

New Drugs Emerging for Nicotine Dependence

BY CARL SHERMAN
Contributing Editor

NEW YORK — With a fuller understanding of the neurobiology of tobacco dependence, potential therapeutic targets have emerged that suggest novel treatments for this devastating health problem, Robert Anthenelli, M.D., said at the annual conference of the Association for Research in Nervous and Mental Disease.

Of particular promise are drugs that target nicotinic receptor subtypes, endocannabinoid antagonists, and selective MAO inhibitors, said Dr. Anthenelli, director of the substance dependence program at the Veterans Affairs Medical Center in Cincinnati.

Tobacco is more likely than alcohol or cocaine to produce dependence in users and is responsible for enormous amounts of mortality and morbidity worldwide, but there are only two approved drug treatment modalities—nicotine replacement and bupropion—and neither is terribly effective, he said.

Neurobiologic research has shown that the acetylcholine system plays a key role in nicotine response and dependence.

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Nicotinic receptors, which bind acetylcholine, are present on almost all neurons and mediate attention, arousal, and cognition.

Diversity of subunit composition allows nicotinic receptors to be involved in a

number of different processes. It appears that two subtypes, $\alpha 4 \beta 2$, which predominates in the brain, and $\alpha 7$, are key players in tobacco dependence, he explained.

Initially, nicotine stimulates these receptors (and through them, the firing of dopaminergic neurons), producing tobacco's desired effects. Over time, though, exposure pushes the receptors into a desensitized state that promotes tolerance. Their consequent upregulation contributes to withdrawal symptoms that make smoking cessation difficult, Dr. Anthenelli said at the meeting, which was cosponsored by the New York Academy of Medicine.

Partial agonists to the $\alpha 4 \beta 2$ nicotinic receptor are currently under development. In the presence of nicotine, these drugs work like antagonists, blocking the drug's reinforcing effect; in its absence, they ameliorate withdrawal.

In a phase IIa study, almost half of smokers taking one such drug, varenicline, successfully quit after 7 weeks, compared with 16% taking placebo and one-third taking bupropion. In this and other studies, the drug's side effect profile appeared to be benign, Dr. Anthenelli said.

Other compounds in this class also are under investigation, he said.

Another intriguing target for novel interventions is the endocannabinoid sys-

tem, which acts in the mesolimbic area of the brain and regulates appetite and other functions. Nicotine stimulates the release of endocannabinoids in the limbic forebrain.

Rimonabant, the first compound developed to modulate this system, works through its influence on one type of receptor (cannabinoid-1). It has aroused great interest for its effects on weight and lipid metabolism but appears to be promising as an aid to smoking cessation as well, he said.

In a phase III trial, rimonabant (20

mg/day) achieved significantly greater abstinence rates than did placebo, as measured during the last 4 weeks of a 10-week trial: 27.6% vs. 15.6% by intent-to-treat analysis, 36% vs. 20% among completers. A lower dosage of the drug (5 mg/day) was no more effective than placebo.

It is particularly encouraging, since weight gain is an important obstacle for many who try to quit smoking, that weight changed little for those on the drug: a mean gain of 0.6 kg, compared

with 7.3 kg on placebo, Dr. Anthenelli said.

Selective MAO inhibitors also are being investigated for this application. Cigarette smoke inhibits MAO activity, possibly through components other than nicotine, and the selective MAO inhibitor selegiline reduced craving and smoking in a laboratory study. In a controlled trial, 25% of patients who added selegiline to nicotine replacement achieved abstinence after a year, compared with 11% of those who used nicotine replacement and placebo. ■

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