, FLA. — Pharmacogenetics will play a major role in the war on tobacco, Sean P. David, M.D., predicted at Wonca 2004, the conference of the World Organization of Family Doctors.

It's already possible in research settings to significantly improve upon the traditional and rather unspectacular quit rates of existing first-line smoking cessation therapies by tailoring treatment to patients' individual genetic variation in relevant brain neurotransmitters, said Dr. David, who is director of research in family medicine at Brown University, Providence, R.I.

Twin studies indicate roughly half of the variation in smoking behavior is caused by genetic factors. The dopamine and serotonin systems are logical places to search for genes governing individual differences in the addictive potential of nicotine. These neurotransmitter systems are richly represented in the nucleus accumbens and other pleasure centers of the brain. Dr. David's own recent work has focused on two candidate genes: the dopamine *DRD2* receptor and the serotonin transporter gene.

Polymorphisms in the dopamine *DRD2* receptor have been shown in case-control studies to be associated with nicotine dependence, obesity, and alcohol abuse. A 44-base pair deletion/insertion polymorphism of the serotonin transporter gene has similarly been associated with smoking behavior, depression, and neuroticism.

Dr. David performed a study in which he randomized 30 smokers to bupropion or placebo and conducted detailed interviews regarding nicotine withdrawal symptoms at baseline and after 14 days of treatment. He found that only in the subgroup having the *DRD2-Taq1 A2/A2* genotype was bupropion associated with decreased nicotine craving, irritability, and anxiety in response to environmental smoking cues. In the *A1/A1* and *A1/A2* groups, bupropion wasn't significantly better than placebo at curbing specific symptoms of nicotine withdrawal.

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Next, Dr. David analyzed DNA from blood samples belonging to 292 participants in the Zyban Collaborative Study, a multicenter prospective placebo-controlled trial of bupropion for smoking cessation. In his retrospective secondary analysis, patients with the *DRD2-Taq1 A1/A1 or A1/A2* genotypes had a 23% successful quit rate 6 months after attempting to quit, regardless of whether they'd been assigned to bupropion or placebo.

In contrast, patients with the *A2/A2* polymorphism had a 34% quit rate on bupropion and a mere 13% quit rate on placebo. After adjusting for potential confounders, this worked out to a 3.3-fold greater likelihood of successfully quitting smoking with bupropion as compared with placebo in patients with the *A2/A2* genotype.

"This is just one study and it requires replication, but I know there are colleagues at University of Pennsylvania and SRI International who are seeing the same thing," he said.

In a brain MRI study he conducted in collaboration with investigators at University of Oxford (England), Dr. David determined that healthy volunteers having at least one copy of the S allele of the serotonin transporter gene—indicative of a deletion in the gene's promoter region—had lower levels of serotonin binding in every one of 21 different examined regions of the brain.

Dr. David then gained access to blood samples that had been collected as part of a randomized placebo-controlled trial of nicotine patch therapy conducted at Oxford a decade ago.

He found that smokers with the *SS* or *LS* genotype were 2.3-fold more likely to have a significant response to the nicotine patch as compared with placebo after 4 weeks of use, while those with the *LL* genotype were only 1.4-fold more likely to respond to the active than the placebo patch.

"Pharmacogenetics will be here en masse in the next 5-10 years," Dr. David predicted. "I believe that pharmacogenetics—the ability to individually tailor treatment and prevent adverse events by genotype—is the next Internet for family medicine. And we need to get ready."

Indeed, Dr. David cited a host of difficult ethical and behavioral issues raised by the looming entry of pharmacogenetics into clinical practice: "How will patients respond to information about their genotype, which also increases their risk for obesity, for becoming an alcoholic? Will they become fatalistic or more motivated? We still need to study this. What if this information went to insurance companies? Should it? Should it go to employers?"

Fortunately, the National Human Genome Research Institute has named several centers of excellence to look at the social and ethical issues and develop guidelines. These centers are located at Stanford (Calif.) University, Case Western Reserve University, Duke University, and the University of Washington.

The Society of Teachers of Family Medicine has also been proactive in considering new training paradigms that will incorporate the pharmacogenetic model, Dr. David noted.

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Dr. Sean P. David sees pharmacogenetics as the next frontier in first-line smoking cessation treatment.

It's clear that physicians will need all the help they can get in tackling the problem of global tobacco control. Tobacco-related illness is the No. 1 public health problem in the world today.

The World Health Organization has estimated that by 2020, it will account for 10 million deaths per year.

An estimated 500 million people alive today, including roughly one-third of all males in China, will eventually die prematurely of tobacco-related illnesses.

However, some epidemiologists believe that if the prevalence of smoking can be halved during the next 25 years, 150-200 million of those lives will be saved. That's a difficult but not impossible task. It has been done before, albeit not on a worldwide scale. After all, U.S. tobacco consumption was cut in half between the 1950s and the 1980s.

"Think about this for just a second. We're standing at the crossroads of the greatest public health crisis of our time. We have an opportunity to do something extraordinary: to win the war on smoking. The choice is ours. The people in this room right now, if we so choose, can win this war," Dr. David said.

In addition to promoting tobacco control in their clinical practices, he urged U.S. physicians to speak out on key smoking-related public policy issues, including the need for greater government regulation of the tobacco industry and the pressing need for public funding of smoking cessation therapies.

Less than half of the states provide Medicaid coverage for nicotine patch therapy. Medicare has only a demonstration project. ■